THE
2025-26

Medical-Dental-Legal UPDATE

Medical Malpractice • Risk Management • Practice Management
Healthcare Law • Selected Clinical Topics

American Educational Institute, Inc.

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David R. Victor, JD
CEO

Dear Registrant:

You practice in a dynamic and challenging environment. While keeping clinically current is imperative, it is not enough. You must also develop the skills to manage legal risk, safeguard your professional and personal assets, and adapt to rapid advances in healthcare knowledge and technology. ***The 2025–26 Medical-Dental-Legal Update*** has been designed to assist you in this endeavor.

In a single program you will receive 20 hours of timely instruction from nationally recognized experts in medicine, law, pharmacology, technology, asset protection, and practice management. Their lectures cover a broad array of topics, including updates from recent medical literature, hypertension management, Lyme disease and other tick-borne infections, non-alcoholic fatty liver disease, COPD, diabetes, acute pain management, and the cardiovascular effects of extreme exercise. You will also hear presentations on emerging pharmacologic agents, the role of diet in cardiovascular health, executive physicals, and strategies for professional and personal success. Beyond the medical topics, you will gain vital insight into malpractice litigation, asset protection, practice profitability, and the evolving role of large language models and generative AI in clinical practice.

To help you assess your level of comprehension we offer brief self-evaluations that may be taken either before or after the presentations concerned. These tests are included in this syllabus and are identified by the black edges of the pages on which they are featured.

As always, I am very interested in your reaction to this year's lecture series. Please take the time to complete the evaluation questions presented on screen for each presentation, and feel free to contact our faculty directly with questions or comments.

Finally, I urge you to take advantage of the diversity of professionals enrolled this week. Your colleagues include physicians, dentists, and attorneys. What better way to broaden your perspective on these multi-faceted issues than to discuss them in real time with participants from different disciplines.

Thank you for your participation, and please accept my best wishes for a safe, enjoyable, and enlightening visit.

Cordially,
American Educational Institute, Inc

David R. Victor, Esq
Chief Executive Officer

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COURSE OBJECTIVES

After completing ***The 2025-26 Medical-Dental-Legal-Update*** you should have acquired the knowledge that will better enable you to better:

- Identify **practical updates** from recent medical literature that improve everyday clinical decision-making
- Understand the fundamental principles of **medical malpractice litigation** to better navigate legal risk in clinical practice.
- Identify the clinical features of **Lyme disease and other tick-borne infections** and apply appropriate diagnostic and management strategies.
- Explain the **foundational concepts** behind large language models (LLMs) and their applications in healthcare.
- Identify and explain the clinical relevance and therapeutic implications of **ten recently introduced or reintroduced pharmacologic agents**.
- Appreciate the impact of diet on **cardiovascular health**.
- Understand legal structures, insurance tools, and planning strategies to **protect personal and practice assets** and minimize exposure to lawsuits, creditors, and taxes.
- Understand diagnostic, evaluation and treatment approaches for **Non-alcoholic Fatty Liver Disease**.
- Apply current evidence and historical trial data to inform optimal **hypertension management**.
- Demonstrate **effective prompting strategies** to optimize generative AI performance in healthcare settings.
- Understand the role of **physician leadership** in shaping health policy, advancing advocacy, and improving the future of healthcare delivery.
- Improve understanding of the **cardiovascular risks** associated with extreme exercise, high-intensity interval training, and endurance sports, and explore strategies for mitigating adverse outcomes.
- Better understand evidence-based strategies to the **diagnosis and management of COPD** in the outpatient setting.
- Recognize the **limitations, risks, and ethical considerations** associated with generative AI in clinical environments.
- Discuss the evaluation, diagnosis and treatment of **acute pain**.
- Understand **metrics, analyses and strategies** to better ensure practice profitability
- Learn updated **diabetes treatment** strategies based on recent evidence prioritizing cardiovascular and renal outcomes.
- Recognize the medical-legal risks of **integrating artificial intelligence** into clinical care and develop strategies to mitigate liability.
- Understanding of the element, efficacy, and necessity of **executive health physicals**.
- Provide actionable strategies for **professional and personal success** by exploring the habits, mindsets, and behaviors of high achievers.

All learning objectives above address IOM/ACGME core competencies.

THE 2025-26

Medical-Dental-Legal UPDATE

FACULTY DISCLOSURES

The individuals listed below have control over the content of ***The 2025-26 Medical-Dental-Legal-Update***. None of them have a financial relationship with an ineligible company.

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All relevant financial relationships have been mitigated prior to the start of this activity in accordance with ACCME standards.

Louis Kuritzky, MD

Louis Kuritzky, MD, of Gainsville, Florida, is a board-certified, family practitioner and a certified Specialist in Hypertension with the American Society of Hypertension. He is clinical faculty at the UCF/HCA Family Medicine Residency Program in Gainesville and a clinical assistant professor emeritus at the University of Florida. Dr. Kuritzky has given over 1,000 presentations to national and international medical audiences on dozens of clinical topics and has authored over 150 articles in journals including *New England Journal of Medicine, JAMA, Comprehensive Therapy, Hospital Practice, Consultant, Postgraduate Medicine, Journal of Pain and Palliative Care, and Patient Care.*

You may contact Dr. Kuritzky with any questions or comments at (352) 377–3193 or by email at lkuritzky@aol.com.

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Things I Wish I Knew Last Year 2025

JAMA Internal Medicine | Original Investigation | AGING AND HEALTH

Vitamin K_2 in Managing Nocturnal Leg Cramps
A Randomized Clinical Trial

Jing Tan, MD; Rui Zhu, MM; Ying Li, MM; Li Wang, MD; Shigeng Liao, MB; Lin Cheng, MB; LingXiu Mao, MB; Dan Jing, MB

Tan J, et al *JAMA Int Med* 2024;184(12):1443-1447

Nocturnal Leg Cramps: Dead End?

"Currently, there are no treatments of nocturnal leg cramps that have been proven to be both safe and effective."

Tan J, et al *JAMA Int Med* 2024;184(12):1443-1447

Nocturnal Leg Cramps (NLCs): Vit K_2

- Study: RDBPCT seniors (n = 199)
- Inclusion
  - Age ≥65
  - NLCs ≥2x over the previous 2 weeks
  - Female: 54.3%
  - No known 2^0 cause
- Rx: Vit K2 (menaquinone 7) 180 mcg PO QD vs PBO
- Outcomes (at 8 weeks):
  - 1^0: #NLCs/week
  - 2^0: NLC severity, duration

Tan J, et al *JAMA Int Med* 2024;184(12):1443-1447

Nocturnal Leg Cramps Vit K_2 : Results

"…the vitamin K2 group experienced a reduction in… frequency of cramps…NLC severity…and duration."*

*All statistically significant

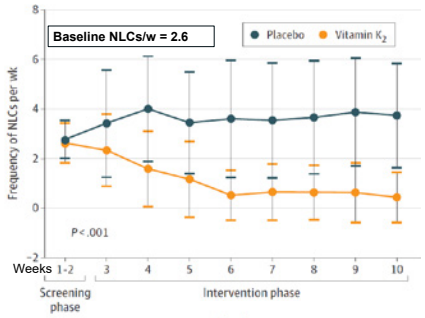
Tan J, et al *JAMA Int Med* 2024;184(12):1443-1447

Nocturnal Leg Cramps Vit K_2 : Baseline Demographics

	Vit K2 N=103	PBO N =96
Male	51 (49.5%)	40 (41.7%)
Female	52 (50.5%)	56 (58.3%)
Age (mean)	72.8	71.8
HTN	74 (71.8%)	62 (64.6%)
DM	55 (53.4%)	46 (47.9%)
Cr mg/dK	0.87	0.91

Tan J, et al *JAMA Int Med* 2024;184(12):1443-1447

Nocturnal Leg Cramps Vit K_2 : Results



Nocturnal Leg Cramps Vit K_2 : Results 2^0 Endpoints

	PBO	Vit K2	Δ
NLC **Duration**	0.98 min	0.25 min	-0.73 min
NLC **Severity**	2.08	1.12	-0.97

Tan J, et al *JAMA Int Med* 2024;184(12):1443-1447

Nocturnal Leg Cramps Vit K_2 : Safety

"No adverse events related to vitamin K_2 were observed among our participants…."

Tan J, et al *JAMA Int Med* 2024;184(12):1443-1447

Nocturnal Leg Cramps Vit K_2 : Safety THERE MUST BE SOMETHING!!

Warfarin

Tan J, et al *JAMA Int Med* 2024;184(12):1443-1447

Nocturnal Leg Cramps Vit K2 : Safety

"Vitamin K2 has been well documented to be a safe supplement, as the lack of adverse effects in healthy humans precluded the WHO and the Food and Agriculture Organization of the United Nations from setting a tolerable upper intake level…."

Tan J, et al *JAMA Int Med* 2024;184(12):1443-1447

OTC Vit K_2 (menaquinone-7)

Micro Ingredients Vitamin K2 MK-7 Supplement, 200 mcg Per Serving, 300 Coconut Oi…

Vitamin K2

300 Count (Pack of 1)

★★★★½ 2,114

7K+ bought multiple times

$19.99 ($0.07/Count)

$17.99 with Subscribe & Save discount

Amazon.com accessed 1/4/2025

Alcohol Use Disorder Sx & Semaglutide Case Series


Case Series

Significant Decrease in Alcohol Use Disorder Symptoms Secondary to Semaglutide Therapy for Weight Loss:

A Case Series

Jesse R. Richards, DO; Madisen Fae Dorand, MD; Kyleigh Royal; Lana Mnajjed; Maria Paszkowiak; and W. Kyle Simmons, PhD

Richards JR, et al. J Clin Psych 2024;85(1):27-31

Alcohol Use Disorder Sx & Semaglutide Case Series

"Despite being a major cause of preventable death worldwide, alcohol use disorder currently has only 3* FDA-approved pharmacotherapies."

*acamprosate (Campral), naltrexone (Vivitrol, Revia), disulfiram (Antabuse)

Richards JR, et al. J Clin Psych 2024;85(1):27-31

Alcohol Use Disorder Sx & Semaglutide Case Series

"…semaglutide has shown promise in preclinical studies for reducing alcohol consumption, but there are currently no RCTs…."

Richards JR, et al. J Clin Psych 2024;85(1):27-31

Alcohol Use Disorder Sx & Semaglutide
Case Series

- **Study**: retrospective chart review N=6
- **Inclusion**: Persons AUDIT (Alcohol Use Disorder Identification Test) score >8 prior to starting semaglutide for another indication
- **Outcome**: AUDIT Score Δ post-semaglutide

Richards JR, et al. J Clin Psych 2024;85(1):27-31

Alcohol Use Disorder Identification Test

The Alcohol Use Disorders Identification Test (AUDIT) World Health Organization (WHO) has been adapted by the Mental Health Commission (Australia), 2018.

0-7: Low Risk
8-14 Hazardous/Harmful Use ≥15: Mod-Severe AUD

Questions	0	1	2	3	4	Score
1. How often do you have a drink containing alcohol?	Never	Monthly or less	2-4 times a month	2-3 times a week	4+ times a week	
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	1 or 2	3 or 4	5 or 6	7 to 9	10 or more	
3. How often do you have six or more standard drinks on one occasion?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
4. How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
5. How often during the last year have you failed to do what was normally expected of you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
6. How often during the last year have you needed a drink first thing in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
7. How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
8. How often during the last year have you been unable to remember what happened the night before because of your drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily	
9. Have you or someone else been injured because of your drinking?	No		Yes, but not in the last year		Yes, during the last year	
10. Has a relative, friend, doctor or other healthcare worker been concerned about your drinking or suggested you cut down?	No		Yes, but not in the last year		Yes, during the last year	

http://pubs.niaaa.nih.gov/publications/Practitioner/pocketguide/pocket_guide2.htm

Alcohol Use Disorder Sx & Semaglutide
Obesity & Bariatric Surgery Clinic Case Series: Case 1

- **Case:** ♀ age 46 evaluated for bariatric surgery
- BMI = 30.8 AUDIT= 13
- Rx: semaglutide 0.25 mg/week
- 4 months F/U
  - BMI 28.0
  - AUDIT = 5

Richards JR, et al. J Clin Psych 2024;85(1):27-31

Alcohol Use Disorder Sx & Semaglutide
Obesity & Bariatric Surgery Clinic Case Series: Case 2

- **Case:** ♀ age 39 evaluated for bariatric surgery
- BMI = 36
- PMH: Bipolar I, ADHD, MDD, AUD (AUDIT = 20)
- Rx: semaglutide 1.0 mg/week
- 4 months F/U
  - BMI = 31.4
  - AUDIT = 6

Richards JR, et al. J Clin Psych 2024;85(1):27-31

Alcohol Use Disorder Sx & Semaglutide
Obesity & Bariatric Surgery Clinic Case Series: Case 3

- **Case:** ♀ age 24 for 'medical weight loss evaluation'
- BMI = 25.4
- PMH: Binge eating/drinking disorder, (AUDIT = 12)
- Rx: semaglutide 0.5 mg/week
- 6 months F/U
  - BMI = 23.1
  - Food cravings controlled, No binge drinking
  - AUDIT = 2

Richards JR, et al. J Clin Psych 2024;85(1):27-31

Alcohol Use Disorder Sx & Semaglutide
Obesity & Bariatric Surgery Clinic Case Series: Case 4

- **Case:** ♀ age 38 3month post-op gastric sleeve
- BMI = 47.5 (AUDIT = 13)
- PMH: Asthma, HTN, Hypothyroid, Depression
- Rx: semaglutide 0.25 mg/week
- 4 months F/U
  - BMI 41.1
  - AUDIT = 6

Richards JR, et al. J Clin Psych 2024;85(1):27-31

Alcohol Use Disorder Sx & Semaglutide
Obesity & Bariatric Surgery Clinic Case Series: Case 5

- **Case:** ♂ age 60 requesting medical obesity Rx
- BMI = 32.9 (AUDIT = 17)
- PMH: Pre-DM, binge eating disorder, HTN
- Rx: semaglutide 0.5 mg/week
- 9 months F/U
  - BMI 30.7
  - AUDIT = 6

Richards JR, et al. J Clin Psych 2024;85(1):27-31

Alcohol Use Disorder Sx & Semaglutide
Obesity & Bariatric Surgery Clinic Case Series: Case 6

- **Case:** ♀ age 51 requesting medical weight management
- Weight = 172.5 # BMI = 26.3 (AUDIT = 9)
- PMH: B12 deficiency, insomnia, binge drinking
- Rx: semaglutide 0.5 mg/week.
- 1 months F/U
  - Weight = 170.9# BMI = 26.1
  - AUDIT = 2

Richards JR, et al. J Clin Psych 2024;85(1):27-31

Alcohol Use Disorder Sx & Semaglutide Conclusions

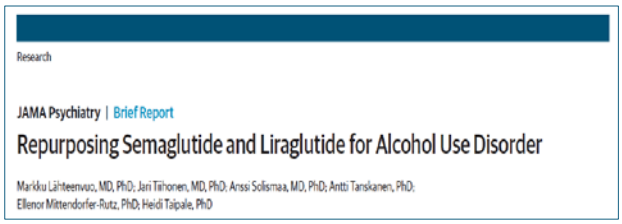
"This case series…suggests that GLP-1RAs have strong potential in the treatment of AUD."

Richards JR, et al. J Clin Psych 2024;85(1):27-31

Alcohol Use Disorder Sx & Semaglutide Respectful Conclusions

"We believe that until [RCTs] are available, evidence-based practice requires that providers point patients toward the psychological and pharmacologic interventions that have already been validated."

Richards JR, et al. J Clin Psych 2024;85(1):27-31



Research

JAMA Psychiatry | Brief Report

Repurposing Semaglutide and Liraglutide for Alcohol Use Disorder

Markku Lähteenvuo, MD, PhD; Jari Tiihonen, MD, PhD; Anssi Solismaa, MD, PhD; Antti Tanskanen, PhD; Ellenor Mittendorfer-Rutz, PhD; Heidi Taipale, PhD

Lahteenvuo M, et al. *JAMA Psych* 2025;82(1):94-98

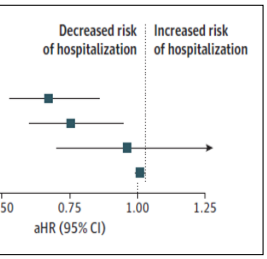
Alcohol Use Disorder: Semaglutide & Liraglutide
Swedish National Registry Dataset

- **Premise**: "Preliminary studies suggest that GLP-1 RA, used to Rx T2DM and obesity, may ↓alcohol consumption."
- **Objective**: "To test whether hospitalization due to AUD is decreased during the use of GLP1-RA, compared with periods of nonuse for the same individual."
- **Goal**: "We aimed to investigate the potential of GLP1-RA as a Rx for reducing alcohol-related harms by analyzing real-world data from Swedish registries."
- **Study**: AUD/SUD subjects (n=227,866) f/u 8.8 yrs (mean)
- **1⁰ Outcome**: AUD hospitalization

Lahteenvuo M, et al. *JAMA Psych* 2025;82(1):94-98

Risk of **Alcohol Use Disorder** Hospitalization
Swedish National Registry Dataset

Drug	No. Users	Events	aHR (95% CI)
GLP-1 agonists			
Semaglutide	4321	222	0.64 (0.50-0.83)
Liraglutide	2509	212	0.72 (0.57-0.92)
Dulaglutide	1118	139	0.93 (0.68-1.28)
AUD medications	75454	30198	0.98 (0.96-1.00)

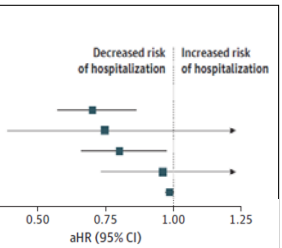


N = 133,210 AUD Hospitalizations amongst 227, 868 AUD Subjects

Lahteenvuo M, et al. *JAMA Psych* 2025;82(1):94-98

Risk of **Substance Use Disorder** Hospitalization
Swedish National Registry Dataset

Drug	No. Users	Events	aHR (95% CI)
GLP-1 agonists			
Semaglutide	4321	281	0.68 (0.54-0.85)
Exenatide	98	13	0.73 (0.34-1.55)
Liraglutide	2509	262	0.78 (0.64-0.97)
Dulaglutide	1118	172	0.96 (0.71-1.28)
AUD medications	75454	32543	0.98 (0.97-1.00)

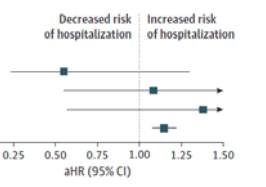


N = 138,390 SUD Hospitalizations amongst 227,868 AUD subjects

Lahteenvuo M, et al. *JAMA Psych* 2025;82(1):94-98

Risk of **Suicide Attempt** Hospitalization
Swedish National Registry Dataset

Drug	No. Users	Events	aHR (95% CI)
GLP-1 agonists			
Semaglutide	4321	32	0.55 (0.23-1.30)
Liraglutide	2509	28	1.08 (0.55-2.15)
Dulaglutide	1118	19	1.38 (0.57-3.34)
AUD medications	75454	3265	1.15 (1.08-1.22)



N = 22,231 Suicide attempt hospitalizations amongst 227,868 AUD subjects

Lahteenvuo M, et al. *JAMA Psych* 2025;82(1):94-98

Risk of Suicide Attempt Hospitalization
Swedish National Registry Dataset

"Among patients with AUD and comorbid obesity/T2DM, the use of semaglutide and liraglutide were associated with substantially ↓ risk of hospitalization due to AUD. This risk was lower than that of officially approved AUD medications."

Lahteenvuo M, et al. *JAMA Psych* 2025;82(1):94-98

Diabetes Care

American Diabetes Association.

Effect of 5:2 Regimens: Energy-Restricted Diet or Low-Volume High-Intensity Interval Training Combined With Resistance Exercise on Glycemic Control and Cardiometabolic Health in Adults With Overweight/Obesity and Type 2 Diabetes: A Three-Arm Randomized Controlled Trial

Li M, et al. *Diabetes Care* 2024;47:1074-1083

DM: Exercise vs Diet
What if It's an 'Either/Or' Situation

- Study: RCT T2DM Overweight/Obese (n = 326)
- Interventions (x 12 weeks):
  - Diet (5:2)
  - Exercise (5:2)
  - Usual Care
- 1^0 Outcome: Δ A1c

Li M, et al. *Diabetes Care* 2024;47:1074-1083

DM: Exercise vs Diet
What if It's an 'Either/Or' Situation

- 5:2 Exercise (twice weekly supervised sessions)
  - 5 min warmup
  - 4 mins HIT on cycle ergometer (85%-90% age predicted max HR)
  - 5 min cooldown
  - 4 machine-based resistance exercises
    - 8-12 reps at 80% 1-rep max
    - 2 sets
- 1^0 Outcome: Δ A1c

Li M, et al. *Diabetes Care* 2024;47:1074-1083

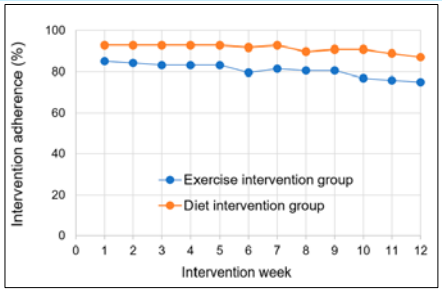
DM: Exercise vs Diet
What if It's an 'Either/Or' Situation

5:2 Diet

- Regular diet (unrestricted) 5 days/week
- Prepared diet (790 kcal/d) 2 days/week
  - Protein = 25%
  - CHO = 55%
  - Fat = 20%

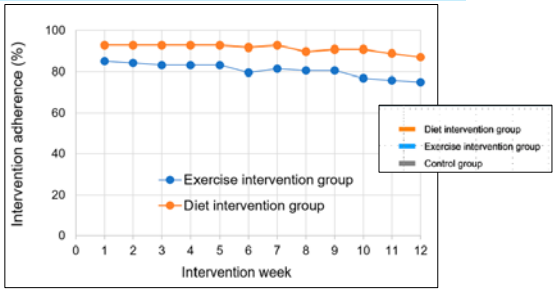
Li M, et al. *Diabetes Care* 2024;47:1074-1083

DM: Exercise vs Diet
Adherence Rates



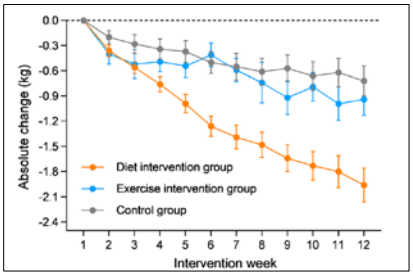
Li M, et al. *Diabetes Care* 2024;47:1074-1083

DM: Exercise vs Diet
Adherence Rates



Li M, et al. *Diabetes Care* 2024;47:1074-1083

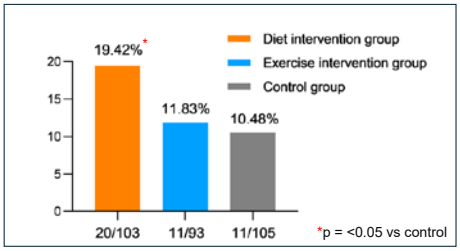
DM: Exercise vs Diet vs Usual Care*
Weight Change (KG)



*All groups: weekly GD lifestyle (diet/exercise) education

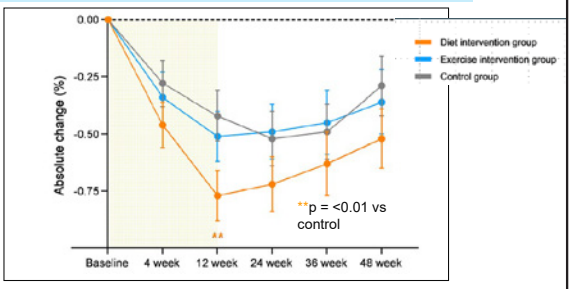
Li M, et al. *Diabetes Care* 2024;47:1074-1083

DM: Exercise vs Diet vs Usual Care*
DM Remission (no meds, A1c < 6.5)



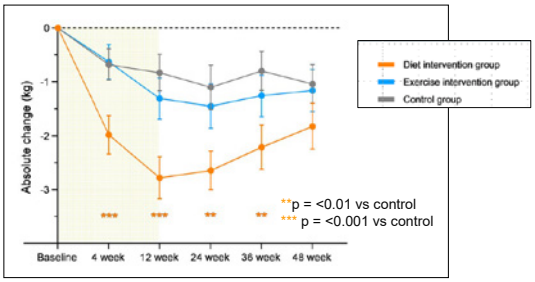
Li M, et al. *Diabetes Care* 2024;47:1074-1083

DM: Exercise vs Diet vs Usual Care A1c Δ



Li M, et al. *Diabetes Care* 2024;47:1074-1083

DM: Exercise vs Diet vs Usual Care Body Weight



Li M, et al. *Diabetes Care* 2024;47:1074-1083

DM: Exercise vs Diet vs Usual Care Conclusions

"These findings challenge the current paradigm of lifestyle intervention in which frequent behavioral change [exercise] is required to see improvements in metabolic health."

Li M, et al. *Diabetes Care* 2024;47:1074-1083

Mirtazepine as an Appetite Stimulant in CA

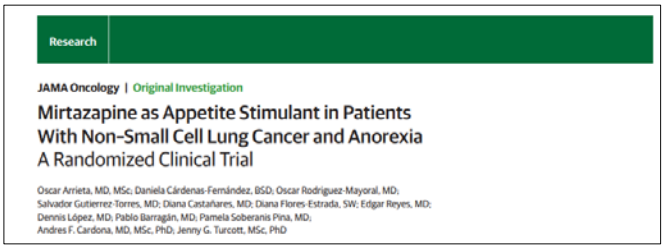
Your patient is a 72 y.o. male with non-resectable small cell lung cancer. He has lost a concerning amount of weight in the last 3 months. His daughter asks you whether mirtazapine (Remeron) help his weight loss. A clinical trial has shown that in CA patients

A) mirtazapine has no meaningful effect on weight

B) Increases appetite slightly but not actual calorie intake

C) increases calorie intake without apparent appetite stimulation

D) Stimulates both appetite and calorie intake



Research

JAMA Oncology | Original Investigation

Mirtazapine as Appetite Stimulant in Patients With Non-Small Cell Lung Cancer and Anorexia
A Randomized Clinical Trial

Oscar Arrieta, MD, MSc; Daniela Cárdenas-Fernández, BSD; Oscar Rodríguez-Mayoral, MD; Salvador Gutierrez-Torres, MD; Diana Castañares, MD; Diana Flores-Estrada, SW; Edgar Reyes, MD; Dennis López, MD; Pablo Barragán, MD; Pamela Soberanis Pina, MD; Andres F. Cardona, MD, MSc, PhD; Jenny G. Turcott, MSc, PhD

Arrieta O, et al. *JAMA Oncology* 2024;10(3):305-314

Lung CA: Anorexia

"Anorexia is a devastating phenomenon that affects > half of patients with lung CA…leading to weight loss, ↓ functionality, reduced tolerance to anticancer Rxs, and poor survival."

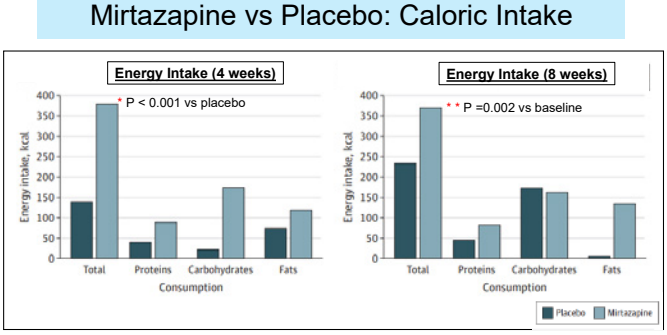
Arrieta O, et al. *JAMA Oncology* 2024;10(3):305-314

Weight Loss in CA: Mirtazepine

- **Study**: RDBPCT NSCLC patients (n=86)
- **Inclusion**:
  - On active oncologic Rx
  - Anorexia Cachexia Scale score ≤32
- **Rx**: mirtazapine 15 mg/d x 15 d, then 30 mg/d thru 8 weeks vs PBO
- **1⁰ Outcomes**
  - Appetite Score
  - Energy Consumption

Arrieta O, et al. *JAMA Oncology* 2024;10(3):305-314

Mirtazapine vs Placebo: Caloric Intake



Arrieta O, et al. *JAMA Oncology* 2024;10(3):305-314

Mirtazapine: Conclusions

"…the mirtazapine group had a significant in energy intake through the 4- and 8-week follow-up, mainly in fat intake, which is a better and crucial source of energy."

Arrieta O, et al. *JAMA Oncology* 2024;10(3):305-314

Mirtazepine: MOA?

"…there was NO DIFFERENCE in APPETITE SCORES in all patients who received mirtazapine or placebo…

Arrieta O, et al. *JAMA Oncology* 2024;10(3):305-314

Mirtazepine: MOA?

- Perhaps: antidepressant, analgesic effects, antiemetic effects
- "Nevertheless, the exact mechanism remains unknown."

Arrieta O, et al. *JAMA Oncology* 2024;10(3):305-314

Antibiotic Use and Vaccine Antibody Levels

Timothy J. Chapman, PhD,[a] Minh Pham, PhD,[b] Peter Bajorski, PhD,[b] Michael E. Pichichero, MD[a]

PEDIATRICS Volume 149, number 5, May 2022:e2021052061
http://publications.aap.org/pediatrics/article-pdf/149/5/e2021052061/1554056/peds_2021052061.pdf

Chapman TJ, et al *Pediatrics* 2022;149(5):e2021052061

Antibiotics Exposure and Vaccine Efficacy

"The majority of children are prescribed antibiotics in the first 2 years of life while vaccine immunity develops. Researchers have suggested a negative association of antibiotic use with vaccine-induced immunity in adults, but data are lacking in children."

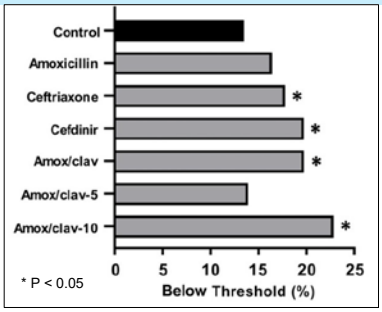
Chapman TJ, et al *Pediatrics* 2022;149(5):e2021052061

Antibiotics Exposure and Vaccine Efficacy

- **Study**: Prospective Cohort (n=560) Peds URI age 6-24 months
- **Method**:
  - Vaccine Antibodies measured: DTaP, IPV, PCV, Hib
  - Antibody level sampling age 6, 9, 12, 15, 18, 24 months
  - Additional antibody level at URI (especially otitis) events
- **Outcomes:**
  - % with subprotective antibodies (antibiotics vs none)
  - Age at which subprotective antibodies most prominent
  - Stratification of individual antibiotic risk

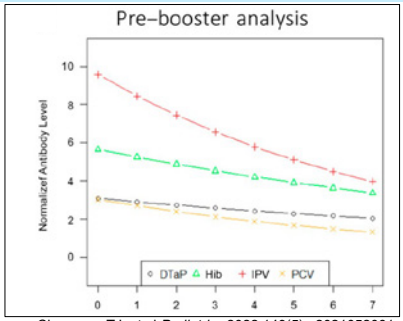
Chapman TJ, et al *Pediatrics* 2022;149(5):e2021052061

Below-Threshold Vaccine Efficacy as Per Antibiotic Rx



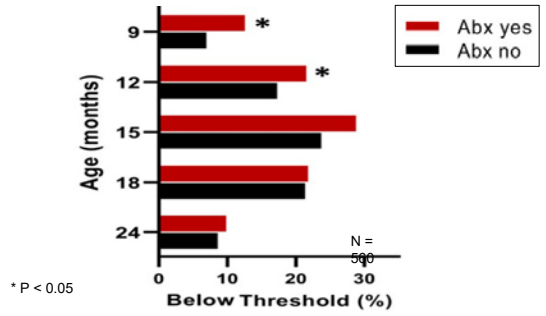
Chapman TJ, et al *Pediatrics* 2022;149(5):e2021052061

Vaccine Antibody as per # Antibiotic Rx Courses



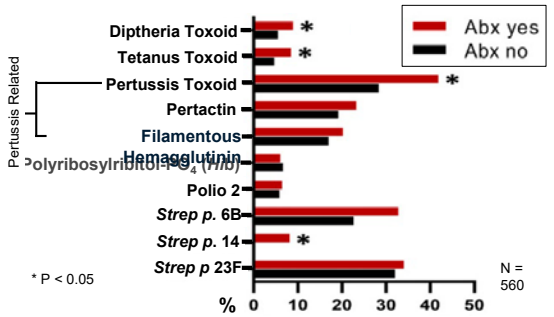
Chapman TJ, et al *Pediatrics* 2022;149(5):e2021052061

% Total Vaccinees Below Protective Threshold by Age



Chapman TJ, et al *Pediatrics* 2022;149(5):e2021052061

% Vaccine Recipients Below Protective Threshold



Chapman TJ, et al *Pediatrics* 2022;149(5):e2021052061

Antibiotics Exposure and Vaccine Efficacy Conclusions*

"For each antibiotic course the child received….antibody levels…were reduced by…."

	Prebooster	Postbooster
DTaP	5.8%	18.1%
Hib	6.8%	21.3%
IPV	11.3%	18.9%
PCV	10.4%	12.2%

*** All p < 0.05**

Chapman TJ, et al *Pediatrics* 2022;149(5):e2021052061

Why Might Antibiotics Effect Vaccine Efficacy

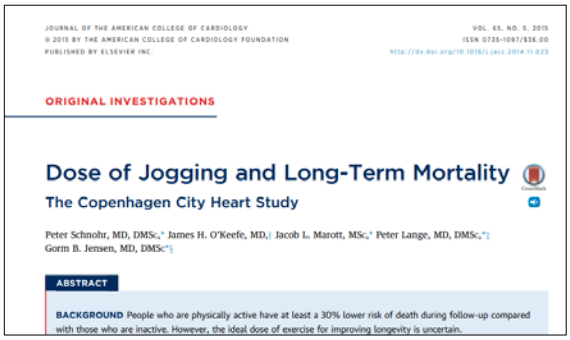
"Given the appreciated connection between microbiome and immunity, antibiotic usage may affect the immune response to vaccines."

Chapman TJ, et al *Pediatrics* 2022;149(5):e2021052061

Why Might Antibiotics Effect Vaccine Efficacy And It's Not Just Kids

"...antibiotics given…to adults before seasonal influenza vaccination...demonstrat[ed] that antibiotics kill important commensal bacteria in the gut that favorably modulate immune responses to vaccination."

Chapman TJ, et al *Pediatrics* 2022;149(5):e2021052061



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ORIGINAL INVESTIGATIONS

Dose of Jogging and Long-Term Mortality

The Copenhagen City Heart Study

Peter Schnohr, MD, DMSc,* James H. O'Keefe, MD,† Jacob L. Marott, MSc,* Peter Lange, MD, DMSc,*‡
Gorm B. Jensen, MD, DMSc*‡

ABSTRACT

BACKGROUND People who are physically active have at least a 30% lower risk of death during follow-up compared with those who are inactive. However, the ideal dose of exercise for improving longevity is uncertain.

Schnohr P, et al. *J Am Coll Cardiol* 2015;65(5):411-419

Exercise: What Part of YES Did You Not Understand?

"People who are physically active have at least a 30% lower risk of death during follow-up compared with those who are inactive. However, the ideal dose of exercise for improving longevity is uncertain."

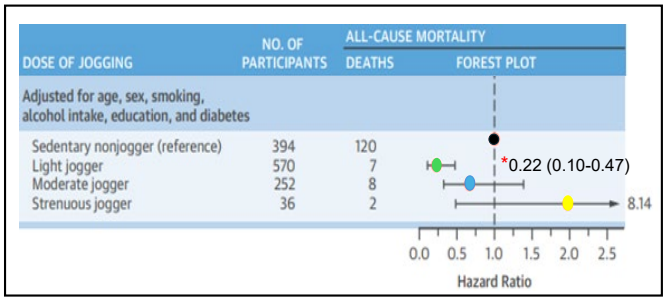
Schnohr P, et al. *J Am Coll Cardiol* 2015;65(5):411-419

The Copenhagen City Heart Study

- Study: Prospective observational (n = 5.048 healthy adults)
- Joggers = 1,098; Nonjoggers = 3,950
- Jogging Intensity Definition*
  - Light: 12 min/mile. ≤3x/week, ≤2.5hr/week
  - Moderate: 12 min/mile, ≤3x/week, ≥2.5 hr/week
  - Strenuous: <8.7 min/mile, > 3x/week, ≥ 2.5 hr/week
- Endpoint: All cause mortality (at 12 years)

* Definitions varied by pace, duration, and frequency

Schnohr P, et al. *J Am Coll Cardiol* 2015;65(5):411-419



Schnohr P, et al. *J Am Coll Cardiol* 2015;65(5):411-419

Exercise & Mortality: U shaped Association

CONCLUSIONS

The findings suggest a U-shaped association between all-cause mortality and dose of jogging…Light and moderate joggers have lower mortality than sedentary nonjoggers, whereas **strenuous joggers have a mortality rate not statistically different from that of the sedentary** group.

Schnohr P, et al. *J Am Coll Cardiol* 2015;65(5):411-419

AJH 2001; 14:27-31

Sexual Activity in Hypertensive Men Treated With Valsartan or Carvedilol: A Crossover Study

Roberto Fogari, Annalisa Zoppi, Luigi Poletti, Gianluigi Marasi, Amedeo Mugellini, and Luca Corradi

Fogari R, et al. *Am J Hypertens* 2001;14:27-31

Valsartan vs Carvedilol in Hypertensive Men Sexual Function Impact

- **Study**: DBRPCXOT Newly Dx ♂ HTN Patients (n = 160)
- **Inclusion**
  - Age 40-49
  - Married, No prior sexual dysfunction
- **Exclusions**
  - DM
  - Obesity
  - Smoking
  - CVD
  - Concomitant Meds (any)

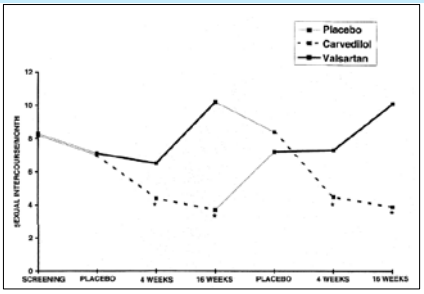
Fogari R, et al. *Am J Hypertens* 2001;14:27-31

Valsartan vs Carvedilol in Hypertensive Men Sexual Function Impact

- **Intervention (XO over 16 weeks)**:
  - Carvedilol 50 mg QD
  - Valsartan 80 mg QD
  - Placebo
- **Endpoints**
  - 1^0: #episodes intercourse/month
  - 2^0: BP

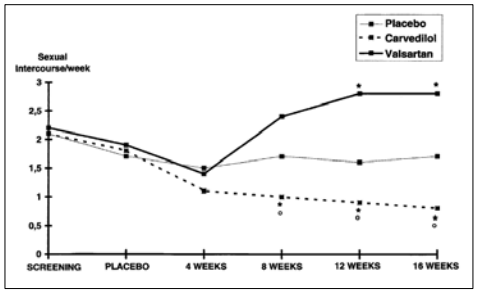
Fogari R, et al. *Am J Hypertens* 2001;14:27-31

Valsartan vs Carvedilol in Hypertensive Men Sexual Intercourse/Month



Fogari R, et al. *Am J Hypertens* 2001;14:27-31

Valsartan vs Carvedilol in Hypertensive Men Sexual Intercourse/Week



Fogari R, et al. *Am J Hypertens* 2001;14:27-31

Valsartan vs Carvedilol in Hypertensive Men Conclusions

"In conclusion….carvedilol and…valsartan have different effects on sexual function…despite similar antihypertensive efficacy…."

Fogari R, et al. *Am J Hypertens* 2001;14:27-31

European Heart Journal (2013) 34, 2933–2939
doi:10.1093/eurheartj/eht219

CLINICAL RESEARCH
Hypertension

Adherence to antihypertensive therapy prior to the first presentation of stroke in hypertensive adults: population-based study

Kimmo Herttua[1]*, Adam G. Tabák[2,3], Pekka Martikainen[1], Jussi Vahtera[4,5] and Mika Kivimäki[2,6]

Herttua K, et al. *Euro Heart J* 2013;34:2933-2939

Adherence
The View from 50 years of Clinical Experience

Non-adherence is a **rational** decision….

Our responsibility is to try and help patients make a **more rational** decision.

The 'Real Life' Costs of Non-adherence

- **Study**: Finnish National Registers data analysis (1995-2007)
- **Inclusion**: HTN patients age >30 with no known CVD
- **Method**: compare outcomes in adherent vs non-adherent patients (n = 73,527)
- **Outcomes** (at years 2-10 post HTN med initiation):
  - Stroke death
  - Stroke hospitalization

Herttua K, et al. *Euro Heart J* 2013;34:2933-2939

How Was 'Non-adherent' Defined?

"…adherence and non-adherence were defined…by purchases of antihypertensive drugs….to an adherence level of **<80%**, a generally used definition of poor medication adherence."

Herttua K, et al. *Euro Heart J* 2013;34:2933-2939

Just How Much Does Non-Adherence Cost?
Fatal/Non-Fatal Stroke: Followup Years 2-10

Year	Fatal Stroke OR	Non-fatal Stroke OR
2	3.81 (2.85-5.10)	2.74 (2.35-3.20)
3	3.95 (3.01-5.18)	2.74 (2.37-3.16)
4	4.10 (3.21-5.24)	2.79 (2.45-3.19)
5	3.68 (2.92-4.65)	2.28 (2.00-2.60)
6	2.85 (2.24-3.62)	2.13 (1.97-2.43)
7	3.09 (2.46-3.89)	2.22 (1.95-2.52)
8	2.72 (2.13-3.47)	2.03 (1.78-2.32)
9	2.82 (2.22-3.58)	1.78 (1.49-1.96)
10	3.01 (2.37-3.83)	1.71 (1.49-1.96)

Herttua K, et al. *Euro Heart J* 2013;34:2933-2939

The 'Real Life' Costs of Non-adherence

"These data suggest that poor adherence to antihypertensive therapy substantially increases near-and long-term risk of stroke among hypertensive patients."

Herttua K, et al. *Euro Heart J* 2013;34:2933-2939

What Constitutes "Adherent"?

"A patient is considered adherent if they take **80%** of their prescribed medicine(s). If patients take < 80%…they are considered nonadherent."

https://edhub.ama-assn.org/steps-forward/module/2702595 accessed 1/12/25

Diet Drink Consumption and the Risk of Cardiovascular Events: A Report from the Women's Health Initiative

Ankur Vyas, MD[1], Linda Rubenstein, PhD[2], Jennifer Robinson, MD, MPH[1,2], Rebecca A. Seguin, PhD, CSCS[3], Mara Z. Vitolins, DrPH, MPH, RD[4], Rasa Kazlauskaite, MD, MSc, FACE[5,6], James M. Shikany, DrPH[7], Karen C. Johnson, MD, MPH[8], Linda Snetselaar, RD, PhD[2], and Robert Wallace, MD, MSc[2,9]

Vyas A, et al. *J Gen Int Med* 2014;30(4):462-468

Diet Soda: CV Friend or Faux?

- **Study**: Retrospective Cohort Study (n = 59,614)
- **Inclusion** (WHI)
  - Postmenopausal women (mean age 62.8)
  - No known CVD at enrollment
  - Diet drink data available
- **1^0 Outcome** (at 8.7 years): MACE

Vyas A, et al. *J Gen Int Med* 2014;30(4):462-468

Diet Soda: CV Friend or Faux?

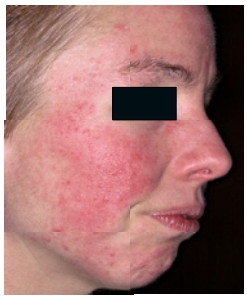
Outcome (at 8.7 years)	≥2/d vs 0-3/month HR (C.I.)
MACE* (1^0)	1.3 (1.1-1.5)*
CVD Mortality	1.5 (1.03-2.3)*
Overall Mortality	1.3 (1.04-1.5)*

*CHD, CHF, MI, coronary revascularization, ischemic stroke, PAD, CVD death

*p < 0.05

Vyas A, et al. *J Gen Int Med* 2014;30(4):462-468

Rosacea



Habif TP Clinical Dermatology (6th Edition) 2016 Elsevier

Open Access Research

BMJ Open **Randomised controlled trial of topical kanuka honey for the treatment of rosacea**

Irene Braithwaite,[1] Anna Hunt,[1] Judith Riley,[1] James Fingleton,[1] Janwillem Kocks,[1] Andrew Corin,[2] Colin Helm,[2] Davitt Sheahan,[3] Christopher Tofield,[4] Barney Montgomery,[5] Mark Holliday,[1] Mark Weatherall,[6] Richard Beasley[1]

Braithwaite I, et al. *BMJ Open* 2015;5:1-7

Rosacea: Kanuka Honey
Why Bother?

- "There is no cure, and affected individuals may experience substantial morbidity.."
- "There is a range of Rx options…however, these are only partially effective, and side effects may limit their use."
- "…there are global concerns about ↑…resistance to antibiotics…particularly with long-term use in chronic conditions."

Braithwaite I, et al. *BMJ Open* 2015;5:1-7

Rosacea: Kanuka Honey

- **Study**: RSBPCT Rosacea Patients (n = 138)
- **Inclusion**:
  - Age ≥16
  - Facial Rosacea IGA-RSS score ≥ 2 (0 = clear; 6 = severe)
- **Exclusions**
  - Systemic steroids within 4 weeks
  - Current antibiotic Rx (oral or topical)
- **Rx**: Medical Grade Kanuka Honey in 10% glycerine (Honevo) vs placebo (topical paraffin emollient) x 8 weeks
- **Outcome**: % with ≥ 2 improvement in IGA-RSS Score

Braithwaite I, et al. *BMJ Open* 2015;5:1-7

Rosacea: Kanuka Honey
Outcomes (ITT Analysis)

	Kanuka Honey	Control	P
↓IGA-RSS ≥2	34.3%	17.4%	0.02
IGA-RSS = 0*	13.2%	2.9%	0.031

* Post-Hoc analysis

IGA-RSS: Investigator Global Assessment of Rosacea Severity Score (baseline score: 3

Braithwaite I, et al. *BMJ Open* 2015;5:1-7

Inflammation in Rosacea:
Do We Know The/A Cause?

"…antigenic proteins related to *Bacillus oleronius* isolated from the *Demodex folliculorum* mite, which infests the skin in rosacea, exacerbates this inflammatory response."

Braithwaite I, et al. *BMJ Open* 2015;5:1-7

Rosacea:
Why Kanuka Honey?

- Potent antibacterial activity
- Potent anti-inflammatory activity

Braithwaite I, et al. *BMJ Open* 2015;5:1-7

New Zealand 100% Pure & Raw Kanuka Honey 500g (1.1 lb)
Brand New
$29.99
Buy It Now
Free delivery
Free returns
Jan-27 09:55
Top Rated Plus

https://www.ebay.com/sch/i.html?_nkw=kanuka+honey&_sacat=0&_from=R40&_trksid=p2332490.m570.l1313
accessed 2/14/25

[Original Research **Asthma**]

CHEST

What Is the Role of Tiotropium in Asthma?
A Systematic Review With Meta-analysis

Gustavo J. Rodrigo, MD; and José A. Castro-Rodríguez, MD, PhD

Rodrigo GJ, Castro-Rodriguez JA *CHEST* 2015;147(2):3898-396

Asthma:
Are We Underutilizing Anticholinergics?

"[Two prior smaller] reviews concluded that tiotropium may play a beneficial role in the Rx of inadequately controlled asthma, compared with placebo, without an ↑ in AEs."

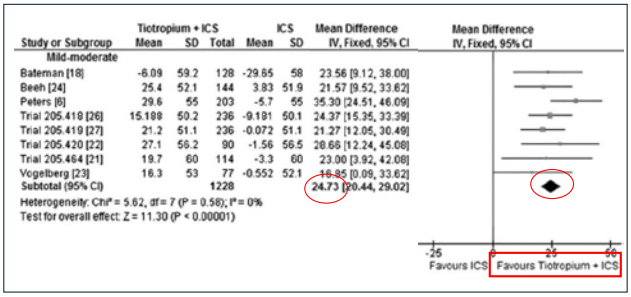
Rodrigo GJ, Castro-Rodriguez JA *CHEST* 2015;147(2):3898-396

Asthma:
Are We Underutilizing Anticholinergics?

- Systematic Review: 13 Asthma Studies (n=4,966)
  - Tiotropium/ICS vs ICS (mild-mod asthma)
  - Tiotropium/ICS vs LABA/ICS (mod-severe asthma)
  - Tiotropium/LABA/ICS vs LABA/ICS (severe asthma)
- Inclusion (adolescents and adults)
  - Dx asthma (FEV_1 reversibility >12% and 200mL)
  - Current non-smokers
- Endpoint: Improvement in FEV_1 (PEFR)

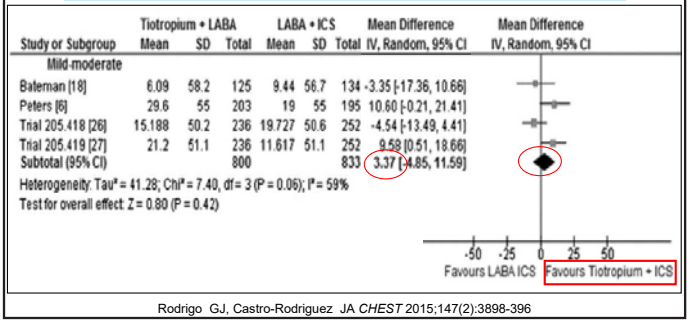
Rodrigo GJ, Castro-Rodriguez JA *CHEST* 2015;147(2):3898-396

Asthma: ICS vs Tiotropium/ICS
ΔPM PEFR



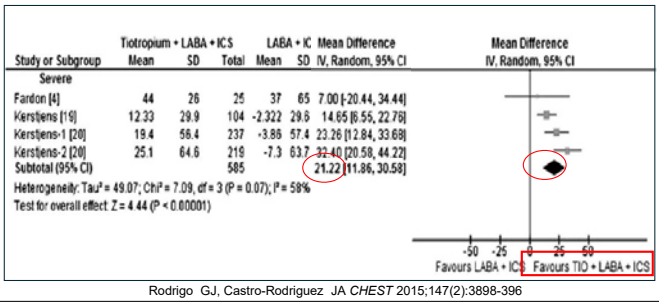
Rodrigo GJ, Castro-Rodriguez JA *CHEST* 2015;147(2):3898-396

Asthma: LABA/ICS vs Tiotropium/ICS
ΔPM PEFR



Rodrigo GJ, Castro-Rodriguez JA *CHEST* 2015;147(2):3898-396

Asthma: LABA/ICS vs Tiotropium/LABA/ICS
ΔPM PEFR



Rodrigo GJ, Castro-Rodriguez JA *CHEST* 2015;147(2):3898-396

Asthma: Tiotropium Benefits

"Major benefits were…in the increase in lung function and in the case of patients with severe asthma, in the reduction of exacerbations."

Rodrigo GJ, Castro-Rodriguez JA *CHEST* 2015;147(2):3898-396


Traumatic Head Injuries Caused by Ceiling Fans Among Children Treated in US Emergency Departments

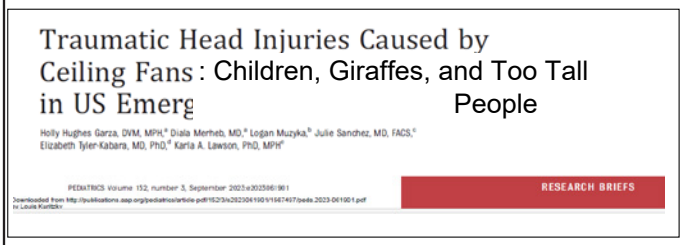
Holly Hughes Garza, DVM, MPH,[a] Diala Merheb, MD,[a] Logan Muzyka,[b] Julie Sanchez, MD, FACS,[c] Elizabeth Tyler-Kabara, MD, PhD,[d] Karla A. Lawson, PhD, MPH[e]

PEDIATRICS Volume 152, number 3, September 2023:e2023061901

RESEARCH BRIEFS

Garza HH, et al. *Pediatrics* 2023;152(3):e2023061901

It *SHOULD* Have Read


Traumatic Head Injuries Caused by Ceiling Fans: Children, Giraffes, and Too Tall People in US Emerg

Holly Hughes Garza, DVM, MPH,[a] Diala Merheb, MD,[a] Logan Muzyka,[b] Julie Sanchez, MD, FACS,[c] Elizabeth Tyler-Kabara, MD, PhD,[d] Karla A. Lawson, PhD, MPH[e]

PEDIATRICS Volume 152, number 3, September 2023:e2023061901

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Ceiling Fan Head Injury….

Seems *Possible*, but How Often Does It *Really* Happen?

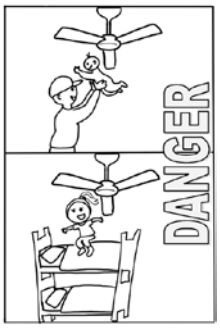
- US Emergency Rooms *Annual* Visits
  - A) ± 10
  - B) ± 100
  - C) ± 500
  - D) ± 1,000
  - E) ± 2,000

Ceiling Fan Head Injuries
Probably a More Frequent Dilemma Than You Thought

"Approximately **2300** pediatric head injures from contact with ceiling fans were seen in US EDs/**per year**, from 2013-2021…. The median child age was 5 years"

Garza HH, et al. *Pediatrics* 2023;152(3):e2023061901

Ceiling Fan Head Injuries
The Setting



Garza HH, et al. *Pediatrics* 2023;152(3):e2023061901

Ceiling Fan Head Injuries
What *Might* Help

- Patient Information Sheets
- Fan labeling by industry
- Bunk bed labeling by industry
- Nurture shorter friends*

* Not a recommendation derived from the article

Garza HH, et al. *Pediatrics* 2023;152(3):e2023061901

Poinsettia: How Poisonous?

A 26-year-old woman calls in on Christmas morning upset about her 2 y.o. son who has just ingested a handful of red poinsettia leaves and berries. He has no Sx, and is acting normally.
Your advice?
A) Administer ipecac immediately
B) Go directly to the nearest emergency room
C) Administer 4 oz of milk as an antidote
D) Reassurance

Low-toxicity Poinsettia

"Young children are often tempted to sample the bright leaves of the poinsettia plant, but despite the widespread belief that the *Euphorbia pulcherrima* is deadly, most exposures don't require any therapy…"

Roberts JR "Emergency Tips from the Literature" Emergency Med 1997;December:6-7

Poinsettia Popping
Apparently, the Game The Whole Family Can Play

- STUDY: electronic database search of American Association of Poison Control Centers 1985-1992
- Exposures Identified: 22,783 (93% children)

Krenzelok EP, Jacobsen TD, Aronis JM "Poinsettia exposures have good outcomes…just as we thought" *Am J Emerg Med* 1996;14:671

Low Toxicity Poinsettia

"A comparison of outcomes for Rx and unRx asymptomatic patients failed to show a benefit from any therapy."

Roberts JR "Emergency Tips from the Literature" Emergency Med 1997;December:6-7

Low-Toxicity Poinsettia

"Not only were the investigators unable to identify a single poinsettia-related fatality, but 92.4% of the patients suffered no adverse effects…the authors maintain that GI decontamination is unwarranted after poinsettia ingestions"

Roberts JR "Emergency Tips from the Literature" Emergency Med 1997;December:6-7

SELF EVALUATION

Things I Wish I Knew Last Year 2025

1. T/F - Vitamin K2 supplementation has been shown to significantly reduce the frequency, severity, and duration of nocturnal leg cramps in older adults.

2. T/F - In a case series, semaglutide was associated with decreased alcohol cravings and lower Alcohol Use Disorder Identification Test (AUDIT) scores.

3. In patients with lung cancer and anorexia, mirtazapine has been shown to:

a. Significantly improve appetite scores
b. Increase energy intake without improving appetite scores
c. Have no measurable effect on caloric intake
d. Worsen fatigue and cachexia

4. T/F - Antibiotic use in early childhood has no measurable effect on vaccine-induced immunity.

5. Which jogging pattern was associated with the lowest mortality in the Copenhagen City Heart Study?

a. Sedentary lifestyle
b. Light to moderate jogging
c. Strenuous jogging
d. No difference between joggers and non-joggers

Answer Key: 1. T, 2. T, 3. B, 4. F, 5. B

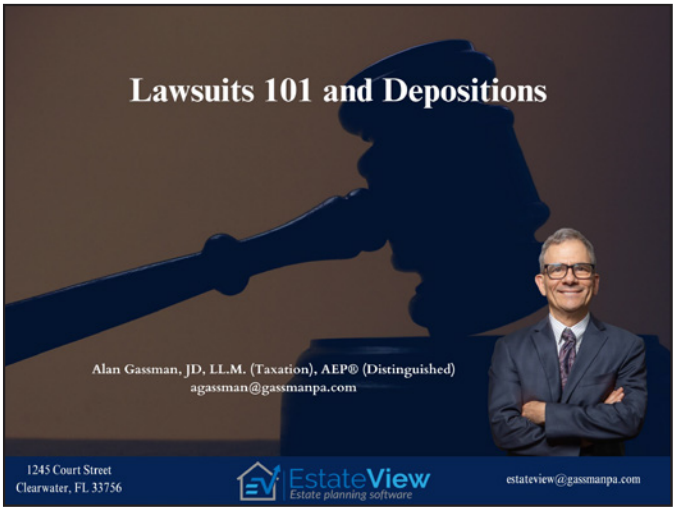
Alan S. Gassman, Esq

Alan S. Gassman, Esq is a Florida attorney specializing in estate planning, asset protection, and advising physicians and healthcare professionals. A partner at Gassman, Denicolo & Ketron, P.A., he has over 40 years of experience helping doctors and business owners navigate legal, tax, and liability challenges. Board Certified in Wills, Trusts & Estates and an Accredited Estate Planner®, he is recognized by Florida Super Lawyers and holds Martindale-Hubbell's AV Preeminent rating. Mr. Gassman is a nationally published author of multiple books and over 200 articles, and he frequently lectures on topics such as medical practice law, creditor protection, and strategies to reduce legal risk for healthcare providers.

You may contact Mr. Gassman with your questions or comments at AGassman@gassmanpa.com.

Lawsuits 101: Essential Legal Concepts for Healthcare Professionals

Alan S. Gassman, Esq



3 Things You Want to Get Out of This Workshop

Item	Why is this important?	Next steps forward.
1.		
2.		
3.		

THE 16 COMMANDMENTS FOR PHYSICIANS

1. Thou shalt not accept any remuneration, gifts, or even favors as the direct or indirect result of referring patients for any product or service whatsoever.
2. Thou shalt not spend significant time or even socialize with those who offer to pay, bribe, do favors for, or otherwise might appear to be so doing.
3. Thou shalt not accept a medical directorship or the referral of patients from any nursing home or other facility that directly or indirectly requests prescriptions, protocols, or other orders that enhance the income or revenues of such organization unless any and all patient interaction and services rendered are handled carefully, ethically, and within normal guidelines.

THE 16 COMMANDMENTS FOR PHYSICIANS

4. Thou shalt not refer patients for diagnostic imaging, prescriptions, physical therapy, or other "designated health services" even to your own practice unless the practice qualifies as a "Group Practice" under the Stark and Florida Patient Self-Referral Act:
   a) One (1) entity exists that treats all patients under one (1) identification number, particularly as to anything paid for by Medicare, Medicaid, Tricare, or other federal programs, which may include Medicare HMO work.
   b) Each physician in the group performs the full range of services that he or she normally performs.
   c) In the aggregate, 75% of patient encounters by the physician members of the group are billed in the name of the group.
   d) Other requirements are met.

THE 16 COMMANDMENTS FOR PHYSICIANS

5. Thou shalt not bill for your services or allow others to bill for your services in any dishonest manner, including putting one doctor on the bill when another doctor performs the services, even if the service providing doctor is not yet on a particular panel or registered.
6. Thou shalt not write off deductibles or co-pays for any patient unless based upon inability to pay as verified by a reputable collection agency or other third party.
7. Thou shalt not talk to the government or any representative from the government under any circumstances whatsoever unless accompanied by a lawyer who specifically practices in the area of law.

"I'm from the government and I'm here to help you."

Ronald Reagan, The President's News Conference, held August 12, 1986.

THE 16 COMMANDMENTS FOR PHYSICIANS

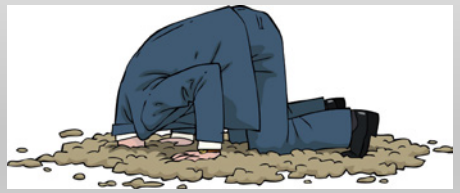
8. Thou shalt make sure that coding is accurate, that bills are appropriate, and that chart notes and appropriate testing support diagnosis.
9. Thou shalt have an independent consultant hired under attorney/client privilege to spot check medical charts, medical notes, coding, billing, and follow-up and deposits to assure compliance with the above Commandments above.
10. Thou shalt not mark up services or products without being given clearance by a reputable health lawyer.
11. Thou shalt not do business with anyone known to violate the above commandments.
12. Thou shalt immediately terminate or correct the actions of any employee or employer who is violating the above commandments or who puts patients into harm's way.

THE 16 COMMANDMENTS FOR PHYSICIANS

13. Thou shalt always put patient care as the primary priority for any and all business or legal decisions that in any way impact patient care.
14. Thou shalt have an accounting system that separates the receipt of monies and people involved therewith from the billing computer and accounting. The person who receives the money or checks and makes deposits should not have the ability to tell the billing computer that a patient has paid the bill.
15. Thou shalt be courteous, positive (as opposed to negative), and professional in all means of communications and relationships.
16. Review the first 15 Commandments with your lawyer, your health care lawyer, your CPA, and your medical practice consultant once a year . . . and pay them well and buy them nice gifts!

The First Rule of Physics

Go for help early – don't put your head in the sand.



The Second Rule of Physics

Anyone who acts as his own lawyer has a fool for a client.

- F. Lee Bailey

The Third Rule of Physics

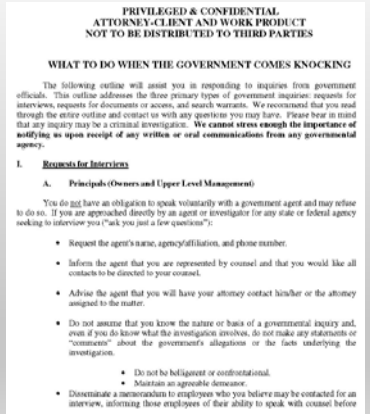
- There is no "get out of jail free" card for direct or indirect payment for referrals.
- There is no "get out of jail free" card for dishonesty or significant exaggeration in coding or medical records.
- The best way to become a multi-millionaire is to work in the billing department of a large medical practice and become a whistle blower.
- A high percentage of medical groups are breaking technical rules while doing the right thing. They may nevertheless be fined millions of dollars, medical licenses will be lost, and some doctors will even end up in jail.
- An example is the Stark Law Rule that prevents doctors from being compensated based upon their referrals to diagnostic and certain treatment modalities within the same practice!

The Third Rule of Physics, Continued

- Don't break any laws in your business and operation:
  - Being dishonest in any way by U.S. Mail or on the Internet is "wire fraud" and punishable by prison sentence.
  - You lose the lawyer/client confidentiality privilege under the crime fraud exception, if the lawyer or CPA is furthering this bad act.
  - In whistleblower situations, your own employee can become like a prosecutor and has immunity from prosecution for turning you in.
  - Have an independent legal compliance review under lawyer/client privilege, if you want to reduce risk in this area, and follow the advice of reputable consultants.

What To Do When The Government Comes Knocking

by Gabriel Imperato, Esquire, Broad and Cassel Law Firm



PRIVILEGED & CONFIDENTIAL
ATTORNEY-CLIENT AND WORK PRODUCT
NOT TO BE DISTRIBUTED TO THIRD PARTIES

WHAT TO DO WHEN THE GOVERNMENT COMES KNOCKING

The following outline will assist you in responding to inquiries from government officials. This outline addresses the three primary types of government inquiries: requests for interviews, requests for documents or access, and search warrants. We recommend that you read through the entire outline and contact us with any questions you may have. Please bear in mind that any inquiry may be a criminal investigation. **We cannot stress enough the importance of notifying us upon receipt of any written or oral communications from any governmental agency.**

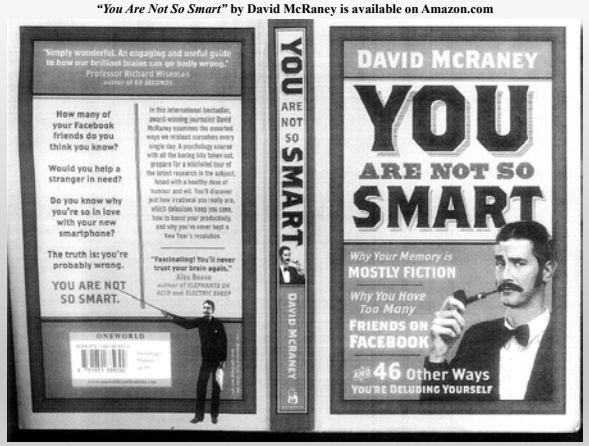
I. Requests for Interviews

A. Principals (Owners and Upper Level Management)

You do not have an obligation to speak voluntarily with a government agent and may refuse to do so. If you are approached directly by an agent or investigator for any state or federal agency seeking to interview you ("ask you just a few questions"):

- Request the agent's name, agency/affiliation, and phone number.
- Inform the agent that you are represented by counsel and that you would like all contacts to be directed to your counsel.
- Advise the agent that you will have your attorney contact him/her or the attorney assigned to the matter.
- Do not assume that you know the nature or basis of a governmental inquiry and, even if you do know what the investigation involves, do not make any statements or "comments" about the government's allegations or the facts underlying the investigation.
  - Do not be belligerent or confrontational.
  - Maintain an agreeable demeanor.
- Disseminate a memorandum to employees who you believe may be contacted for an interview, informing those employees of their ability to speak with counsel before

"You Are Not So Smart" by David McRaney is available on Amazon.com



You Are Not So Smart

(Excerpts from the book *You Are Not So* Smart by David McRaney)

Chapter Title	The Misconception	The Truth
Introduction	You are a rational logical being who sees the world as it really is.	You are as deluded as the rest of us, but that's okay - it keeps you sane.
Chapter 3 - Confirmation Bias	Your opinions are the result of years of rational, objective analysis	Your opinions are the result of years of paying attention to information that confirmed what you believed, while ignoring information that challenged your preconceived notions.
Chapter 5 - The Texas Sharpshooter Fallacy	You take randomness into account when determining cause and effect.	You tend to ignore random chance when the results seem meaningful or when you want a random event to have a meaningful cause.
Chapter 25 - The Affect Heuristic	You calculate what is risky or rewarding and always choose to maximize gains while minimizing losses.	You depend on emotions to tell you if something is good or bad, greatly overestimate rewards, and tend to stick to your first impressions.
Chapter 28 - Self-Serving Bias	You evaluate yourself based on past successes and defeats.	You excuse your failures and see yourself as more successful, more intelligent, and more skilled than you are.
Chapter 32 - The Misinformation Effect	Memories are played back like recordings.	Memories are constructed anew each time from whatever information is currently available, which makes them highly permeable to influences from the present.
Chapter 37 - Learned Helplessness	If you are in a bad situation, you will do whatever you can do to escape it.	If you feel like you aren't in control of your destiny, you will give up and accept whatever situation you are in.
Chapter 38 - Embodied Cognition	Your opinions of people and events are based on objective evaluation.	You translate your physical world into words, and then believe those words.
Chapter 41 - Self-Handicapping	In all you do, you strive for success.	You often create conditions for failure ahead of time to protect your ego.
Chapter 42 - Self-Fulfilling Prophecies	Predictions about your future are subject to forces beyond your control.	Just believing a future event will happen can cause it to happen if the event depends on human behavior.
Chapter 47 - The Illusion of Control	You know how much control you have over your surroundings.	You often believe you have control over outcomes that are either random or are too complex to predict.

Habits to Change

How to change a habit?

Slowly!

Change one step at a time.

Example – Put carrots in the refrigerator where you normally keep the high carbohydrate fruits.

Sexual Harassment – Have a policy and Agreement signed by all employees.

Company Policy on Sexual Harassment

GASSMAN, CROTTY & DENICOLO, P.A. will not tolerate harassment of any kind toward any of its employees. We have taken steps to protect you from harassment in the workplace.

Your cooperation is vital for your protection and well-being. Please observe the following procedures and know your rights as stated below:

1. It is against our policy for any worker, whether male or female, to harass another worker in words or actions. Each of the following is against our policy.
   a) Making unwelcome sexual advances or requesting sexual favors;
   b) Making comments on a worker's physical appearance or body, or making comments on a worker's presumed sexual habits, preferences, desires, etc.;
   c) Touching or caressing a worker without the worker's prior, express permission;
   d) Displaying obscene or sexually-oriented or suggested photographs, drawings or other visual or oral material;
   e) Engaging in obscene or sexually-oriented gestures, activities or comments;
   f) Creating an intimidating, hostile or offensive work environment to any employee or any class or group of employees.
2. It is against our policy for any worker to use a worker's submission to or rejection of the above conduct by another worker as a factor in any employment decision affecting the worker submitting to or rejecting the conduct.
3. We will not condone any harassment of employees. All workers, including, but not limited to, supervisors and management personnel, will be subject to severe discipline, including discharge for any harassing behavior.
4. Any employee who feels victimized by harassment should immediately report it to Alan Gassman or their appropriate supervisor. We will undertake a careful investigation, which may include interviewing other employees who have knowledge of the alleged incident or similar situations. Your complaint, along with the investigative steps and findings, will be documented as thoroughly as possible. Any appeals from this decision will be handled in accordance with our dispute resolution procedures.
5. No employee will be subject to any form of retaliation or discipline for pursuing a harassment complaint.

Employee Non-Compliance

- **Date:**_____
- **Employee Name:**_____
- **Date of Non-Compliance:**_____
- **Description of Non-Compliance:**_____
- _____
- _____
- **Employee acknowledges the above was discussed:**_____
- **By:**_____

Innovative Termination Techniques

1. Terminate by letter.
2. Terminate by phone call.
3. Terminate away from the office.
4. Don't have the announcer at a football stadium fire the employee.
5. Go on a cruise and call them from the farthest port away.

What Documentation is in the Personnel File?

- **Acknowledgement of 90-day Probationary Period**
- **Acknowledgement of handbook/company policies**
- **Restrictive Covenants**
- **Confidentiality Agreements**
- **Performance reviews**
- **Disciplinary Actions**
- **Investigation and Notes**
- **Complaints by clients**
- **Complaints by Co-workers**
- **Complaints by Employee**
- **Attendance Records**

Dale Carnegie Had It Right!

Principles from *How to Win Friends and Influence People*		
	My present rating and what I will improve.	**Anonymous Rating from People In My Office (Do I dare ask?)**
BECOME A FRIENDLIER PERSON		
• Don't criticize, condemn or complain.		
• Give honest, sincere appreciation.		
• Arouse in the other person an eager want.		
• Become genuinely interested in other people.		
• Smile.		
• Remember that a person's name is to that person the sweetest and most important sound in any language.		
• Be a good listener. Encourage others to talk about themselves.		
• Talk in terms of the other person's interests.		
• Make the other people feel important – and do it sincerely.		

Dale Carnegie Had It Right!

Principles from *How to Win Friends and Influence People*	
	My present rating and what I will improve.
WIN PEOPLE TO YOUR WAY OF THINKING	
• The only way to get the best of an argument is to avoid it.	
• Show respect for the other person's opinion. Never say "*You're wrong.*"	
• If you are wrong, admit it quickly and emphatically.	
• Begin in a friendly way.	
• Get the other person saying "*Yes, Yes*" immediately.	
• Let the other person do a great deal of the talking.	
• Let the other person feel that the idea is his or hers.	
• Try honestly to see things from the other person's point of view.	
• Be sympathetic with the other person's ideas and desires.	
• Appeal to their nobler ideas.	
• Dramatize your ideas.	
• Throw down a challenge.	

Dale Carnegie Had It Right!

Principles from *How to Win Friends and Influence People*	
	My present rating and what I will improve.
BE A LEADER	
• Begin with praise and honest appreciation.	
• Call attention to people's mistakes indirectly.	
• Talk about your own mistakes before criticizing the other person.	
• Ask questions instead of giving direct orders.	
• Let the other person save face.	
• Praise the slightest improvement and praise every improvement. Be "hearty in your approbation and laving in your praise."	
• Give the other person a fine reputation to live up to.	
• Use encouragement. Make the fault seem easy to correct.	
• Make the other person happy about doing the thing you suggest.	

Read the book *What Got You Here, Won't Get You There* by Marshall Goldsmith

Dale Carnegie Had It Right!

Principles from *How to Stop Worrying and Start Living*	
	My present rating and what I will improve.
Basic Techniques in Analyzing Worry	
• Get all the facts.	
• Weigh all the facts – then come to a decision.	
• Once a decision is reached, act!	
• Write out and answer the following questions:	
◦ What is the problem?	
◦ What are the causes of the problem?	
◦ What are the possible solutions?	
◦ What is the best possible solution?	
Fundamental Principles for Overcoming Worry	
• How to face trouble:	
◦ Ask yourself, "What is the worst that can possibly happen?"	
◦ Prepare to accept the worst.	
◦ Try to improve on the worst.	
• Live in "day-tight compartments."	
• Remind yourself of the exorbitant price you can pay for worry in terms of your health.	

Dale Carnegie Had It Right!

Principles from *How to Stop Worrying and Start Living*	
	My present rating and what I will improve.
Break the Worry Habit Before it Breaks You	
• Keep busy. (Stay in the flow.)	
• Don't fuss about trifles.	
• Use the law of averages to outlaw your worries.	
• Cooperate with the inevitable.	
• Decide just how much anxiety a thing may be worth and refuse to give it more	
• Don't worry about the past.	
Cultivate a Mental Attitude that will Bring You Peace and Happiness	
• Count your blessings – not your troubles.	
• Try to profit from your losses.	
• Create happiness for others.	
• Fill your mind with thoughts of peace, courage, health and hope.	
• Never try to get even with your enemies.	
• Expect ingratitude.	
• Do not imitate others.	

Dale Carnegie Had It Right!

Principles from *How to Stop Worrying and Start Living*	
	My present rating and what I will improve.
Prevent Fatigue and Worry and Keep Your Energy and Spirits High	
• Rest before you get tired.	
• Learn to relax at your work.	
• Protect your health and appearance by relaxing at home.	
• Apply these four good working habits:	
• Clear your desk of all papers except for those relating to the immediate problem at hand.	
• Do things in the order of their importance.	
• When you face a problem, solve it then and there if you have the facts necessary to make a decision.	
• Learn to organize, deputize and supervise.	
• Put enthusiasm into your work.	
• Don't worry about insomnia.	
Common Misconceptions:	
a. People cannot work effectively more than 10 hours a day – that is hogwash – you can work 16 hours a day if and when you need to.	
b. If I do not get 7.5 hours of sleep I cannot function properly – that is hogwash – in time of need you can do without sleep almost completely.	
c. What are other self-limiting techniques?	

Put Basic Dale Carnegie Skills Into Place

Dale Carnegie founded schools for businesspeople in the New York City YMCA organization in the 1930's.

His ground rules for successful living, relationships, and personal effectiveness were well organized, well phrased, and well explained.

Read *How to Win Friends and Influence People* and *How to Stop Worrying and Start Living* without delay if you have not done so, and then every three years on average.

Consider the Dale Carnegie multiple week evening program that covers these two books and also public speaking in a very effective way.

It can change your life!

Hold Your Loved Ones Close, and Your Enemies Closer.

Always be as friendly as possible to everyone you work with.

"Feed the dog, not the wolf."
- Srikumar S. Rao, Ph.D. –

Every person has a good dog and a bad wolf in them -
by feeding the dog with positivity as much as possible,
the behavior of the person will be as positive as possible.

Beware of the Rescuer

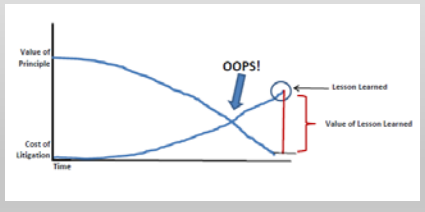
The rescuer makes you look like a bad person, so that they can rescue the people that they encourage to feel hurt by and then take advantage of you.

Many lawyers are rescuers – it's great for business! Don't be manipulated by rescuers. Make your own decisions.

Matters of Principle Only Last So Long

Well, Mr. Client…

How much is the matter of principle worth?



I fought the law and the lawyer won!

Follow Up Checklist for presentation entitled: Protecting Medical Practice Assets from Creditors

General Strategies and Common Mistakes

ITEM	DONE	NEEDS TO BE DONE	NOT SURE	DELEGATE TO
1. Malpractice insurance in place with calendaring for renewal.				
2. Corporate malpractice insurance policy in place or considered.				
3. Nurse practitioners and nurses having separate policies?				
4. Insurance for automobile liability?				
5. Employment agreements in place to document that wages paid to the doctor should be exempt from creditor claims of the doctor.				
6. Does the PA lease real estate from a related entity? Is there a long-term lease agreement in place to insulate the owner entity from accidents on the property?				
7. Does the long-term lease give the landlord entity a UCC-1 field lien against the assets of the medical practice?				
8. Does the medical practice owe money to "friendly creditors" like a bank?				
9. Are the medical practice assets properly pledged as collateral for the loan by filing of UCC-1 financing statements?				
10. Will the practice acquire expensive equipment or other assets that can be held by an entity for the family to not be owned by the practice, or that can be leased in the same manner?				

Follow Up Checklist for presentation entitled:
Protecting Medical Practice Assets from Creditors

General Strategies and Common Mistakes

ITEM	DONE	NEEDS TO BE DONE	NOT SURE	DELEGATE TO
11. Are there any loans on buildings, to family members or otherwise, that can be collateralized by medical practice assets, by proper documentation that will normally include a guaranty by the practice entity and a UCC-1 financing statement/security agreement being executed?				
12. Are there employment agreements in place which clearly delineate wages, and are wages being paid and appropriately thereafter saved in creditor protected ways? Are dividends being spent first and wages being saved?				
13. Are there separate medical practice endeavors that should be separated into separate corporations, such as a specialty practice, a weight loss center, and/or a sleep center?				
14. Assure proper ownership configuration to also comply with Florida anti-referral laws.				
15. Do the doctors have non-competition covenants and/or have they given the medical practice patient file rights that might conceivably be enforceable by a creditor?				
16. If a shareholder/physician may have personal creditor problems, is the transferability of entity ownership properly limited, and perhaps pledged as collateral to a "friendly lender?"				
17. Are there Letters of Protection or other significant receivables that should perhaps be factored or otherwise handled in order to be less exposed to potential creditors?				
18. Review materials with advisors for further possible items of follow up?				

I. The plaintiff became a patient

- Did the patient sign up providing complete medical history?
- Were prior patient files ordered (requested) and available for review?
- Was patient asked to sign an arbitration agreement?
- Were there any red flags that would cause the physician to no longer take this type of patient?
- What did you or your office staff do to build a rapport with the patient? Did you do anything to damage your relationship?
- Your office staff and waiting room are your first line of defense.
- Your attitude and attention to detail are next in line.

II. Rapport Building Ideas

- Note one unique thing about the patient and one unique thing about you that they might identify with.
- "I see you were hurt working in the yard – my parents were serious gardeners."
- The next time you see the patient, you can say "It's the gardener person – what's growing this season?
- Those few words can make a big difference in the psychology of the patient.

II. Rapport Building Ideas, Cont'd

- Studies have shown that individuals are much more trusting and respectful of someone who they have even a small amount of background information on, and who has recognized them as being more than just a number.
  - "I see you were born in Wisconsin."
  - "My grandfather was born in _____ County, Wisconsin, but I never went there."
- Compliment whenever you can.
  - "I love that handbag. Where did you get it?"
- Also check out "Neurolinguistics Programming" (NLP) which offers a number of effective techniques for building and maintaining a good rapport.

III. The Patient Received Treatment

- How are the file (chart) notes?
- Are calls that the patient made to the office properly documented?
- Are contacts that your office made with the patient or with other providers documented in the chart?
- Was the patient warned of risks? Is this documented?
  - Does your specialty group have approved forms for informed consent?
    - Is the informed consent witnessed by a loyal staff member?

III. The Patient Received Treatment

- Were reminders sent to the patient with respect to coming back for further treatment or follow-up for testing or with referred specialists?
  - Is this reflected in the medical record?
- Were x-rays and test results carefully reviewed and re-reviewed?
  - Is your reliance on other specialists documented?

IV. A Bad Result Occurs

- Did the doctor immediately notify his malpractice insurance carrier?
- Prepare immediately, a narrative of the incident, your thoughts and concerns and keep it somewhere safe.
  - Don't keep it in the chart!
  - It should be reviewed only by your attorneys and the malpractice carrier.
- Retain Personal Counsel.

V. Did The Doctor Do Anything that Would Cause the Jury to Look Unfavorably at Him or Her?

- Forging medical reports?
- Losing medical records?
- Writing off balances owed?
- Saying anything to anyone other than the doctor's attorney that would be discoverable in litigation?
- Sloppy or inaccurate chart notes will lead a jury to believe that a doctor was probably sloppy in treatment.

VI. A Lawyer or the Family Asks for Copies of the Patient's Files

THIS IS AN EVENT WHICH REQUIRES YOUR PERSONAL ATTENTION!

- Make sure they receive an exact copy.
- Make an extra exact copy and put it somewhere safe in case the file disappears.
- Before the file request is honored, the doctor should review the file to see if anything needs to be clarified with the guidance of appropriate counsel and without "forgery" or "back-dating".

VII. The Doctor May Be Contacted…

- The doctor may be contacted by a personal injury lawyer who "just wants to talk to him about what the other doctors did wrong."
- Anything the doctor says or does can be used against him – the plaintiff's lawyer is not Joe Friday!
- Better for the doctor's lawyer to talk to the plaintiff's lawyer.

VIII. The Doctor Receives a Statutory Notice.

- Immediately involve the malpractice insurance (the bad result insurance) carrier.
- Request immediate assignment of a Martindale-Hubbell® AV rated malpractice defense lawyer from the insurance company's list who has a good relationship with private counsel.
  - Typically, the doctor can call the carrier and ask who they usually hire and what his or her choices might be.
  - The doctor can then ask their business and/or estate planning lawyer for a recommendation from that list to assure there will be a top notch, responsive, and caring lawyer involved in the file.

IX. Sometimes It Is Best to Wait…

- If the plaintiff does not have minor children or a spouse, and may die during the suit, then there may be limited damages.
- If the patient died and left a spouse who is older and feeble, then death during the pendency of the suit may resolve the significant exposure and it may be best to wait.

X. Discovery, Discovery, Discovery.

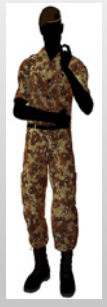
- After the suit is filed the litigation system provides for each side to investigate by taking depositions under oath, serving interrogatories, and presentation and interview of witnesses.
- What depositions will the defense lawyer intend to take?
- What might a detective find out?

"Plead" With The Judge

- Fine tune or eliminate the litigation on questions that can be answered without a jury.
  - "Questions of law"
  - Facts "admitted" by both parties
- A motion to dismiss may be filed.
- A summary judgment may be issued.
- Often, these rulings will be appealed, and the appeal may be after the jury trial.

BACKGROUND:

- **What is a deposition?**
  - Oral testimony taken under oath in response to questions posed by attorneys
  - Often video taped
  - Testimony is transcribed but the Judge/Jury are not present - only the lawyers, the witness, the court reporter and a representative of each party are usually in attendance
  - The transcript and/or video is ALWAYS available for use at trial if you are a PARTY



WHAT TO DO…

AND WHAT TO SAY

BE AGILE…

AND NOT A GREEN BERET!

BACKGROUND

- **What is the purpose of a deposition?**
  - Fact finding – to discover the contents of trial testimony ahead of time
  - To pin down your story to eliminate surprises at trial
  - To try to evoke misstatements as an opportunity to show that you are dishonest or untruthful at trial
  - To get an overall impression of you as a witness to determine what effect you will have on the jury

Rates of Payment

- **The rate of payment depends on the type of deposition you are asked to give.**

Expert Witness

- **As an expert witness you are asked to give an opinion on causation and standard of care.**
- **As an expert witness you can set your own rate of payment (some charge as much as $1,000 to $1,200 per hour).**

NOTE: Opposing counsel does not have to pay the fee the hiring attorney has agreed to. The opposing counsel is only required to pay what the Court determines is reasonable.

As an expert witness you have two choices with regard to payment from opposing counsel:

1. Agree to the rate the opposing counsel is willing to pay; or

2. Challenge the amount offered by the opposing counsel. In most instances the court will take the highest fee paid by opposing counsel and apply that.

Rates of Payment (Cont'd)

Fact Witness

- As a fact witness you are asked to give a deposition as the treating physician.
- As a fact witness your deposition can be taken at any time and any place by sending you a subpoena and demand that you be there.
- If you have to be subpoenaed you will only be paid a witness fee, which can be as little as $10.
- Most lawyers do not like to invoke their right to subpoena a witness.
- Cooperation is key. The lawyer requesting the deposition would like your cooperation and would like you to give an honest and educated testimony and will ask you to charge a reasonable fee.

Do You Have Your Malpractice Insurance Carrier Involved If It Is A Patient That You Have Treated?

Most malpractice insurance carriers have local offices that you can call on in the event you are asked to give a deposition.

Most carriers will provide courtesy defense including a lawyer to review your records, arrange the deposition and talk with you about your case.

Location, Location, Location

The location of the deposition is an important factor in a deposition.

Do not agree to give the deposition in your office.

Periodicals and other literature you have in your office can be used against you.

Call and request a mutually beneficial location for the deposition and be as nice as possible when requesting the change.

Requests for Changes in Location, Date and Time

- Do not ignore requests for scheduling a deposition.
- Be involved and know the specifics of the case including when, where, and to whom the deposition will be given.
- Opposing counsel can and will find out the details of your schedule and they will subpoena you to appear during times when you are not available. Most law firms have private investigators to find out this information.
- Don't be caught on the golf course or playing tennis when you say you are too busy to give a deposition.
- Have a trusted employee call (or call yourself) to schedule the deposition and be as nice as possible on the phone with the scheduler. Do not give this task to the "low man on the pole" in your office.
- Do not become the doctor who is difficult to request a deposition with.

The power of the subpoenaed a/k/a how is the food in jail?

Do not ignore requests for scheduling a deposition.

Lawyers will invoke their right to subpoena you and will not hesitate to have a bench warrant issued if you do not show up.

THE VIDEO DEPOSITION: LISTEN & LOOK

- Ask if your deposition can be videotaped if attendance at trial may be difficult.
- Look at the person asking the questions and NOT at the camera.
- By looking at the person asking the questions you will be more relaxed, and you will be able to show the kind, compassionate doctor you strive to be everyday.

DEPOSITIONS ARE SERIOUS BUSINESS

THE GOAL IS FOR YOU TO BECOME A CONFIDENT, INFORMED, SOLID AND UNSHAKEABLE WITNESS

PRACTICE MAKES PERFECT

- Have rehearsal time with your lawyer scheduled for at least the amount of time of the deposition.
- Ask the lawyer whether the carrier will provide you with professional coaching – it can be a very good investment for all communications skills.
  - The last person who knows that there is a communications skill deficiency is the person with the deficiency.
- The best lawyers will do everything they can to help clients deal with that, including having a mock deposition taken by a colleague who shows no mercy.
- If you have never been deposed, or want to get a good refresher, ask a lawyer to give you a copy of a videotaped deposition, so that you can prepare yourself mentally for the experience.

TIPS FOR A SUCCESSFUL DEPOSITION

A.T.F.T.

Always tell the frigging truth!

TIPS FOR A SUCCESSFUL DEPOSITION (Cont'd)

KISS/KISS

Keep it **S**imple **S**tupid
Keep it **S**hort and **S**weet

TIPS FOR A SUCCESSFUL DEPOSITION (Cont'd)

LISTEN CLOSELY

Be a good listener and thoroughly understand the questions being asked of you so that you can answer honestly and educationally.

LISTEN…
TO YOUR ATTORNEY
TO THE OTHER ATTORNEYS
TO YOURSELF

TIPS FOR A SUCCESSFUL DEPOSITION (Cont'd)

CORRECT YOUR MISTAKES

BUT…DON'T CORRECT THE PLAINTIFF'S ATTORNEY'S MISTAKES

If you find yourself in a situation where you remember that you answered a question incorrectly, let the attorney know and give them the correct answer

TIPS FOR A SUCCESSFUL DEPOSITION (Cont'd)

- Be respectful
  - Most lawyers will show you mutual respect if you present yourself in a positive and respectful manner.
- Be patient
- Understand and rephrase
  If you are in the middle of a deposition and are not on trial, it is perfectly acceptable to ask that the question be rephrased so that you can understand and answer properly.
- No guessing or speculation
  If you do not know the answer to a question do not guess or give the answer you think will get the deposition over the quickest. It is okay to say that you do not know or that you do not recall.
- Practice makes perfect
  Many litigation lawyers recommend deposition pre-meetings or rehearsals based upon the same amount of hours as the deposition is expected to go.

TIPS FOR A SUCCESSFUL DEPOSITION (Cont'd)

REFER TO THE PATIENT AS MR./MRS.

USE "I" INSTEAD OF "WE"

TIPS FOR A SUCCESSFUL DEPOSITION (Cont'd)

- Avoid the "God complex"

"I have an M.D. from Harvard, I am board certified in cardio-thoracic medicine and trauma surgery, I have been awarded citations from seven different medical boards in New England, and I am never, ever sick at sea. So I ask you; when someone goes into that chapel and they fall on their knees and they pray to God that their wife doesn't miscarry or that their daughter doesn't bleed to death or that their mother doesn't suffer acute neural trauma from postoperative shock, who do you think they're praying to? Now, go ahead and read your Bible, and you go to your church, and, with any luck, you might win the annual raffle, but if you're looking for God, he was in operating room number two on November 17, and he doesn't like to be second guessed. You ask me if I have a God complex. Let me tell you something: I am God."

- Alec Baldwin as Jed in the 1993 movie *Malice*

TIPS FOR A SUCCESSFUL DEPOSITION (Cont'd)

- Be sure you are viewed as
  - Kind
  - Compassionate
  - Caring
- Do not have an inflated view of your own self-worth.

SELF EVALUATION

Lawsuits 101: Essential Legal Concepts for Healthcare Professionals

True/False

1. Doctors and employees should never speak with government agents or health care plan auditors without a lawyer present.

2. It is acceptable to waive a patient's co-pay or deductible as a goodwill gesture.

3. Medical practices should regularly conduct independent compliance reviews under attorney-client privilege.

4. Physicians may refer patients to their own practice for diagnostic services without restrictions.

5. It is important to build rapport with patients to reduce the likelihood of lawsuits.

6. Doctors should modify medical charts if errors are discovered after a lawsuit is filed.

7. An exact copy of a medical file must be provided if requested by a patient's lawyer.

Answer Key: 1. T, 2. F, 3. T, 4. F, 5. T, 6. F, 7. T

FACULTY

Jonathan A. Edlow, MD

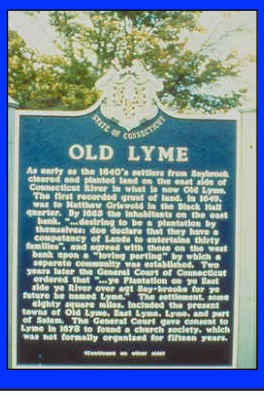
Jonathan A. Edlow, MD, of Lancaster, Virginia, is a Professor of Medicine and Emergency Medicine at Harvard Medical School. He lectures nationally and internationally on topics such as stroke, TIA, subarachnoid hemorrhage, and various causes of weakness and dizziness. He is an internationally renowned expert on neurological emergencies. Dr. Edlow's specialty areas include ED quality assurance, ED physical layout and facilities redesign, physician professional development, and the creation and implementation of clinical practice guidelines. For the past 15 years, Dr. Edlow has contributed to the international development of emergency medicine in a variety of countries, participating in educational, quality assessment, and emergency care systems consulting projects. Practicing medicine since 1981, he is board-certified in both emergency medicine and internal medicine. In addition to being well-published in peer reviewed literature, Dr. Edlow has written a book on stroke, as well as two award-winning books for the lay public; one about the history of Lyme disease titled "Bull's Eye: unraveling the medical mystery of Lyme disease," and the second titled "The Deadly Dinner Party: 15 true medical detective stories."

You may contact Dr. Edlow with your questions or comments at jedlow@bidmc.harvard.edu.

Lyme and Other Tick-Borne Diseases
Jonathan Edlow, MD

Lyme disease - the history

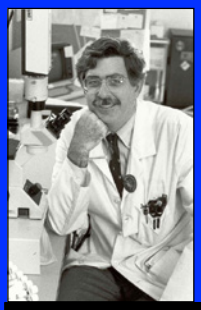
1975



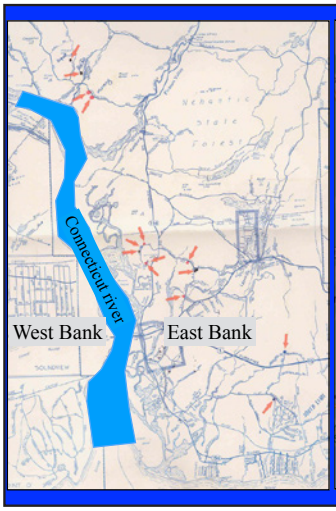

Polly Murray

An outbreak of arthritis - 1975-1976


Allen Steere


David Snydman


Steve Malawista



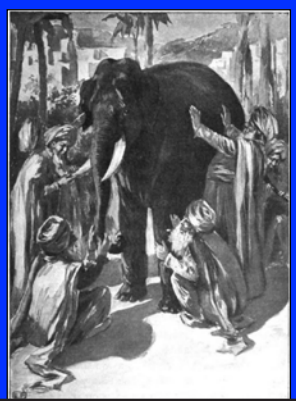
An outbreak of dermatitis - 1975-1976


William Mast


William Burrows

The blind men & the elephant

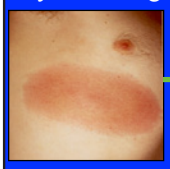
- **Yale group**
  - Focus on joints
  - Antibiotics did not help
  - Thought it was viral
- **The Navy doctors**
  - Focus on rash
  - Antibiotics clearly helped
  - Thought it had to be bacterial

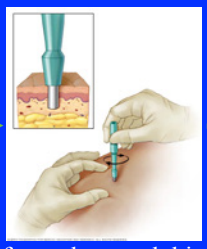


Finding the cause

Binder auto-transplant experiments 1955

Patient with erythema migrans

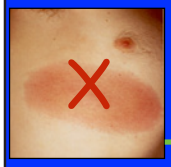


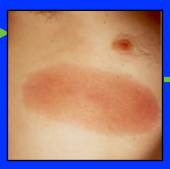


Performed a punch biopsy of leading edge of rash

Treat patient with penicillin

Patient is cured





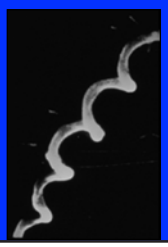
Biopsy tissue given to Dr. #2 who then gets rash
Biopsy Dr. #2, treat & Implant to Dr. #3, repeating

Transplant tissue from biopsy into Dr. Binder, who gets rash

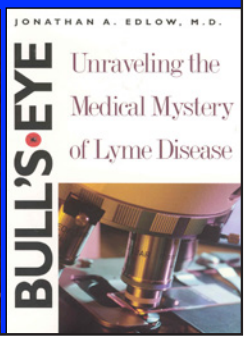
Binder is then biopsied, treated & cured with penicillin

Finding the cause in 1982

- Willy Burgdorfer, while investigating cases of severe Rocky Mountain spotted fever, examined *I scapularis* ticks and isolated a spirochete (a type of bacteria)
- His group did further work using rabbits to prove the spirochetal cause of Lyme disease

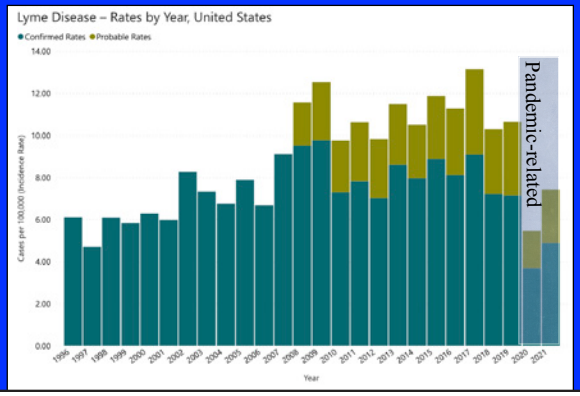


Only 7 years after the outbreak in Lyme CT, Burgdorfer discovers the spirochete

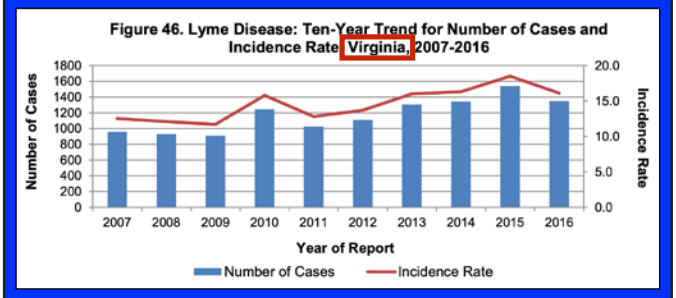


Lyme disease - epidemiology

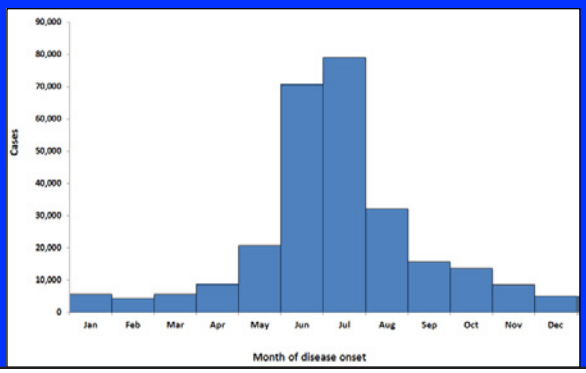
Lyme disease is common



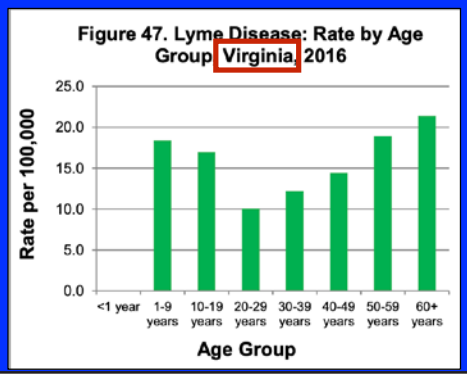
Lyme disease is common

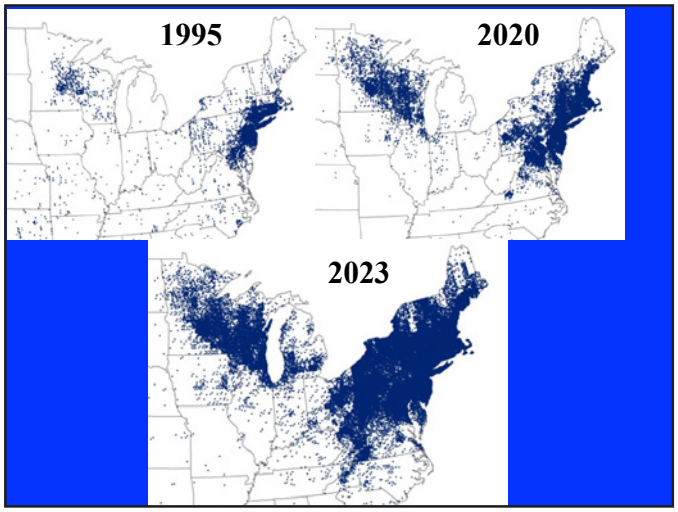


Lyme disease is seasonal
(national data)

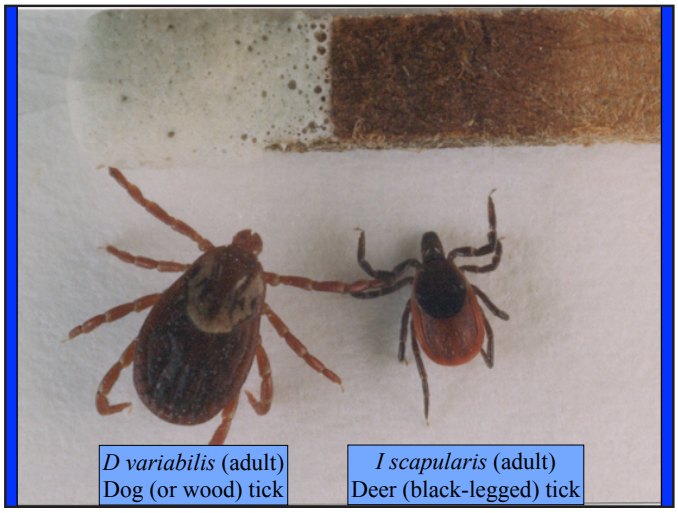


Lyme disease affects everyone



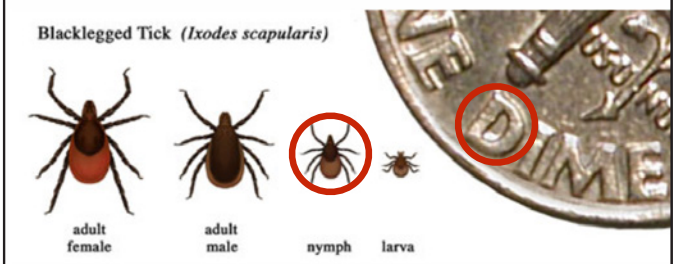


Lyme disease - the ticks



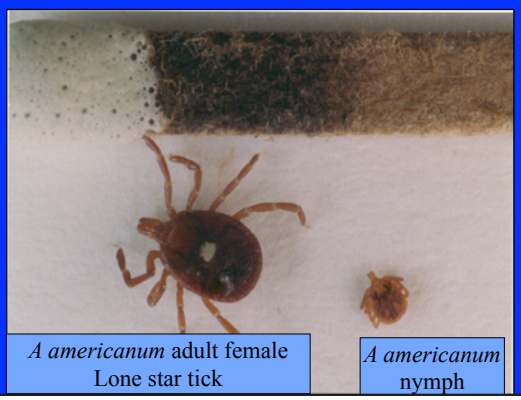
Deer-tick or black-legged tick *Ixodes scapularis*

Common name: Blacklegged tick



Graphic: Centers for Disease Control and Prevention.

There's a (relatively) "new" tick in town - the Lone Star tick



A americanum adult female
Lone star tick

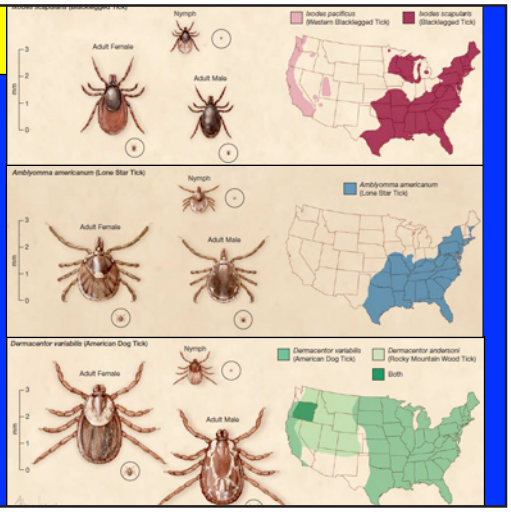
A americanum nymph

Geography (2007)

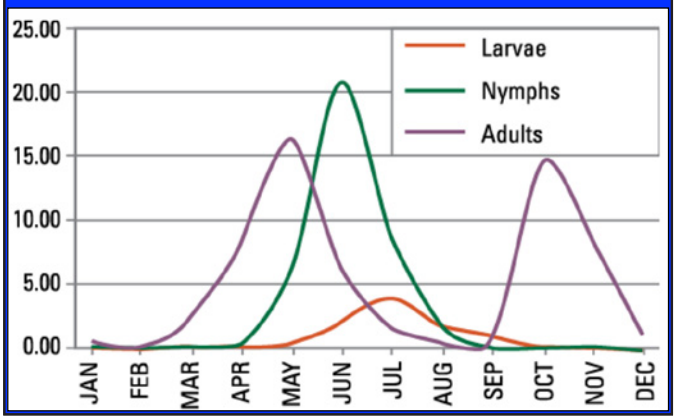
Deer tick

Lone star tick

Dog (wood) tick



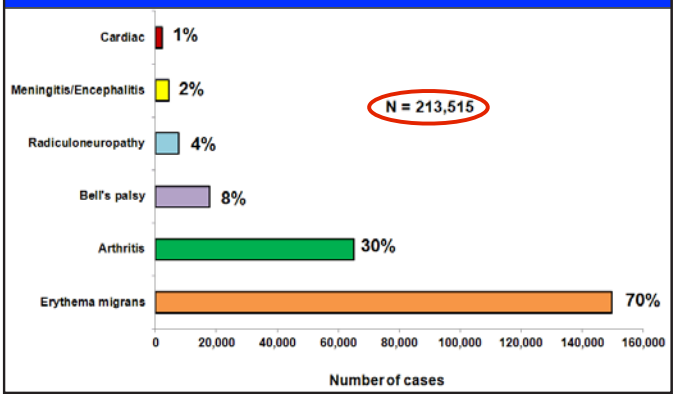
Seasonality of tick activity



Why are there so many ticks?

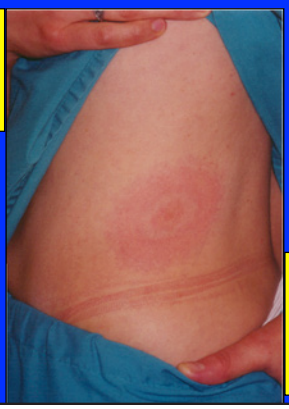
Lyme disease - the rash

Presenting symptoms



Classic Erythema Migrans

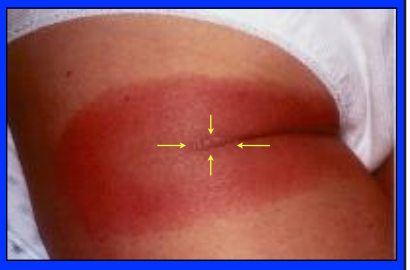
Classic:
1. **Target lesion**
2. **Bull's eye rash**
3. **Central clearing**

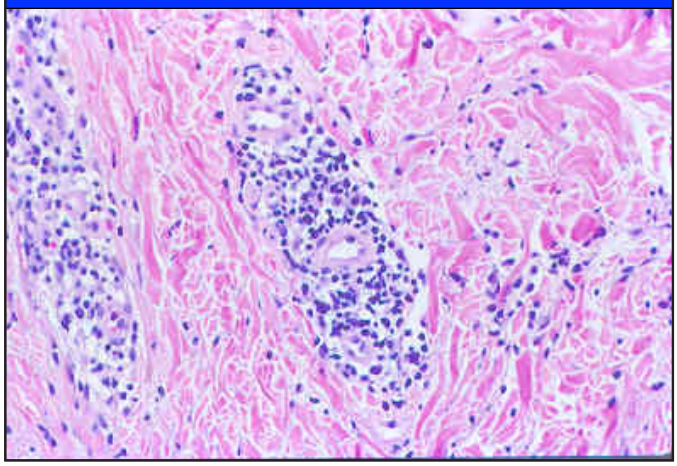


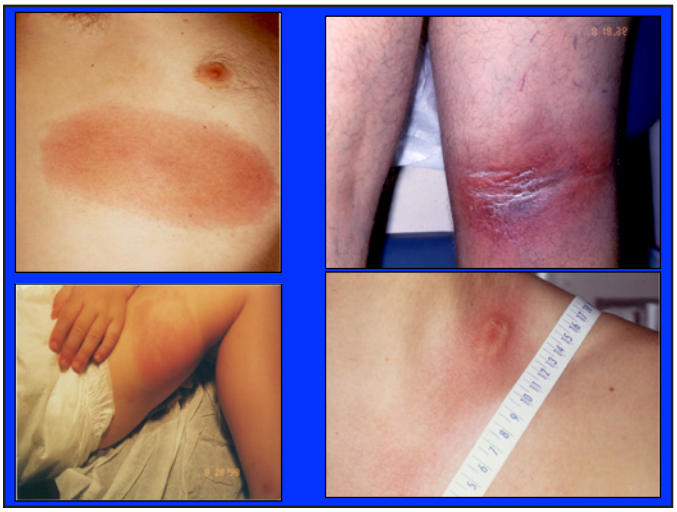
BUT, the classic:
1. **Only occurs in ~ 40% of cases** (in North America)
2. **Variants are more common**

Common Erythema Migrans

- Season
- Location on body
- Geography
- Tick exposure
- Appearance of rash
- Punctum at site
- Minimal pain/itch





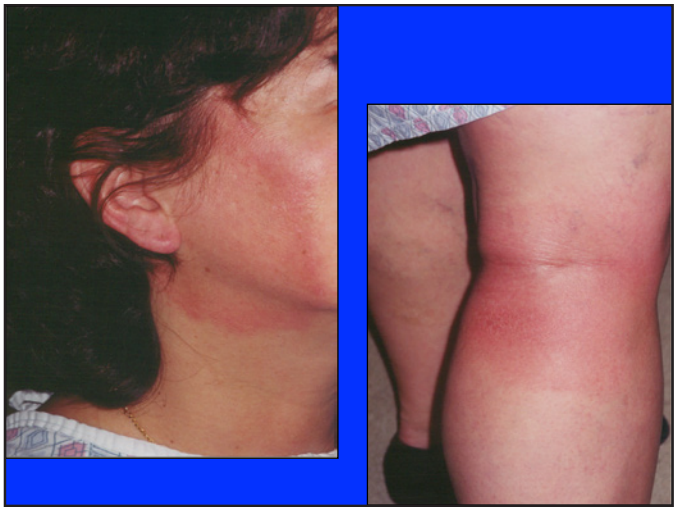


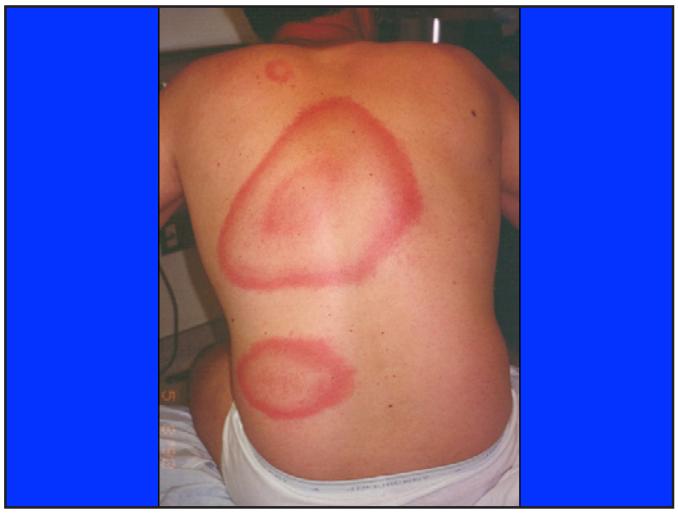
Summer 'flu'

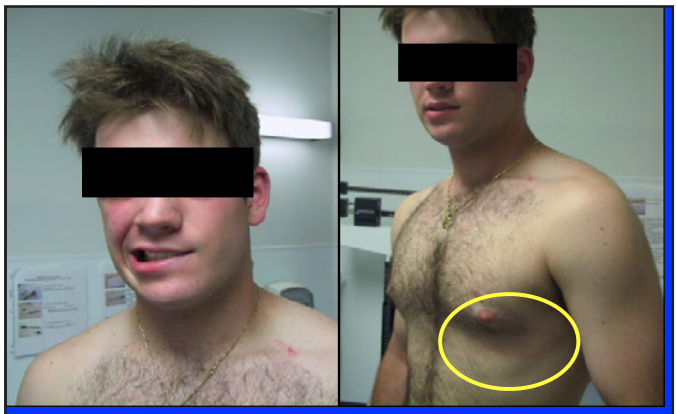
? early Lyme
? other tick-borne diseases

Lyme disease - later manifestations

- Skin - multiple skin lesions
- Neurological
  - Most commonly, a Bell's palsy
  - Lymphocytic meningitis
- Cardiac
  - Heart block - very slow heart rate
  - Heart inflammation - myocarditis & pericarditis
- Arthritis

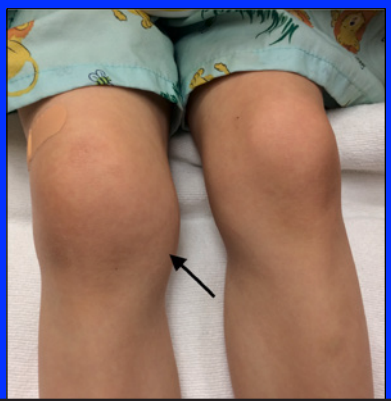


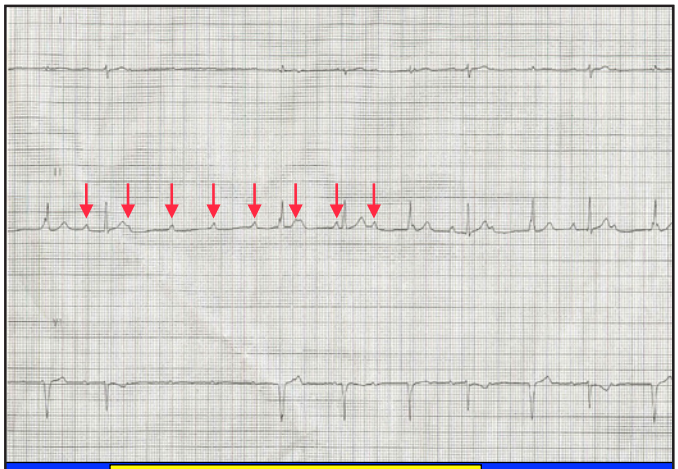




Facial nerve (Bell's) palsy

Lyme arthritis





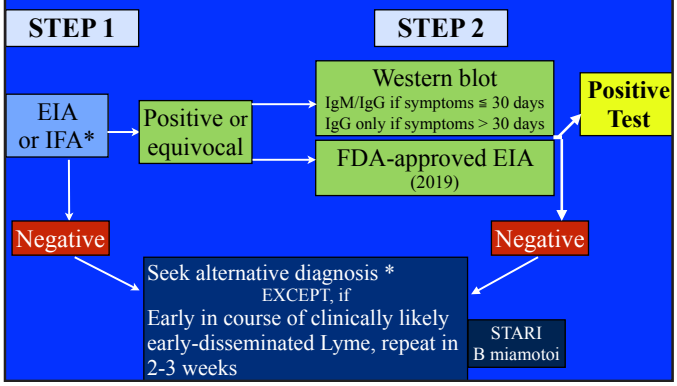
Complete heart block

Lyme blood "test"

- What is the test (what is being measured)?
- When should a patient be tested?
  - Antibodies are **slow to develop** in Lyme disease
  - Early on, testing is **very inaccurate**
- What do the results mean?

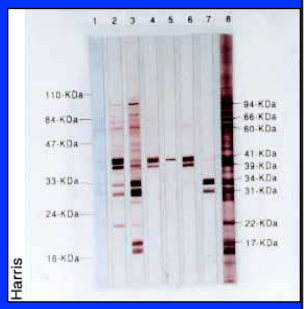
"Lyme test" (serological testing)

What test? When to perform?



Serological testing

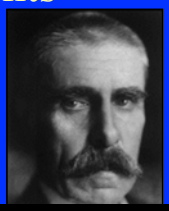
- ***Must be interpreted*** in clinical context
- Early sero-negativity is common
- Late sero-negativity is rare
- Cannot follow serology to follow clinical course (it's not a test of cure)
- Newer testing strategies
  - C-6 peptide alone
  - Double ELISA (WCS/C-6 peptide)
  - PepC10 (conserved Osp-C) protein
  - PCR and culture (not recommended)



History of Treatments

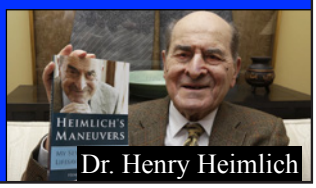
- In the early part of the last century, tertiary syphilis was a very common cause of dementia
- Jauregg-Wagner thought fever could cure it & so innoculated these patients with malaria to cure them. Syphilis is also a spirochetal disease.

He won a Nobel Prize in 1927 for this work!



Dr. Jauregg-Wagner

- Henry Heimlich thought this approach could be used to treat Lyme disease
- He recommended patients go to Mexico, to be intentionally bitten by mosquitoes (to get malaria) in the early 1990's

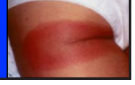


Dr. Henry Heimlich

Antibiotic Treatment

- Most patients with Lyme disease respond rapidly to oral antibiotics. The choice & duration depend on various clinical factors (age, pregnancy, allergies, stage of the disease)

Many frequently used antibiotics for common bacterial skin infections (cefalexin, trimethoprim-sulfamethoxasole and ciprofloxacin) do NOT treat *B. burgdorferi*.



Duration & Route

- Localized EM

10-21 days PO

Serology is NOT recommended

- Early-disseminated (mild)
  - Multiple EM
  - 7th nerve palsy (? CSF)
  - Carditis (PR < 300 msec)

3-4 weeks PO

- Early-disseminated (more severe)
  - Abnormal CSF
  - Higher degrees of AVB

IV ceftriaxone (duration variable)

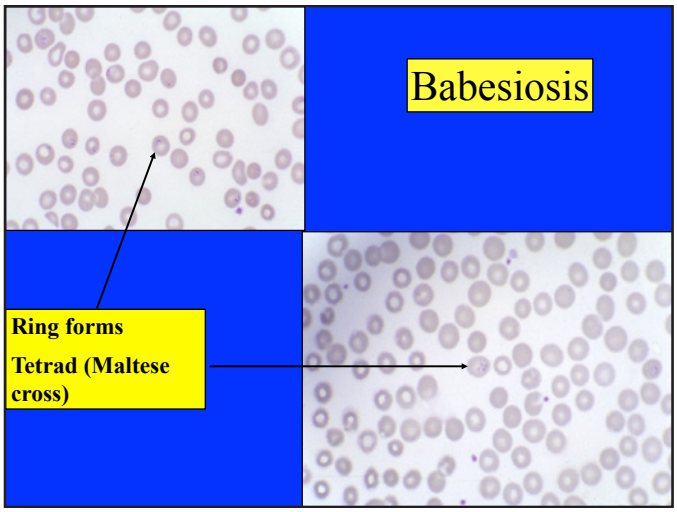
Other tick-borne diseases of North America

Babesiosis
Anaplasmosis (and Ehrlichiosis)

Rocky Mountain spotted fever
Tularemia
Other borrelia species (STARI)

Relapsing fever
Q fever
Colorado tick fever
Powassan virus
Tick paralysis
Alpha-GAL allergy
Others

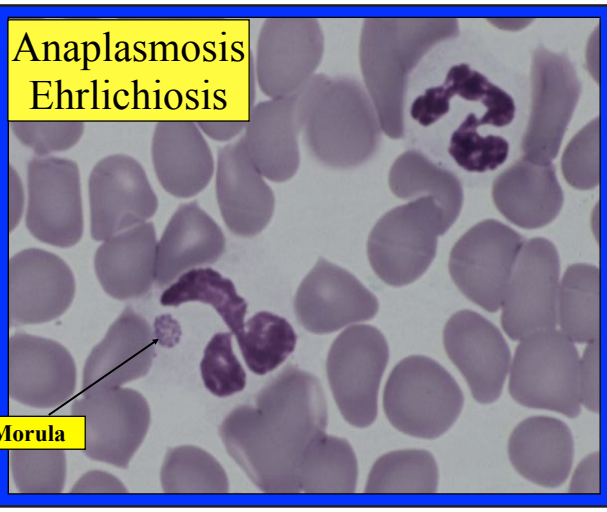
Babesiosis



Ring forms

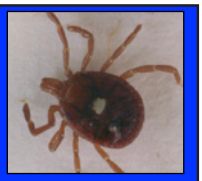
Tetrad (Maltese cross)

Anaplasmosis Ehrlichiosis



Morula

Lone Star ticks



Anaplasmosis (or Ehrlichiosis)

Southern Tick-Associated Rash Illness ("STARI", may be due to an as yet undiscovered Borrelia species)

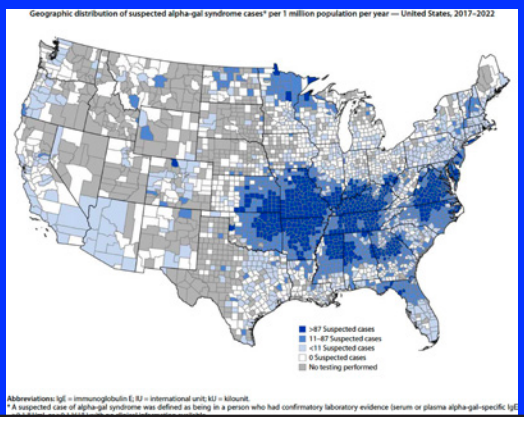
Alpha-GAL red meat allergy (symptoms usually develop 2-6 hours after eating beef, lamb, pork, rabbit & venison)

- **Hives & itchy skin** (70%)
- **Diarrhea & abdominal cramps** (40%)
- **Wheezing & serious anaphylactic reactions**

Alpha-Gal syndrome

- Follows bite of Lone Star ticks
- Being reported with increasing frequency
- Anaphylactic reactions to mammalian red meat
- Delayed symptoms (many hours after eating)
- Prominent GI symptoms, sometimes in the absence of cardiovascular symptoms

Alpha-Gal syndrome



Alpha-Gal syndrome

- The diagnostic test is an IgE level for antibodies to the alpha-gal sugar molecule
- Although it will not result in real-time, consider sending it in cases of acute allergy if the epidemiological context is suggestive

B miyamotoi disease

Table 1. Clinical Features of the 51 Case Patients With BMD

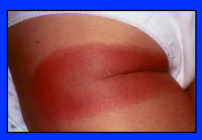
Molloy; 2015 Ann Int Med

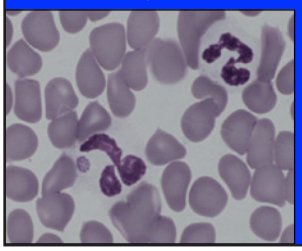
Feature	Value*
Mean age (range), *y*	55 (12-82)
Male	29 (57)
Fever/chills	49 (96)
Headache†	49 (96)
Myalgia	42 (84)
Arthralgia	39 (76)
Malaise/fatigue	42 (82)
Rash	4 (8)
Gastrointestinal symptoms‡	3 (6)
Cardiac/respiratory symptoms§	3 (6)
Neurologic symptoms‖	4 (8)

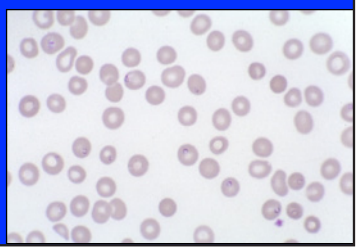
Co-infections

~ 10-15% of cases (of Lyme disease)

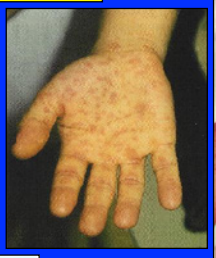
- Babesiosis
- Anaplasmosis/ehrlichiosis
- Triple infections
- Others organisms

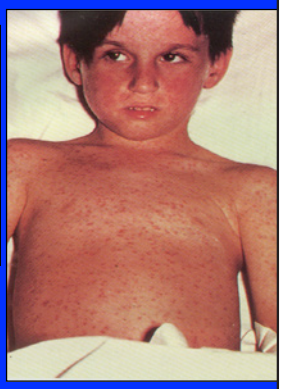


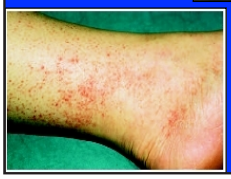




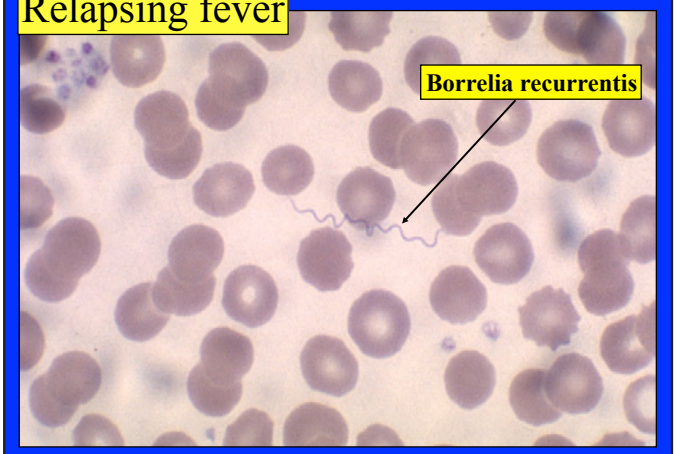
Rocky Mountain spotted fever



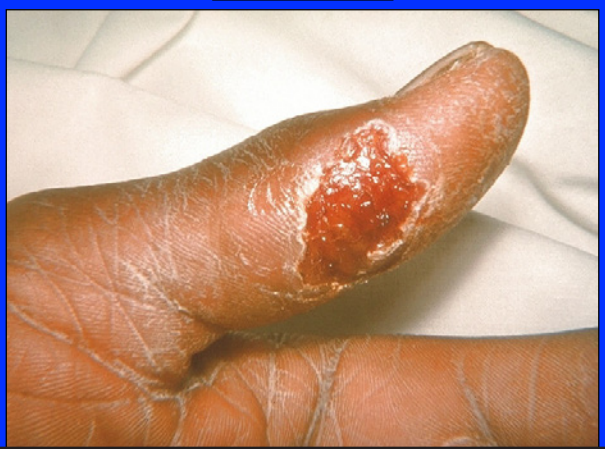




Relapsing fever



Tularemia



Tick paralysis

Tick borne diseases - PREVENTION

Questing deer tick

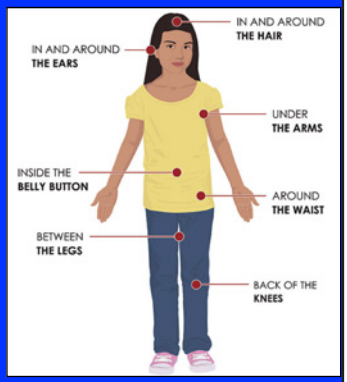
Habitat Control

1	Tick zone	Avoid areas with forest and brush where deer, rodents, and ticks are common.
2	Wood chip barrier	Use a 3 ft. barrier of wood chips or rock to separate the "tick zone" and rock walls from the lawn.
3	Wood pile	Keep wood piles on the wood chip barrier, away from the home.
4	Tick migration zone	Maintain a 9 ft. barrier of lawn between the wood chips and areas such as patios, gardens, and play sets.
5	Tick safe zone	Enjoy daily living activities such as gardening and outdoor play inside this perimeter.
6	Gardens	Plant deer resistant crops. If desired, an 8-ft. fence can keep deer out of the yard.
7	Play sets	Keep play sets in the "tick safe zone" in sunny areas where ticks have difficulty surviving.

Based on a diagram by K. Stafford, Connecticut Agricultural Experiment Station

Personal protection

- Walk in center of trails
- Wear light-colored clothing, tuck pants into socks
- Permethrin (clothing) & DEET (skin); lemon oil/eucalyptus
- Nightly tick checks



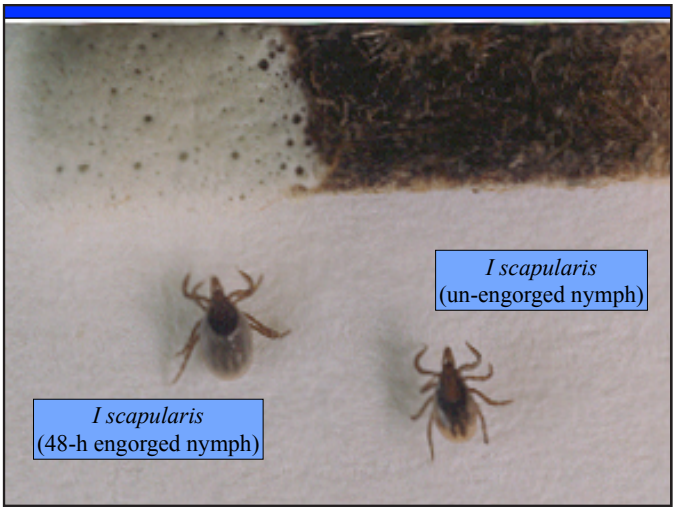
Vaccines

- Two older vaccines taken off the market in late early 2000's
- Pfizer is currently conducting a Phase-3 trial of a new vaccine
- Another study is investigating a single monoclonal antibody injection but its duration of protection is not yet clear

What should you do if you find a tick on you?

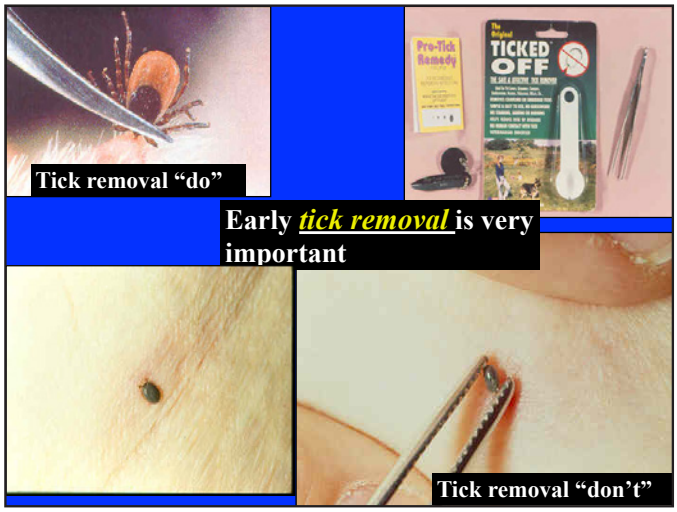
Is the tick engorged with blood?

- Ticks that are still crawling around are not attached and cannot transmit Lyme
- Attached ticks that are flat, not spherical, are not engorged
- Nightly tick checks help to remove ticks before they've had a chance to engorge



Tick removal

Courtesy of the Lyme Wellness Initiative



Tick removal

DO:

- Grab tick as close to skin as possible, using fine forceps/ tweezers
- Pull gently & slowly upwards

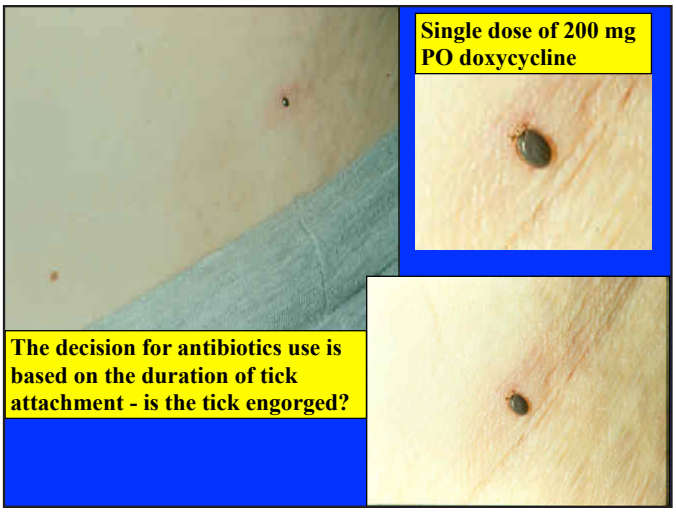
DO NOT:

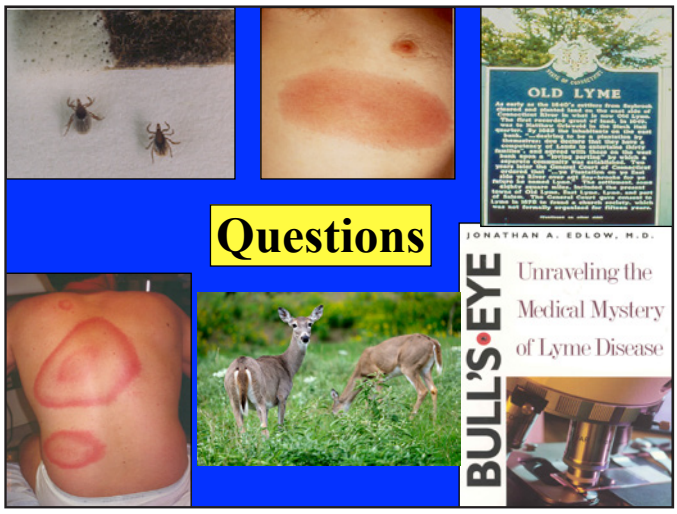
- **Apply vaseline, kerosene, nail polish**
- **Burn it with a match**
- **Squeeze the tick far from the skin surface**

What should I do with the tick?

- I do not recommend sending the tick for analysis


What should you do if you find a tick on you?


Single dose of 200 mg PO doxycycline
The decision for antibiotics use is based on the duration of tick attachment - is the tick engorged?


Questions
OLD LYME
JONATHAN A. EDLOW, M.D.
BULL'S EYE
Unraveling the Medical Mystery of Lyme Disease

SELF EVALUATION

Lyme and Other Tick-Borne Diseases

True/False

1. The incidence of Lyme disease has been stable over the last 20 years in the US.

2. The tick species responsible for Lyme disease transmission is the dog tick, *D. variabilis*.

3. The most common clinical manifestation of Lyme disease is the rash, erythema migrans (EM).

4. To confirm a diagnosis of early Lyme disease, the patient has to have a positive blood test.

5. Cephalexin, trimethoprim-sulfamethoxazole and ciprofloxacin do not treat Lyme disease.

6. Multiple infections from a single tick bite occur between 10-20% of patients with Lyme disease.

7. Alpha-gal syndrome - anaphylaxis can be seen after the bite of the lone star tick – is being reported with increasing frequency due to expansion of the range of the tick.

Answer Key: 1. F, 2. F, 3. T, 4. F, 5. T, 6. T, 7. T

Dong-han Yao, MD

Dong-han Yao, M.D., of Palo Alto, California, is a physician informaticist and emergency physician at Stanford University. Dr. Yao holds a B.A. in Molecular & Cell Biology and Immunology from University of California, Berkeley, and an M.D. from Mount Sinai School of Medicine. He completed his Emergency Medicine Residency training at University of California, Los Angeles, and his fellowship training in Clinical Informatics at Stanford University.

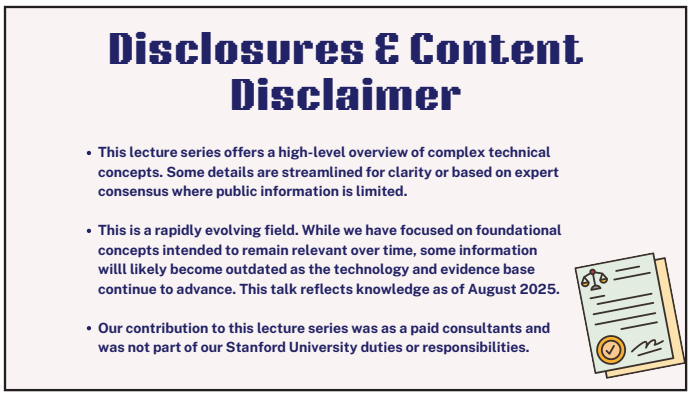
Dr. Yao is an invited speaker at grand rounds, national conferences, and workshops on the topic of prompt engineering and generative AI for both healthcare and non-clinical applications around the country. He collaborates with the Stanford Health Care Data Science Team (DSatSHC) on both enterprise-level AI education and research, as well as co-development and evaluation of novel generative AI platforms and technologies for healthcare.

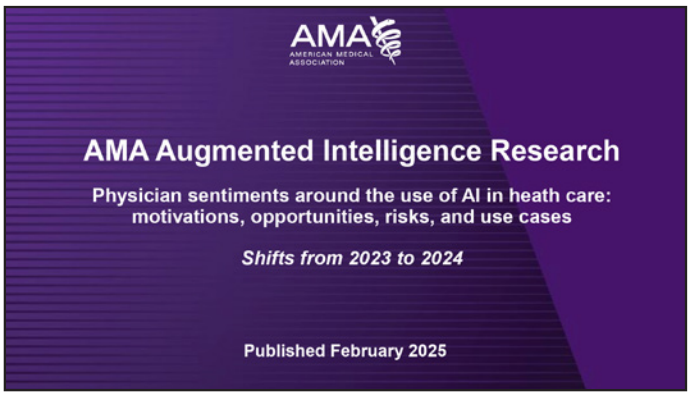
His scholarly and operational work include expanding patient access to acute care via virtual care, responsible integration of AI into medical education and the clinical continuum, and leveraging technology to streamline physician workflow and improve patient outcomes in the emergency department. His past informatics work includes award-winning usage of mobile devices to improve the efficiency and accessibility of medical documentation during the height of the COVID-19 pandemic, creation of novel patient discharge mechanisms for academic hospital centers, and development and implementation of new interdisciplinary clinical pathways for the emergency department. Dr. Yao's clinical interests include critical care, cardiac emergencies, telemedicine, and novel care delivery models in emergency medicine.

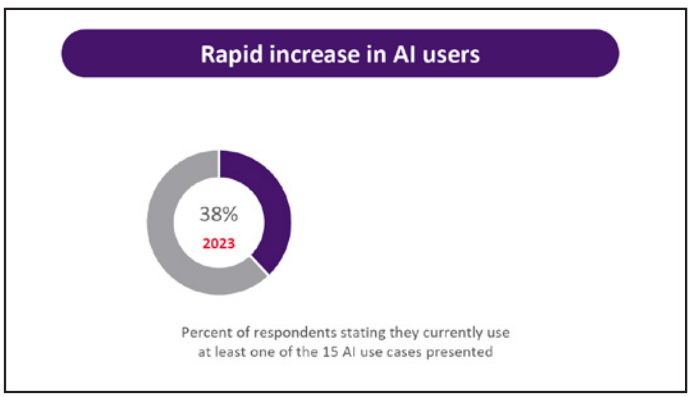
You may contact Dr. Yao with your questions or comments at dongyao@stanford.edu.

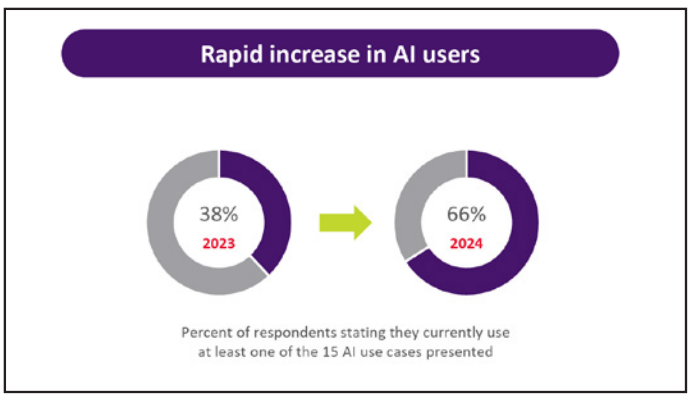
Generative AI in Healthcare - Foundations of LLMs

Dong-han Yao
Shivam Vedak









Survey Report

NVIDIA

State of AI in Healthcare and Life Sciences: 2025 Trends

Perspectives From the Field

The survey was conducted from December 2024 to January 2025 and included more than 600 industry professionals across various segments of healthcare and life sciences.

Survey Report

NVIDIA

State of AI in Healthcare and Life Sciences: 2025 Trends

63% said they're actively using AI.

AI usage is high for healthcare* compared to other industries, with 63 percent of respondents saying they're actively using AI and another 31 percent assessing or piloting AI projects.

Survey Report

NVIDIA

State of AI in Healthcare and Life Sciences: 2025 Trends

81% said AI has helped increase revenue.

Respondents are seeing a present-day impact on their business operations. AI has helped 81 percent of respondents increase revenue, with 45 percent realizing these benefits in less than a year after implementation.

QUOTE

"AI won't replace humans- but humans using AI will replace humans without AI."

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Karim Lakhani, PhD
Hintze Professor of Business Administration
Harvard Business School

QUOTE

"AI won't replace humans- but humans using AI will replace humans without AI."

Michael Bernstein, PhD
Professor of Computer Science
Institute for Human-Centered AI
Stanford University

QUOTE

"AI won't replace humans- but humans using AI will replace humans without AI."

Jesse Ehrenfeld, MD MPH
President, American Medical Association
Professor of Anesthesiology

Learning Objectives

Objective 1
Understand how generative AI fits into the overall **framework** of healthcare AI

Objective 2
Develop an **intuitive understanding** of how Large Language Models (LLMs) work

Objective 3
Recognize the role of **pre-training** and **post-training techniques** in optimizing foundation model behavior

Learning Objectives

Objective 1

Understand how generative AI fits into the overall **framework** of healthcare AI

Objective 2

Objective 3

Understand how LLMs are **trained** (will be important later!)

What is an LLM???

A Brief History

Epoch 1 ~1970 - Symbolic AI & Probabilistic Models

Source: Howell MD, Corrado GS, DeSalvo KB. Three Epochs of Artificial Intelligence in Health Care. JAMA. 2024;331(3):242–244. doi:10.1001/jama.2023.25057

A Brief History

Epoch 1 ~1970 - Symbolic AI & Probabilistic Models

Epoch 2 ~2010 - The Era of Deep Learning

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A Brief History

Epoch 1 ~1970 - Symbolic AI & Probabilistic Models

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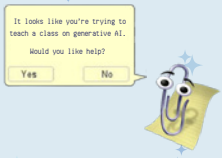
Epoch 3 ~2017 - Foundation Models & Generative AI

Source: Howell MD, Corrado GS, DeSalvo KB. Three Epochs of Artificial Intelligence in Health Care. JAMA. 2024;331(3):242–244. doi:10.1001/jama.2023.25057

Epoch 1: "rules based" AI

~1970 -

- Early Assistants



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Epoch 1: "rules based" AI

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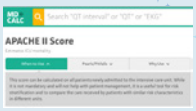
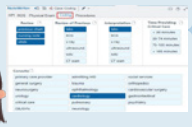
- Early Assistants
- Home / Office Software
- Most Video Game AI
- Almost all CDS (eg OPAs)
- Early Risk Scores



Epoch 1: "rules based" AI

~1970 -

- Early Assistants
- Home / Office Software
- Most Video Game AI
- Almost all CDS (eg BPAs)
- Early Risk Scores
- E/M Billing Algorithms



Heuristics of "rules-based" AI

~1970 -

Logic-based

Non-adaptive, non- "learning"

Hardcoded by experts

Rigid and task-specific

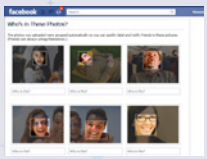
Epoch 2: "machine learning" AI

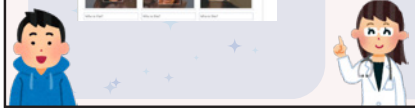
~2010 -

Epoch 2: "machine learning" AI

~2010 -

- Face Detection

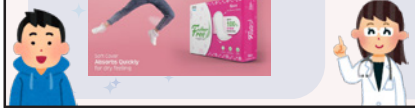




Epoch 2: "machine learning" AI

~2010 -

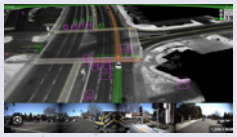
- Face Detection
- Most Ad Tech



Epoch 2: "machine learning" AI

~2010 -

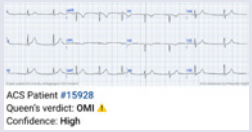
- Face Detection
- Most Ad Tech
- Self-Driving Cars



Epoch 2: "machine learning" AI

~2010 -

- Face Detection
- Most Ad Tech
- Self-Driving Cars
- ECG OMI Detection

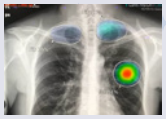


Epoch 2: "machine learning" AI
~2010 -

- Face Detection
- Most Ad Tech
- Self-Driving Cars
- ECG OMI Detection
- Deterioration models

Epoch 2: "machine learning" AI
~2010 -

- Face Detection
- Most Ad Tech
- Self-Driving Cars
- ECG OMI Detection
- Deterioration models
- Radiology automation



Heuristics of "machine learning" AI
~2010 -

"Learning by seeing"

Trained on large labeled data sets

Task-specific, not generalizable

Low interpretability

Epoch 3: "generative" AI
~2017 -

- ChatGPT

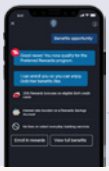
OpenAI

Epoch 3: "generative" AI
~2017 -

- ChatGPT
- AI Summary tools

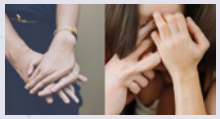
Epoch 3: "generative" AI
~2017 -

- ChatGPT
- AI Summary tools
- Customer Service bots



Epoch 3: "generative" AI
~2017 -

- ChatGPT
- AI Summary tools
- Customer Service bots
- Image generation



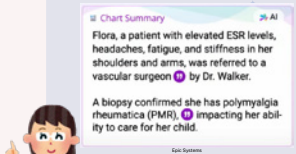
Epoch 3: "generative" AI
~2017 -

- ChatGPT
- AI Summary tools
- Customer Service bots
- Image generation
- Clinical Knowledge Tools

Epoch 3: "generative" AI

~2017 -

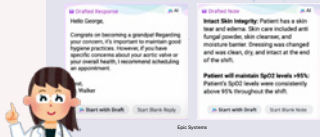
- ChatGPT
- AI Summary tools
- Customer Service bots
- Image generation
- Clinical Knowledge Tools
- Chart Summarization



Epoch 3: "generative" AI

~2017 -

- ChatGPT
- AI Summary tools
- Customer Service bots
- Image generation
- Clinical Knowledge Tools
- Chart Summarization
- Automated Note Drafting



Epoch 3: "generative" AI

~2017 -

- ChatGPT
- AI Summary tools
- Customer Service bots
- Image generation
- Clinical Knowledge Tools
- Chart Summarization
- Automated Note Drafting
- Ambient Note Generation

Heuristics of "generative" AI

~2017 -

General purpose, generative capabilities

Pre-trained on massive data

Multi-modal inputs / outputs

VERY low interpretability

Basic Questions & Tasks → Basic Facts & Actions

How long have Travis and Taylor been together?

What's the weather?

Call Mom

alexa

"According to People.com ..."

"According to Wikipedia, weather is defined as..."

"Calling Mom, mobile"

Abstract Concepts & Thoughts → Abstract Concepts & Thoughts

Help me negotiate with my Chair for more buydown.

Can machines be conscious?

Create a puzzle for my toddler using Object Permanence and Theory of Mind

Gemini

ANTHROPIC

OpenAI

Negotiating for more buydown (protected time from clinical or other duties) requires a strategic approach. Here are five tactics that can help in your conversation with your chair...

The question of whether machines can be conscious is one of the most profound and hotly debated topics in philosophy, cognitive science, and artificial intelligence. At the heart of the debate lies the problem of defining consciousness itself...

Three friends—Alice, Bob, and Carol—are playing with three distinct toys: a red ball, a blue car, and a green doll. Here's what happens:

Abstract Concepts & Thoughts → Black Box → Abstract Concepts & Thoughts

Help me negotiate with my Chair for more buydown.

Can machines be conscious?

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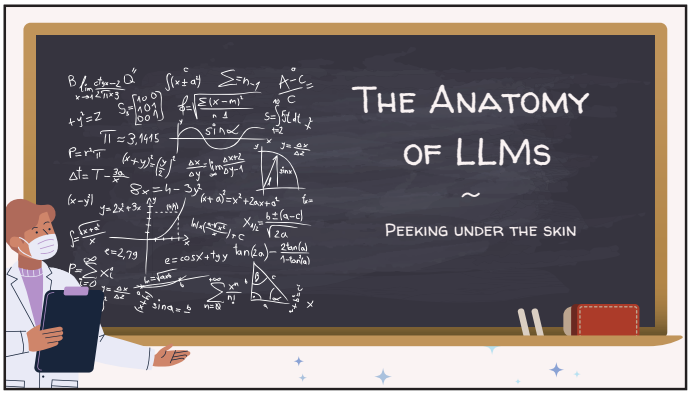
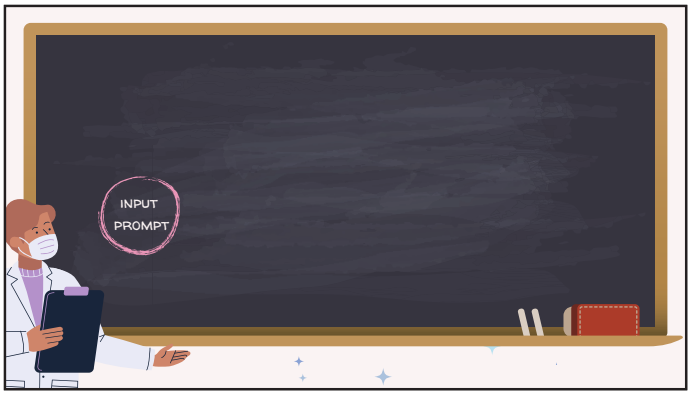
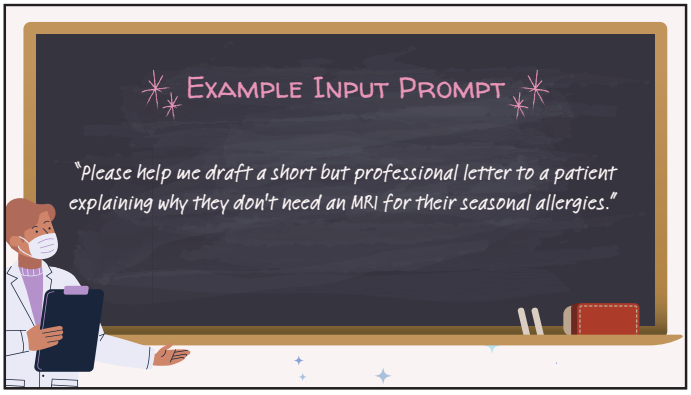
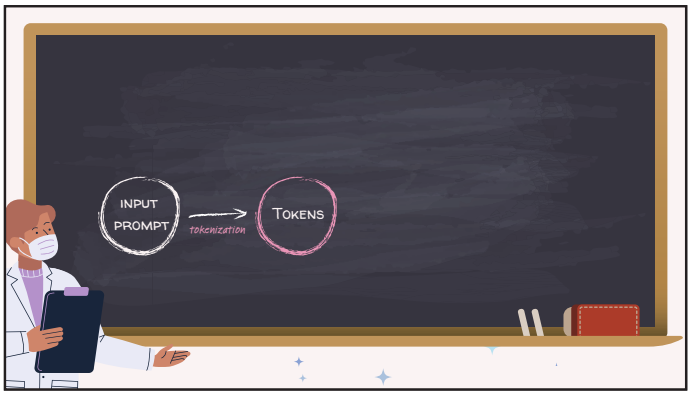
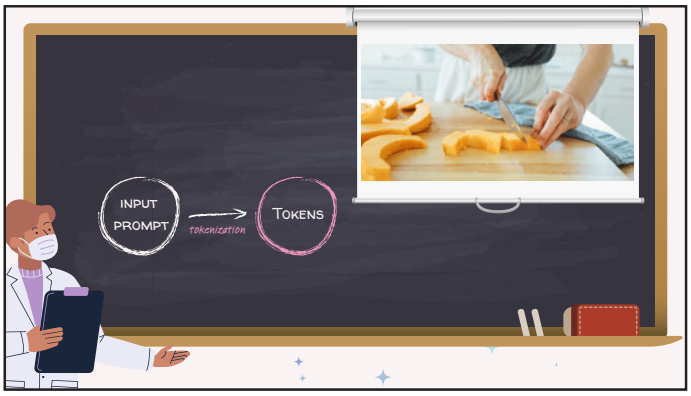
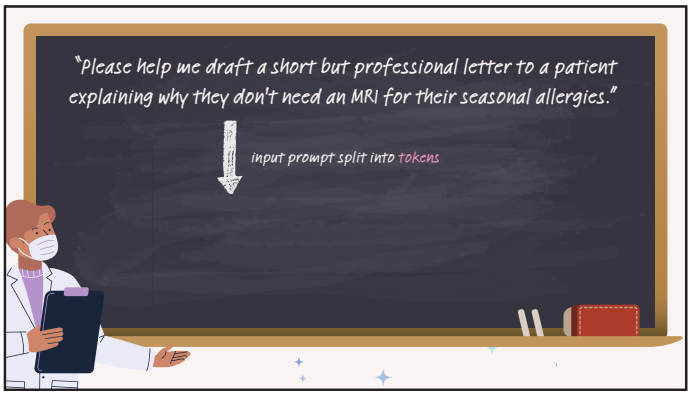


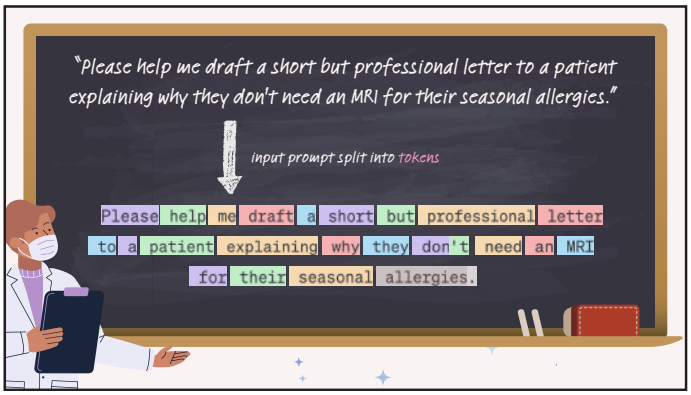

INPUT PROMPT

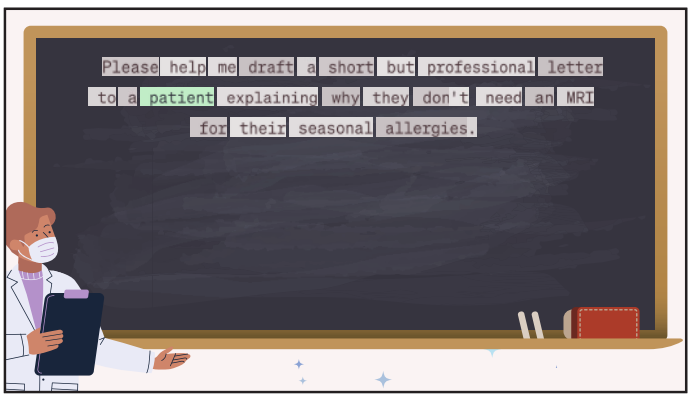

EXAMPLE INPUT PROMPT
"Please help me draft a short but professional letter to a patient explaining why they don't need an MRI for their seasonal allergies."

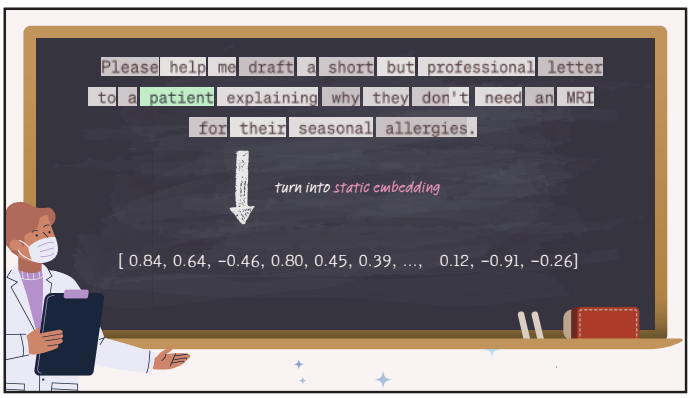

INPUT PROMPT
tokenization
TOKENS

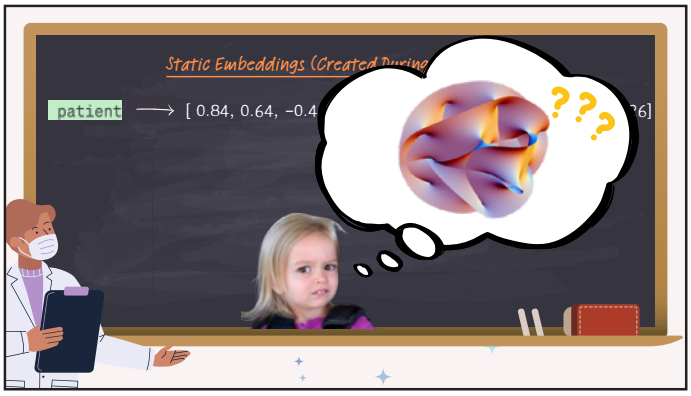

INPUT PROMPT
tokenization
TOKENS

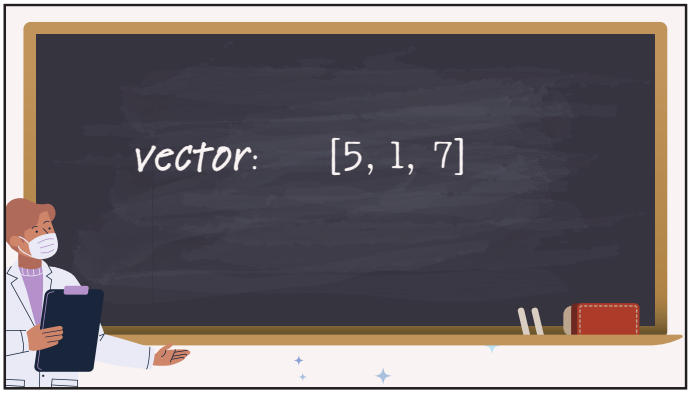

"Please help me draft a short but professional letter to a patient explaining why they don't need an MRI for their seasonal allergies."
input prompt split into tokens

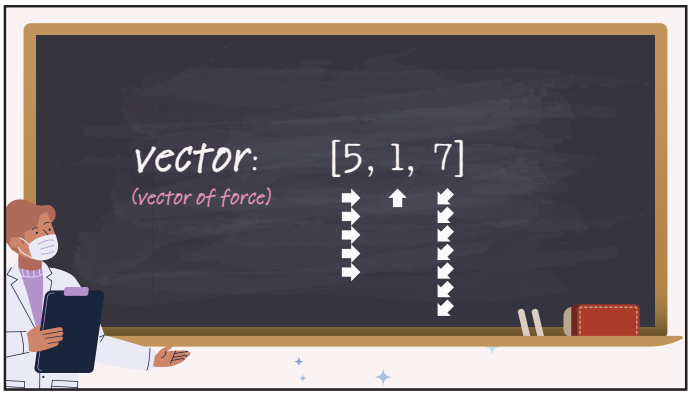

"Please help me draft a short but professional letter to a patient explaining why they don't need an MRI for their seasonal allergies."
input prompt split into tokens
Please help me draft a short but professional letter to a patient explaining why they don't need an MRI for their seasonal allergies.

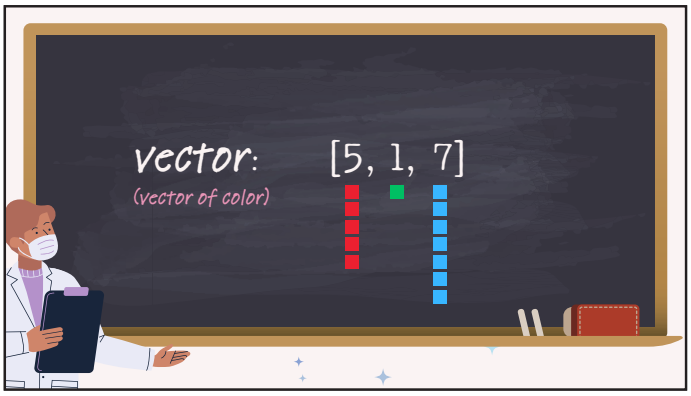

Please help me draft a short but professional letter to a patient explaining why they don't need an MRI for their seasonal allergies.


Please help me draft a short but professional letter to a patient explaining why they don't need an MRI for their seasonal allergies.
turn into static embedding
[0.84, 0.64, -0.46, 0.80, 0.45, 0.39, ..., 0.12, -0.91, -0.26]


Static Embeddings (Created During
patient
[0.84, 0.64, -0.4
26]


vector: [5, 1, 7]


vector: [5, 1, 7]
(vector of force)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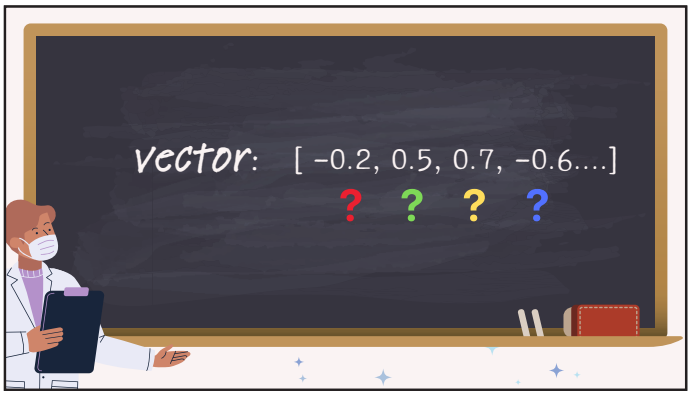
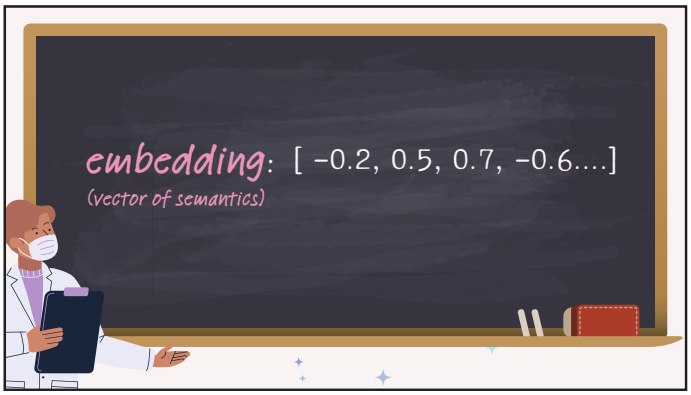
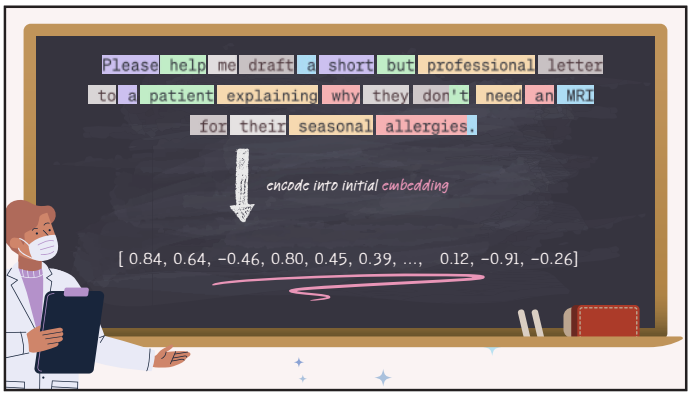
(vector of color)


vector: [-0.2, 0.5, 0.7, -0.6....]
? ? ? ?


embedding: [-0.2, 0.5, 0.7, -0.6....]
(vector of semantics)


Please help me draft a short but professional letter
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for their seasonal allergies.
encode into initial embedding
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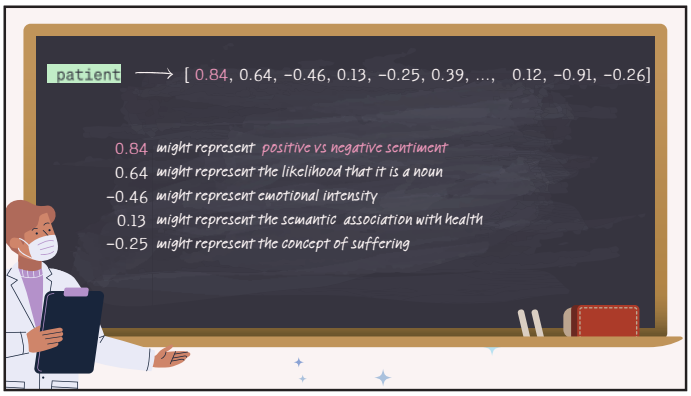
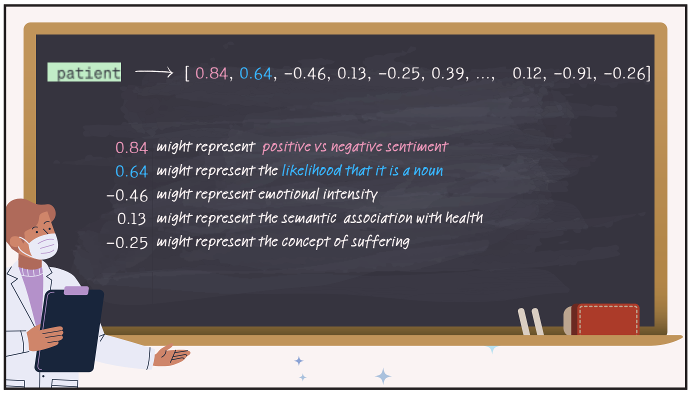

patient
[0.84, 0.64, -0.46, 0.13, -0.25, 0.39, ..., 0.12, -0.91, -0.26]
0.84 might represent positive vs negative sentiment
0.64 might represent the likelihood that it is a noun
-0.46 might represent emotional intensity
0.13 might represent the semantic association with health
-0.25 might represent the concept of suffering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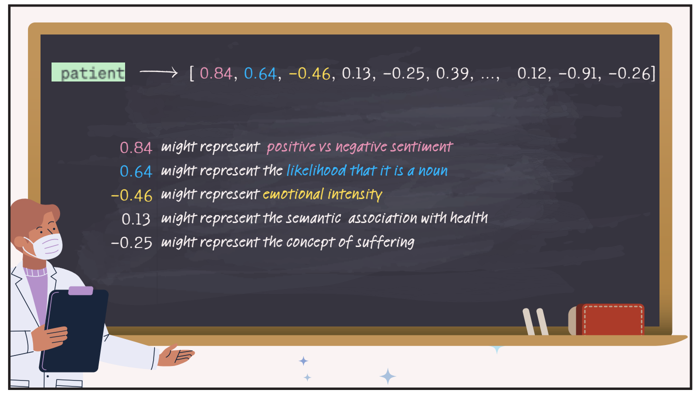
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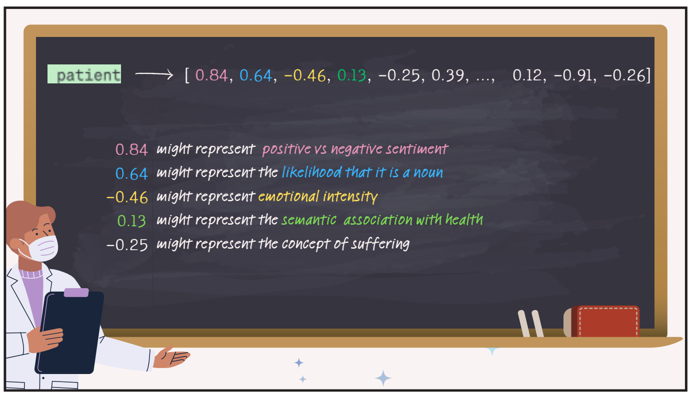
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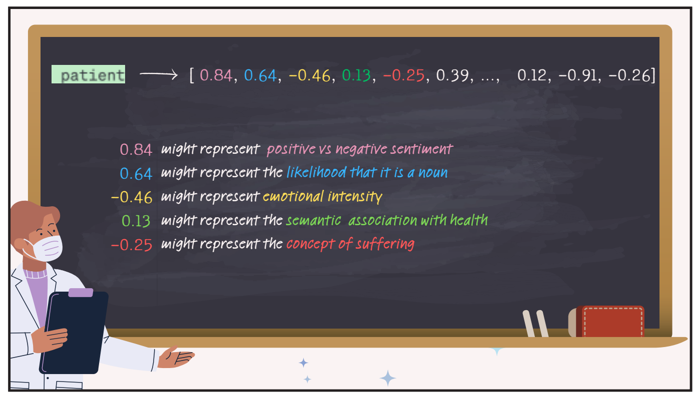
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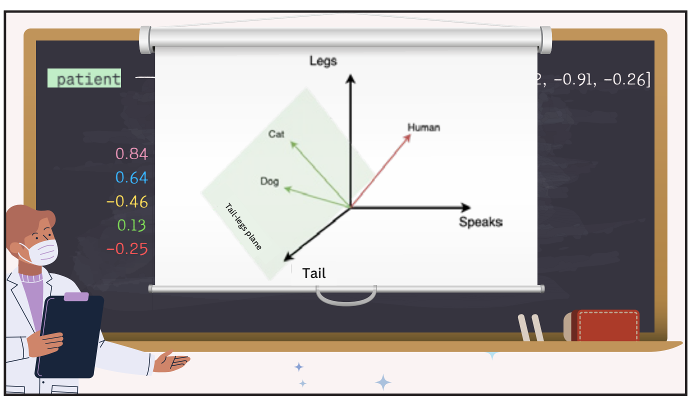
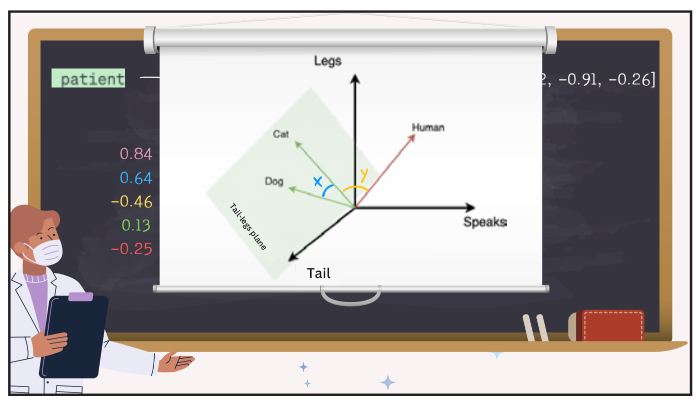

patient
, −0.91, −0.26]
0.84
0.64
−0.46
0.13
−0.25
Legs
Human
Cat
Dog
Tail-legs plane
Speaks
Tail


patient
, −0.91, −0.26]
0.84
0.64
−0.46
0.13
−0.25
Legs
Human
Cat
Dog
x
y
Tail-legs plane
Speaks
Tail


patient
[0.84, 0.64, −0.46, 0.13, −0.25, 0.39, ..., 0.12, −0.91, −0.26]
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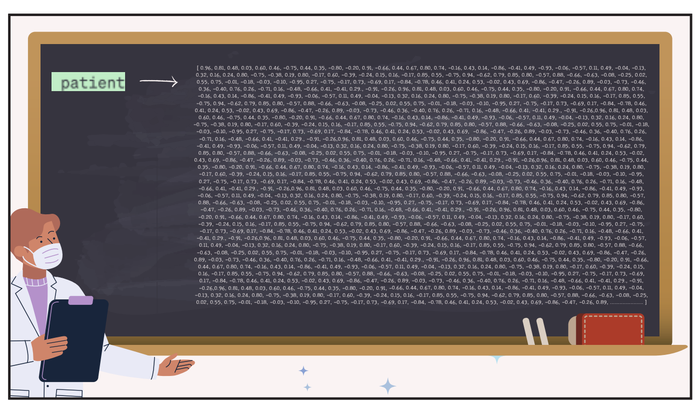
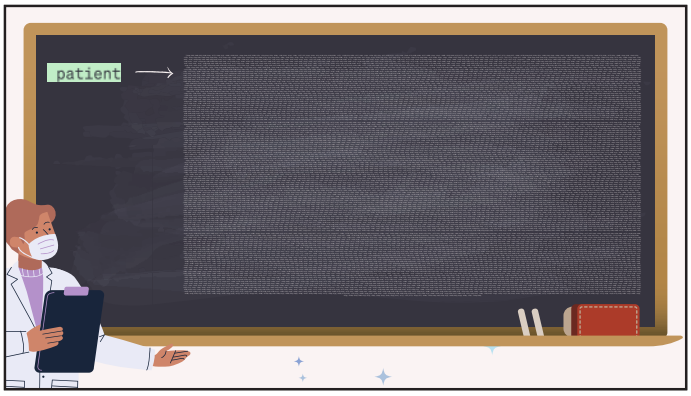
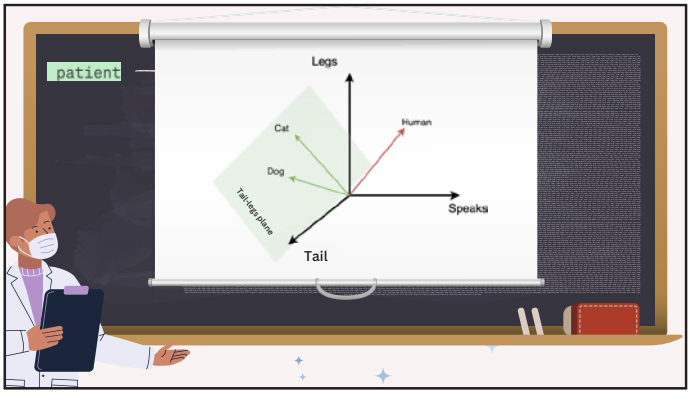
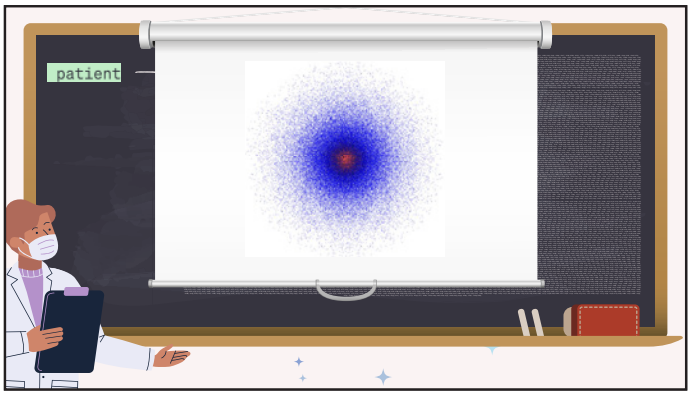
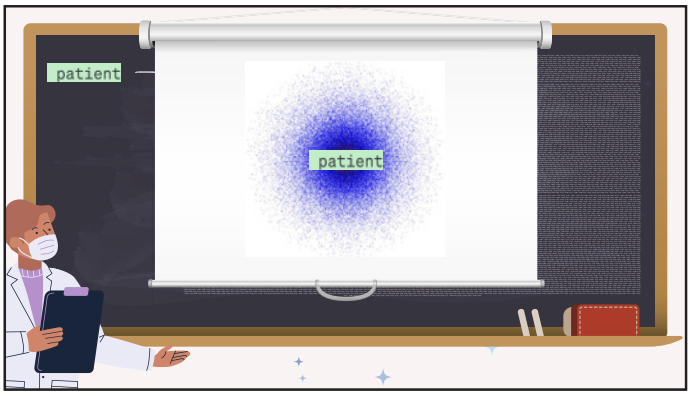
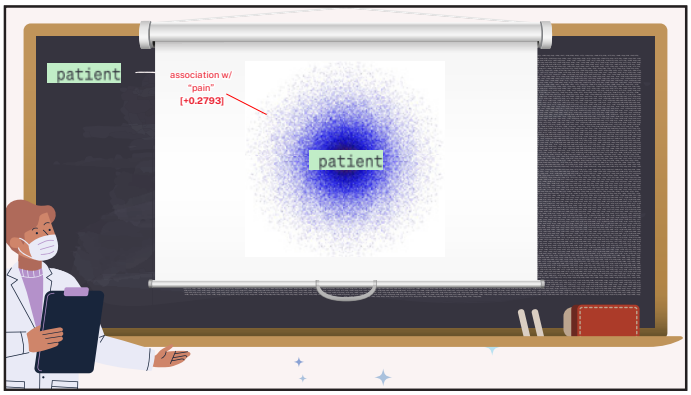

patient

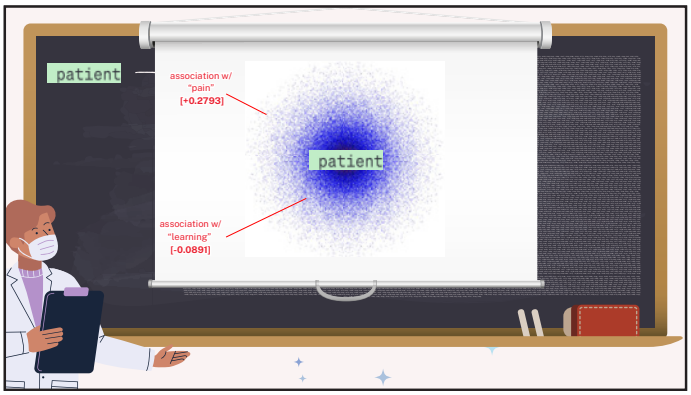

patient

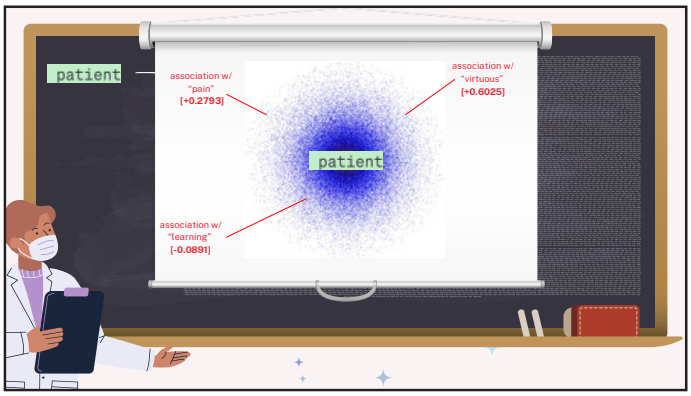

patient
Legs
Cat
Human
Dog
Speaks
Tail-legs plane
Tail

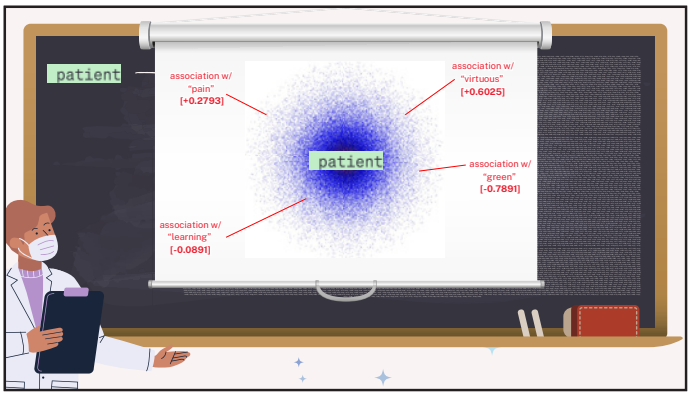

patient

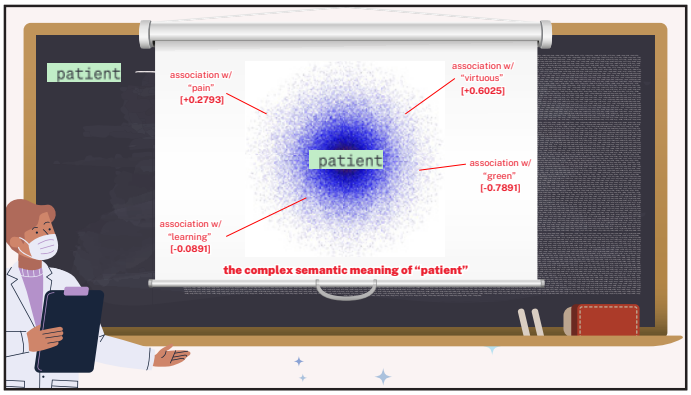

patient
patient

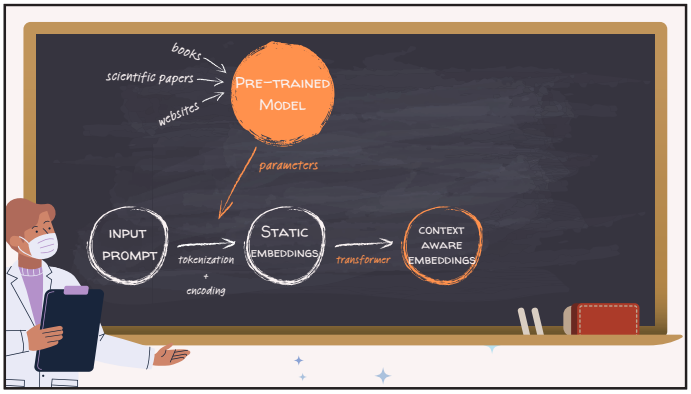

patient
association w/
"pain"
[+0.2793]
patient

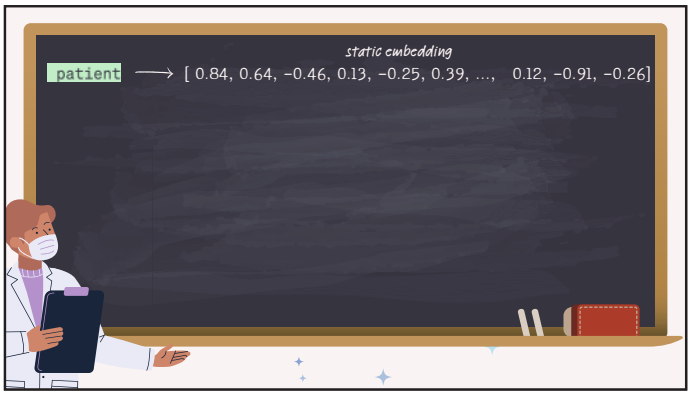

patient
association w/
"pain"
[+0.2793]
patient
association w/
"learning"
[-0.0891]

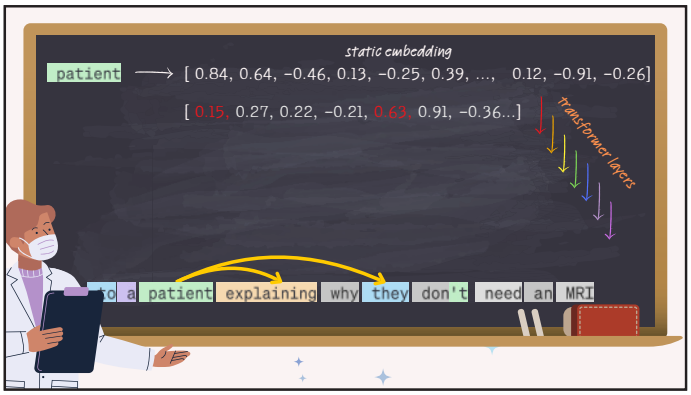

patient
association w/
"pain"
[+0.2793]
association w/
"virtuous"
[+0.6025]
patient
association w/
"learning"
[-0.0891]

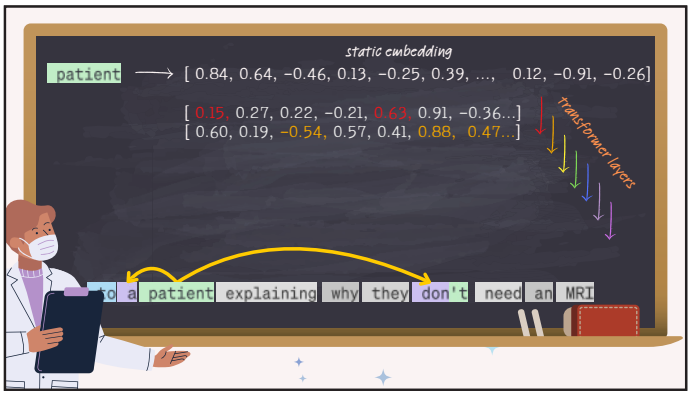

patient
association w/
"pain"
[+0.2793]
association w/
"virtuous"
[+0.6025]
patient
association w/
"green"
[-0.7891]
association w/
"learning"
[-0.0891]

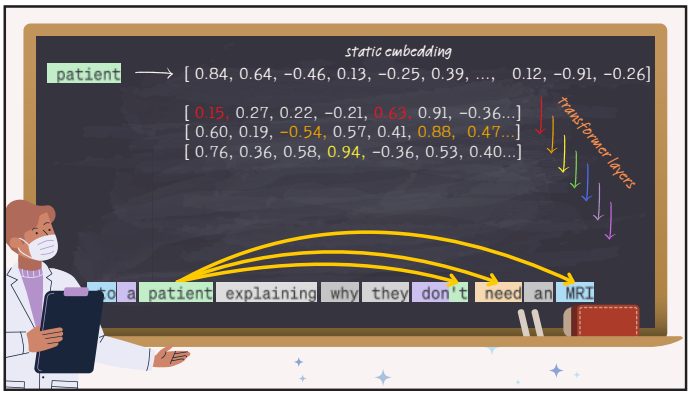

patient
association w/ "pain" [+0.2793]
association w/ "virtuous" [+0.6025]
patient
association w/ "green" [-0.7891]
association w/ "learning" [-0.0891]
the complex semantic meaning of "patient"

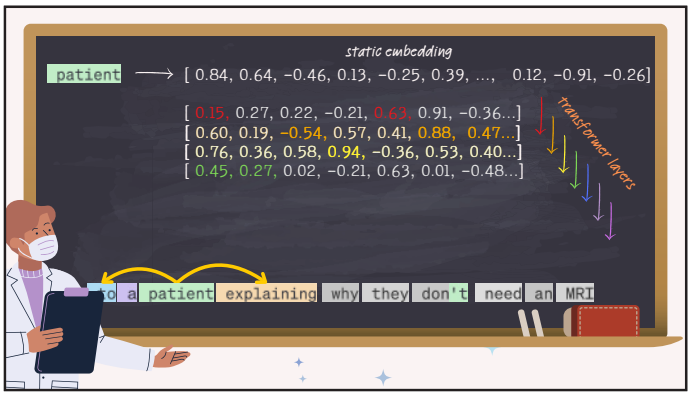

books
scientific papers
websites
PRE-TRAINED MODEL
parameters
INPUT PROMPT
tokenization + encoding
STATIC EMBEDDINGS
transformer
CONTEXT AWARE EMBEDDINGS

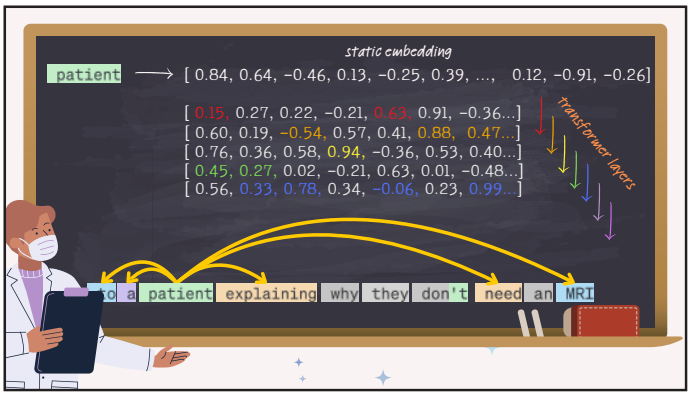

static embedding
patient ⟶ [0.84, 0.64, −0.46, 0.13, −0.25, 0.39, ..., 0.12, −0.91, −0.26]

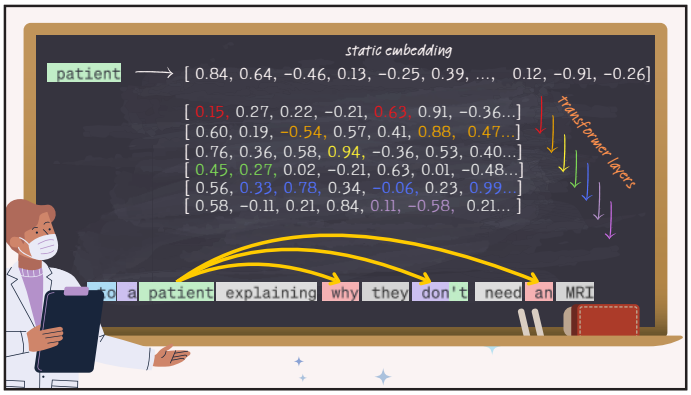

static embedding
patient ⟶ [0.84, 0.64, −0.46, 0.13, −0.25, 0.39, ..., 0.12, −0.91, −0.26]
[0.15, 0.27, 0.22, −0.21, 0.63, 0.91, −0.36...]
transformer layers
to a patient explaining why they don't need an MRI

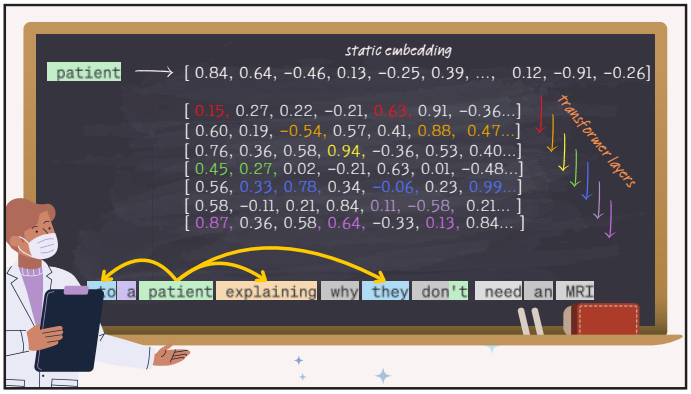

static embedding
patient ⟶ [0.84, 0.64, −0.46, 0.13, −0.25, 0.39, ..., 0.12, −0.91, −0.26]
[0.15, 0.27, 0.22, −0.21, 0.63, 0.91, −0.36...]
[0.60, 0.19, −0.54, 0.57, 0.41, 0.88, 0.47...]
transformer layers
to a patient explaining why they don't need an MRI

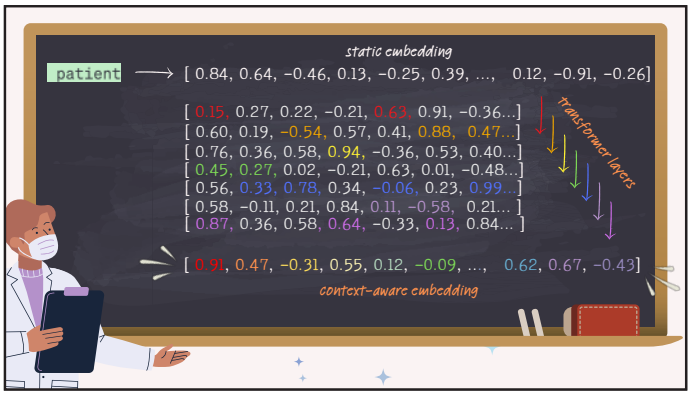

static embedding
patient ⟶ [0.84, 0.64, −0.46, 0.13, −0.25, 0.39, ..., 0.12, −0.91, −0.26]
[0.15, 0.27, 0.22, −0.21, 0.63, 0.91, −0.36...]
[0.60, 0.19, −0.54, 0.57, 0.41, 0.88, 0.47...]
[0.76, 0.36, 0.58, 0.94, −0.36, 0.53, 0.40...]
transformer layers
to a patient explaining why they don't need an MRI

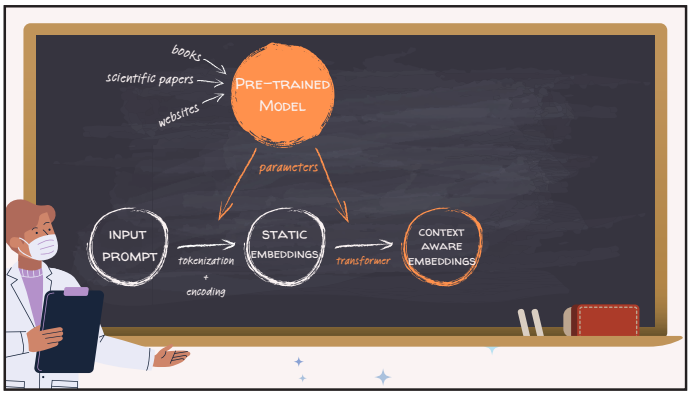

static embedding
patient ⟶ [0.84, 0.64, −0.46, 0.13, −0.25, 0.39, ..., 0.12, −0.91, −0.26]
[0.15, 0.27, 0.22, −0.21, 0.63, 0.91, −0.36...]
[0.60, 0.19, −0.54, 0.57, 0.41, 0.88, 0.47...]
[0.76, 0.36, 0.58, 0.94, −0.36, 0.53, 0.40...]
[0.45, 0.27, 0.02, −0.21, 0.63, 0.01, −0.48...]
transformer layers
to a patient explaining why they don't need an MRI

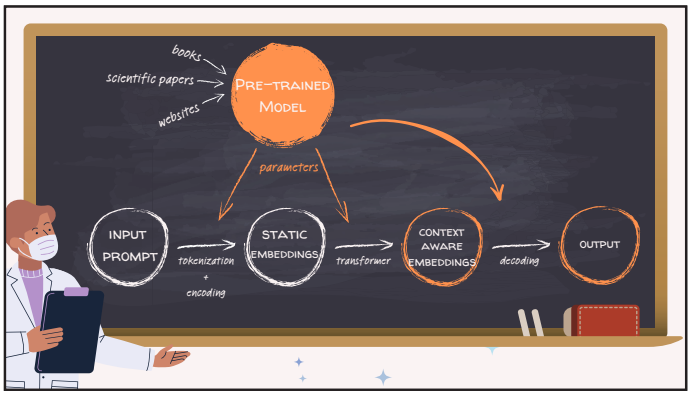

static embedding
patient ⟶ [0.84, 0.64, −0.46, 0.13, −0.25, 0.39, ..., 0.12, −0.91, −0.26]
[0.15, 0.27, 0.22, −0.21, 0.63, 0.91, −0.36...]
[0.60, 0.19, −0.54, 0.57, 0.41, 0.88, 0.47...]
[0.76, 0.36, 0.58, 0.94, −0.36, 0.53, 0.40...]
[0.45, 0.27, 0.02, −0.21, 0.63, 0.01, −0.48...]
[0.56, 0.33, 0.78, 0.34, −0.06, 0.23, 0.99...]
transformer layers
to a patient explaining why they don't need an MRI

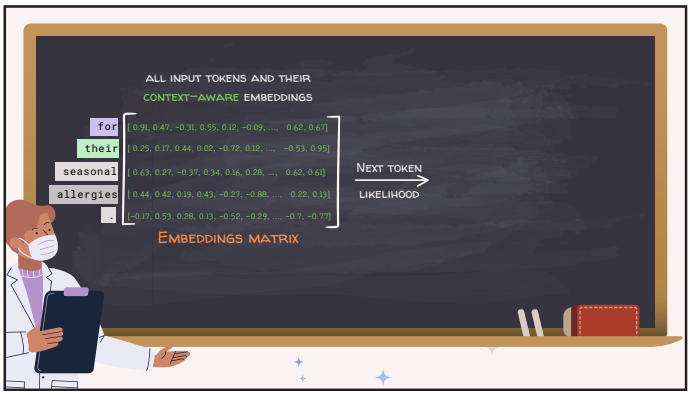

static embedding
patient
[0.84, 0.64, −0.46, 0.13, −0.25, 0.39, ..., 0.12, −0.91, −0.26]
[0.15, 0.27, 0.22, −0.21, 0.63, 0.91, −0.36...]
[0.60, 0.19, −0.54, 0.57, 0.41, 0.88, 0.47...]
[0.76, 0.36, 0.58, 0.94, −0.36, 0.53, 0.40...]
[0.45, 0.27, 0.02, −0.21, 0.63, 0.01, −0.48...]
[0.56, 0.33, 0.78, 0.34, −0.06, 0.23, 0.99...]
[0.58, −0.11, 0.21, 0.84, 0.11, −0.58, 0.21...]
transformer layers
to a patient explaining why they don't need an MRI

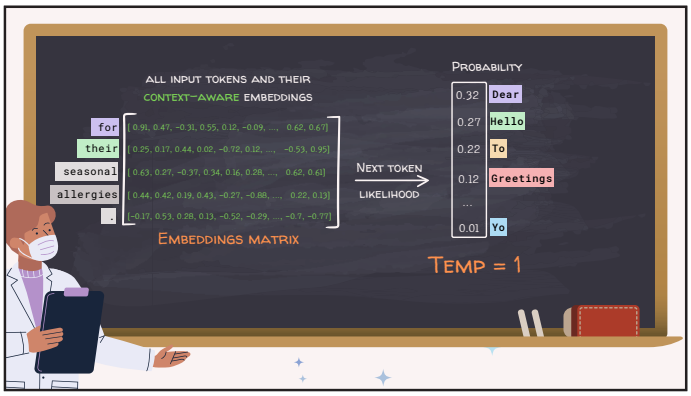

static embedding
patient
[0.84, 0.64, −0.46, 0.13, −0.25, 0.39, ..., 0.12, −0.91, −0.26]
[0.15, 0.27, 0.22, −0.21, 0.63, 0.91, −0.36...]
[0.60, 0.19, −0.54, 0.57, 0.41, 0.88, 0.47...]
[0.76, 0.36, 0.58, 0.94, −0.36, 0.53, 0.40...]
[0.45, 0.27, 0.02, −0.21, 0.63, 0.01, −0.48...]
[0.56, 0.33, 0.78, 0.34, −0.06, 0.23, 0.99...]
[0.58, −0.11, 0.21, 0.84, 0.11, −0.58, 0.21...]
[0.87, 0.36, 0.58, 0.64, −0.33, 0.13, 0.84...]
transformer layers
to a patient explaining why they don't need an MRI

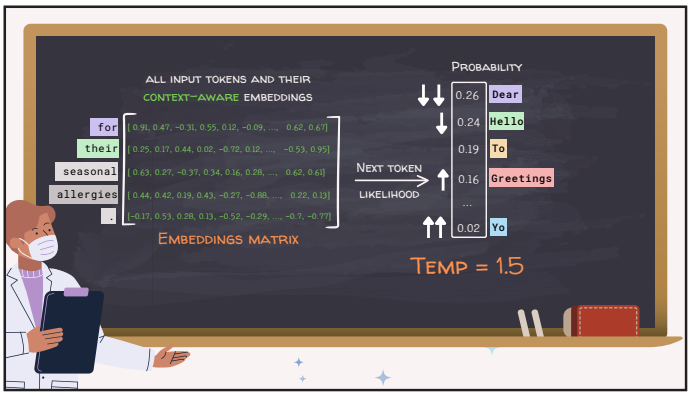

static embedding
patient
[0.84, 0.64, −0.46, 0.13, −0.25, 0.39, ..., 0.12, −0.91, −0.26]
[0.15, 0.27, 0.22, −0.21, 0.63, 0.91, −0.36...]
[0.60, 0.19, −0.54, 0.57, 0.41, 0.88, 0.47...]
[0.76, 0.36, 0.58, 0.94, −0.36, 0.53, 0.40...]
[0.45, 0.27, 0.02, −0.21, 0.63, 0.01, −0.48...]
[0.56, 0.33, 0.78, 0.34, −0.06, 0.23, 0.99...]
[0.58, −0.11, 0.21, 0.84, 0.11, −0.58, 0.21...]
[0.87, 0.36, 0.58, 0.64, −0.33, 0.13, 0.84...]
transformer layers
[0.91, 0.47, −0.31, 0.55, 0.12, −0.09, ..., 0.62, 0.67, −0.43]
context-aware embedding

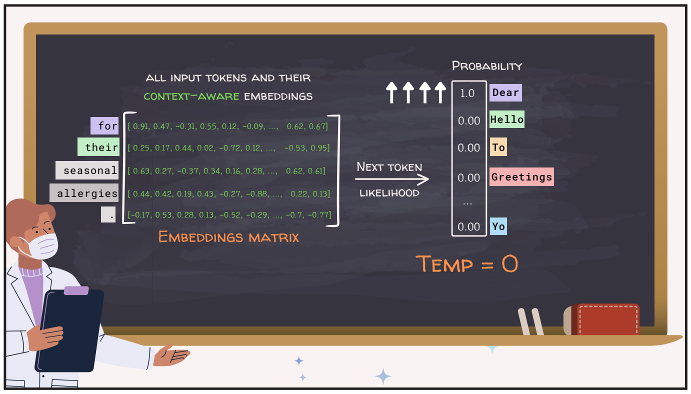

books
scientific papers
websites
Pre-trained Model
parameters
INPUT PROMPT
tokenization + encoding
STATIC EMBEDDINGS
transformer
CONTEXT AWARE EMBEDDINGS

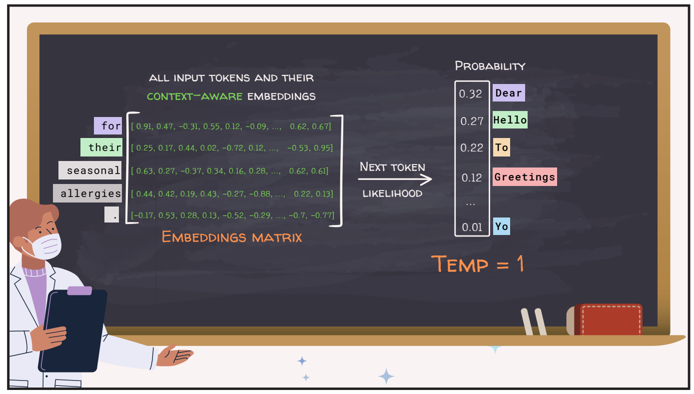

books
scientific papers
websites
Pre-trained Model
parameters
INPUT PROMPT
tokenization + encoding
STATIC EMBEDDINGS
transformer
CONTEXT AWARE EMBEDDINGS
decoding
OUTPUT

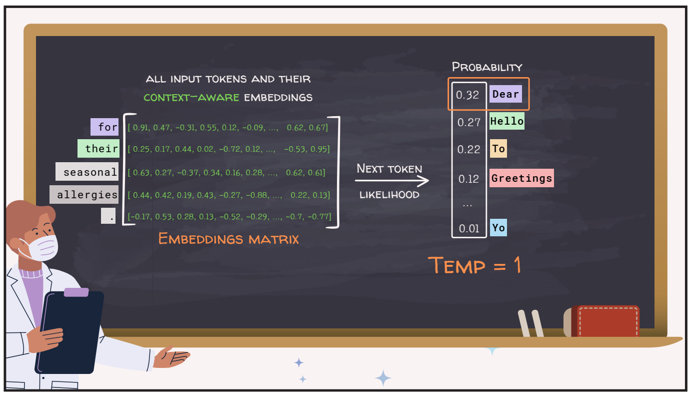

ALL INPUT TOKENS AND THEIR CONTEXT-AWARE EMBEDDINGS
for
their
seasonal
allergies
.
EMBEDDINGS MATRIX
NEXT TOKEN LIKELIHOOD

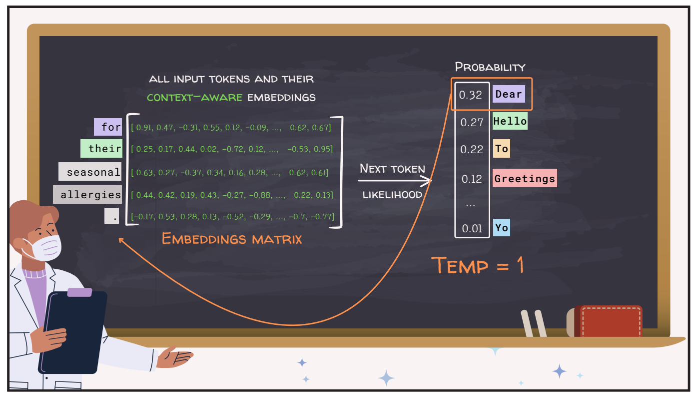

ALL INPUT TOKENS AND THEIR CONTEXT-AWARE EMBEDDINGS
for
their
seasonal
allergies
.
EMBEDDINGS MATRIX
NEXT TOKEN LIKELIHOOD
PROBABILITY
0.32 Dear
0.27 Hello
0.22 To
0.12 Greetings
0.01 Yo
TEMP = 1


ALL INPUT TOKENS AND THEIR CONTEXT-AWARE EMBEDDINGS
for
their
seasonal
allergies
.
EMBEDDINGS MATRIX
NEXT TOKEN LIKELIHOOD
PROBABILITY
0.26 Dear
0.24 Hello
0.19 To
0.16 Greetings
0.02 Yo
TEMP = 1.5


All input tokens and their
context-aware embeddings
for
their
seasonal
allergies
.
Embeddings matrix
Next token
likelihood
Probability
1.0 Dear
0.00 Hello
0.00 To
0.00 Greetings
...
0.00 Yo
Temp = 0

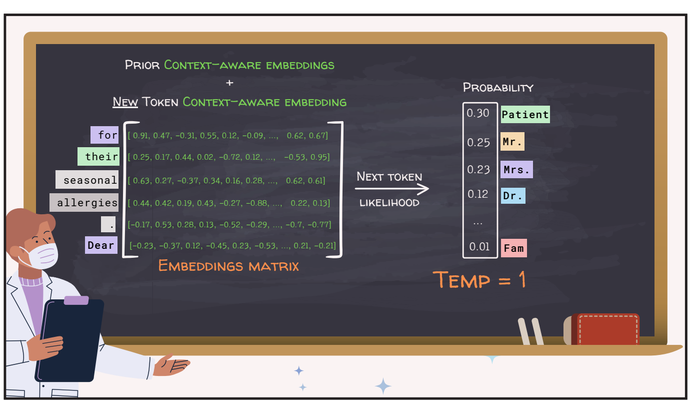

All input tokens and their
context-aware embeddings
for
their
seasonal
allergies
.
Embeddings matrix
Next token
likelihood
Probability
0.32 Dear
0.27 Hello
0.22 To
0.12 Greetings
...
0.01 Yo
Temp = 1

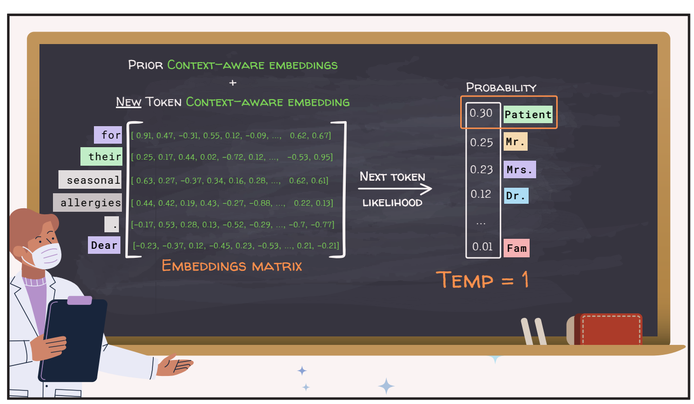

All input tokens and their
context-aware embeddings
for
their
seasonal
allergies
.
Embeddings matrix
Next token
likelihood
Probability
0.32 Dear
0.27 Hello
0.22 To
0.12 Greetings
...
0.01 Yo
Temp = 1

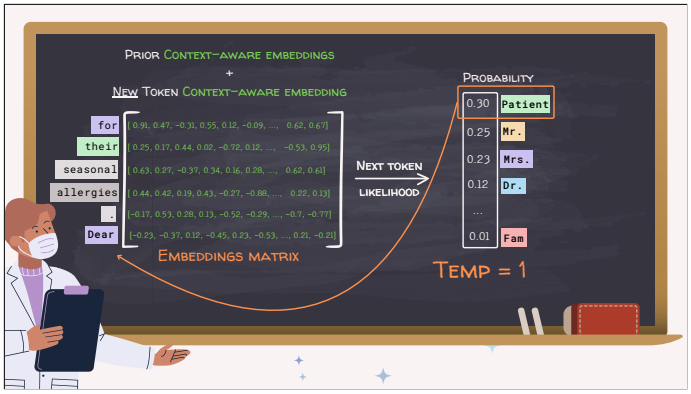

All input tokens and their
context-aware embeddings
for
their
seasonal
allergies
.
Embeddings matrix
Next token
likelihood
Probability
0.32 Dear
0.27 Hello
0.22 To
0.12 Greetings
...
0.01 Yo
Temp = 1


Prior context-aware embeddings
+
New token static embedding
for
their
seasonal
allergies
.
Dear
Embeddings matrix


Prior context-aware embeddings
+
New token context-aware embedding
for
their
seasonal
allergies
.
Dear
Embeddings matrix
Next token
likelihood

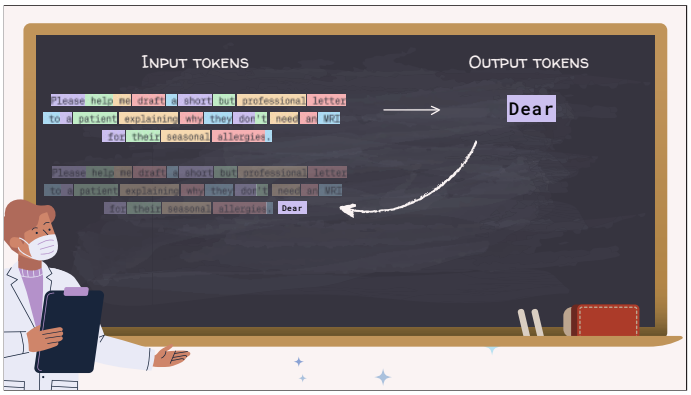

Prior context-aware embeddings
+
New token context-aware embedding
for
their
seasonal
allergies
.
Dear
Embeddings matrix
Next token
likelihood
Probability
0.30 Patient
0.25 Mr.
0.23 Mrs.
0.12 Dr.
...
0.01 Fam
Temp = 1

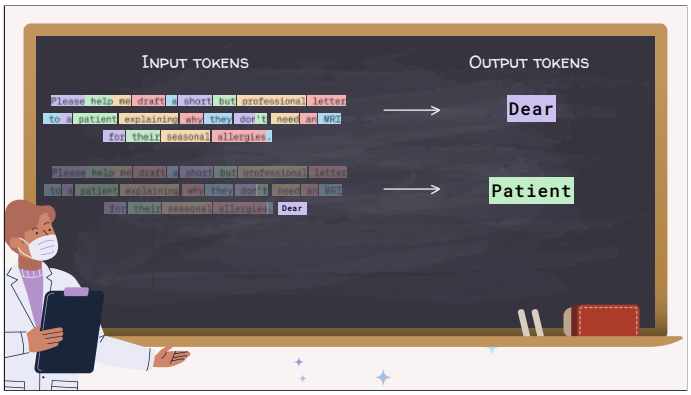

Prior context-aware embeddings
+
New token context-aware embedding
for
their
seasonal
allergies
.
Dear
Embeddings matrix
Next token
likelihood
Probability
0.30 Patient
0.25 Mr.
0.23 Mrs.
0.12 Dr.
...
0.01 Fam
Temp = 1

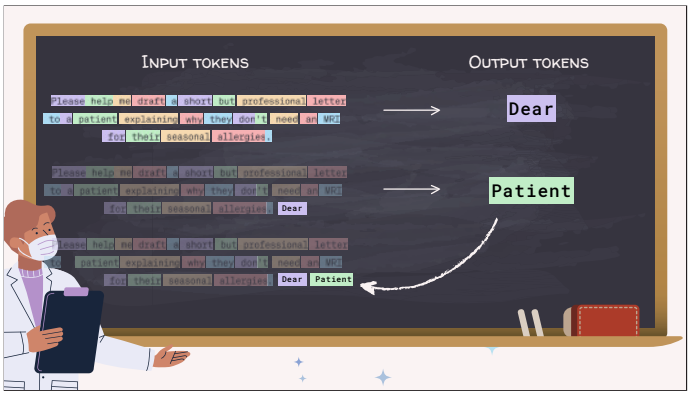

Prior Context-aware embeddings
+
New Token Context-aware embedding
for
their
seasonal
allergies
.
Dear
Embeddings matrix
Next token
likelihood
Probability
0.30
Patient
0.25
Mr.
0.23
Mrs.
0.12
Dr.
...
0.01
Fam
Temp = 1

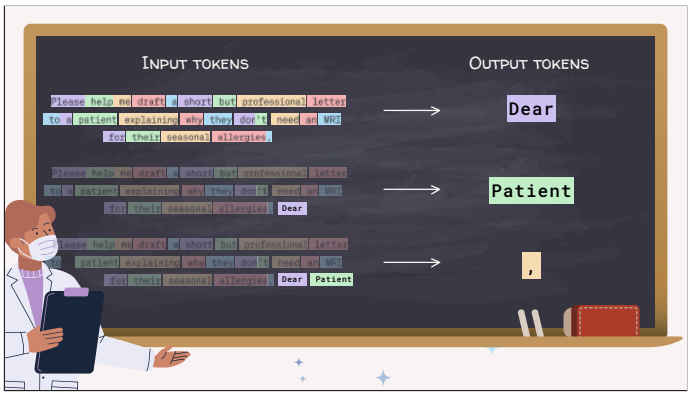

Input tokens
Output tokens

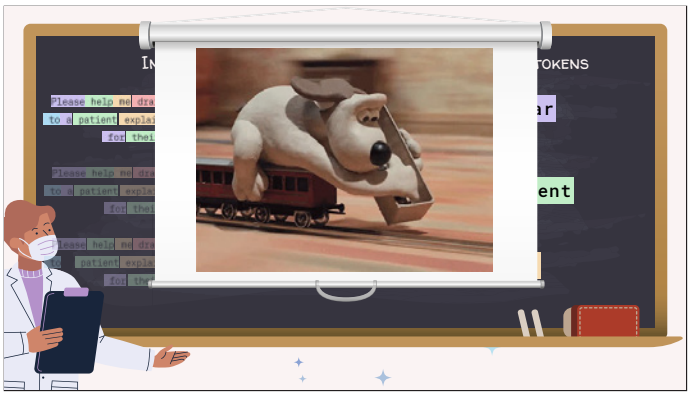

Input tokens
Output tokens
Dear

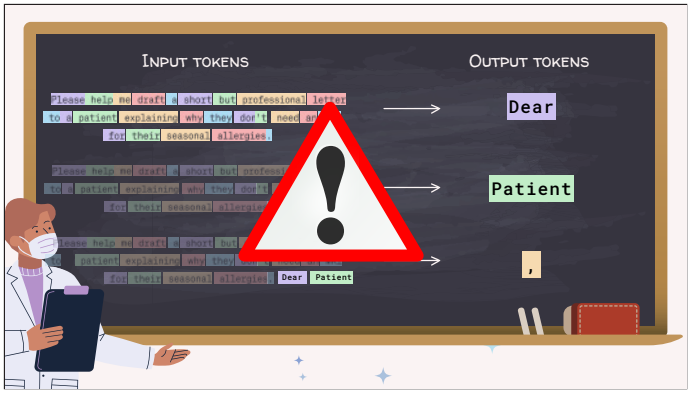

Input tokens
Output tokens
Dear

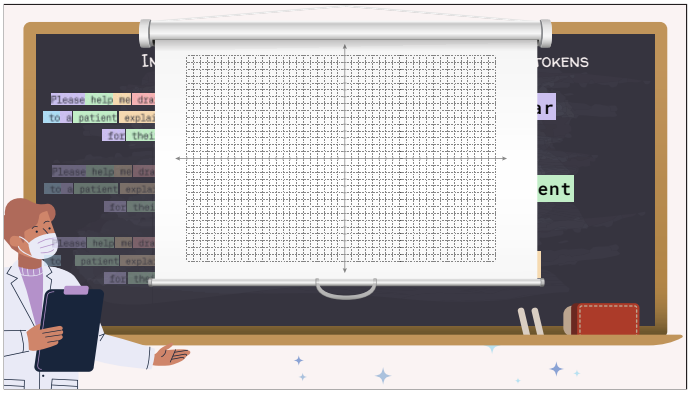

Input tokens
Output tokens
Dear
Patient

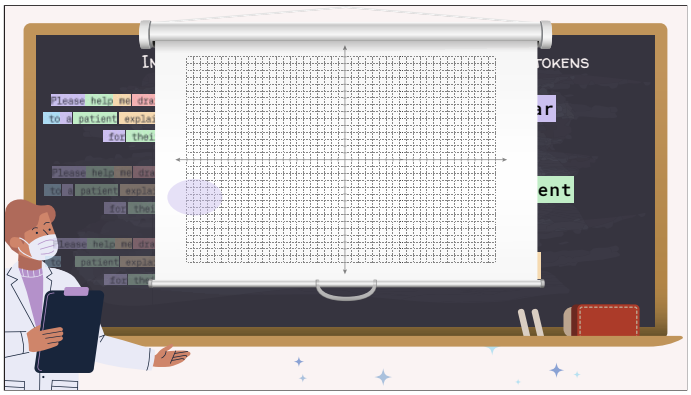

Input tokens
Output tokens
Dear
Patient

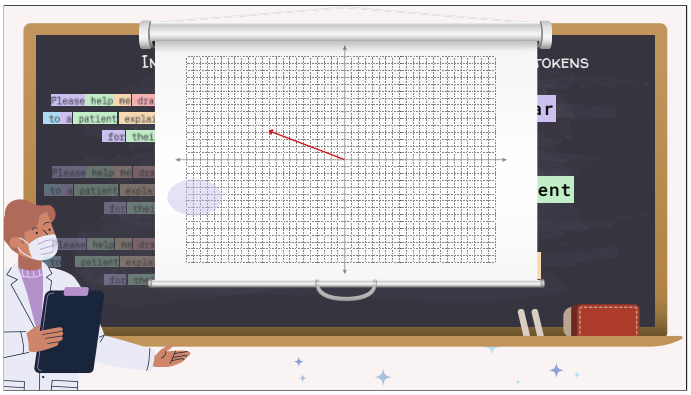

Input tokens
Output tokens
Dear
Patient
,

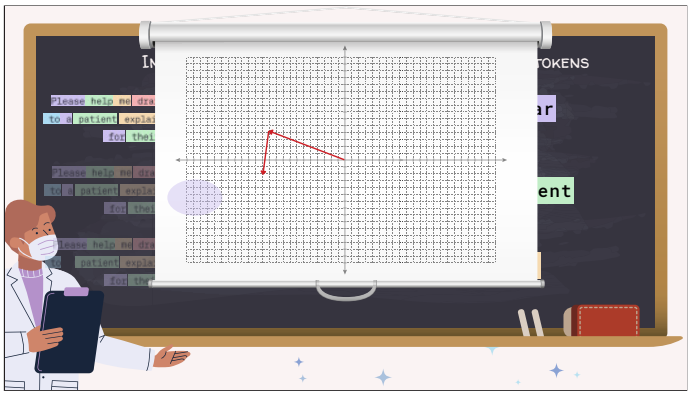

Input tokens
Output tokens

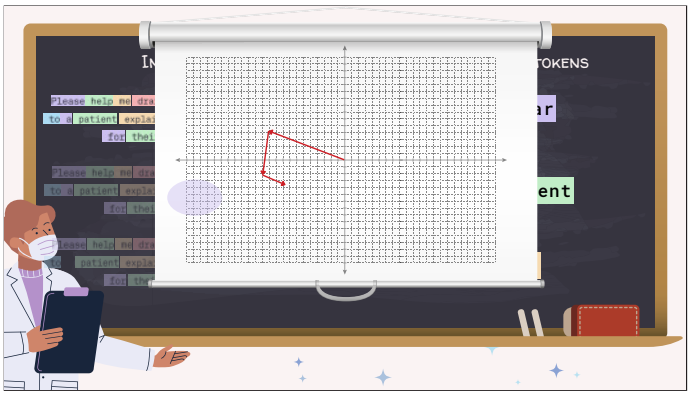

Input tokens
Output tokens
Dear
Patient
,

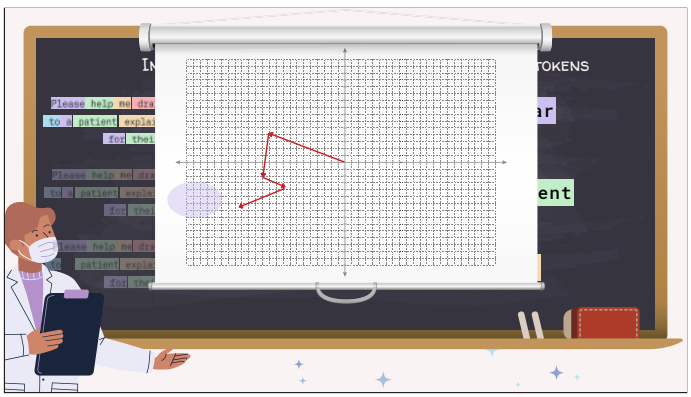


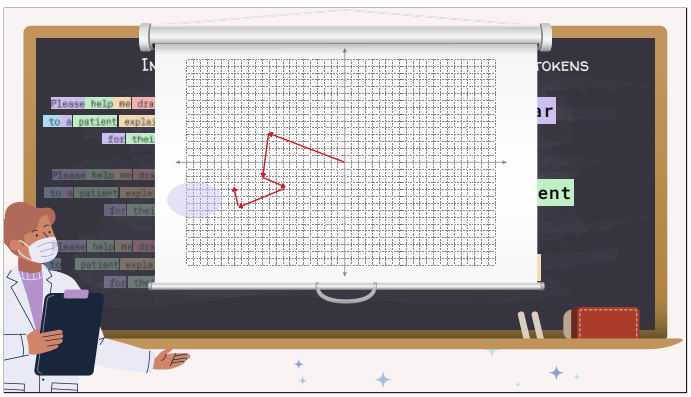


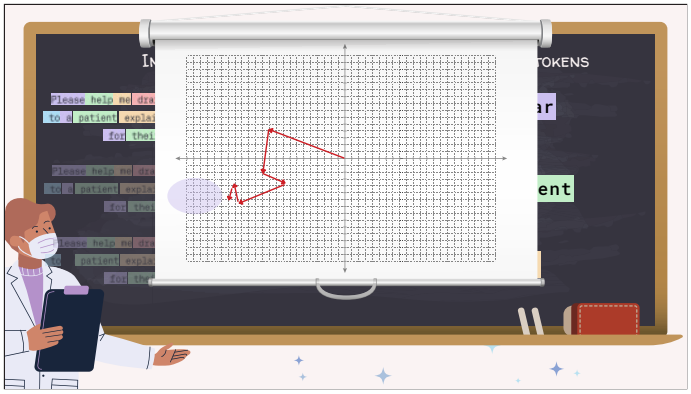


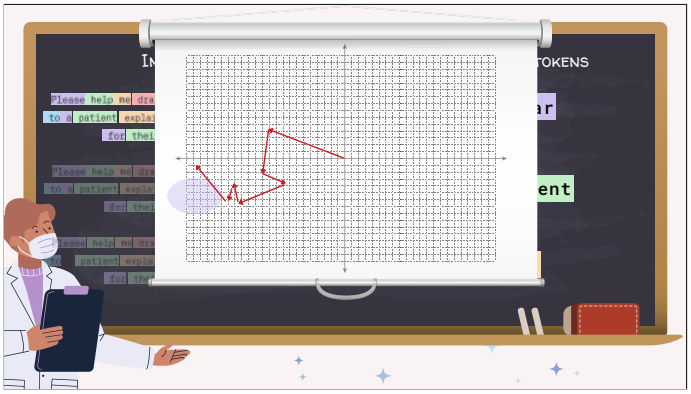


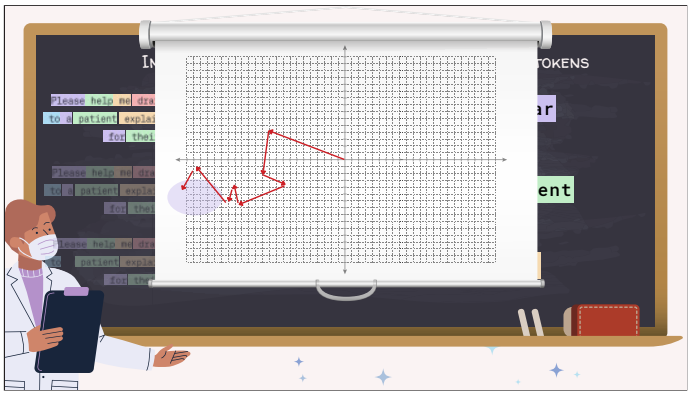


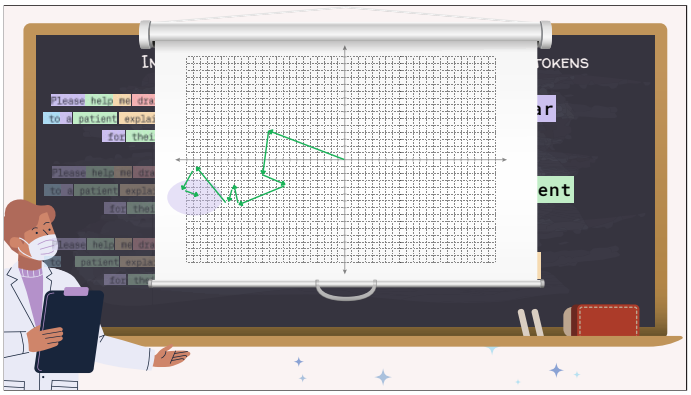


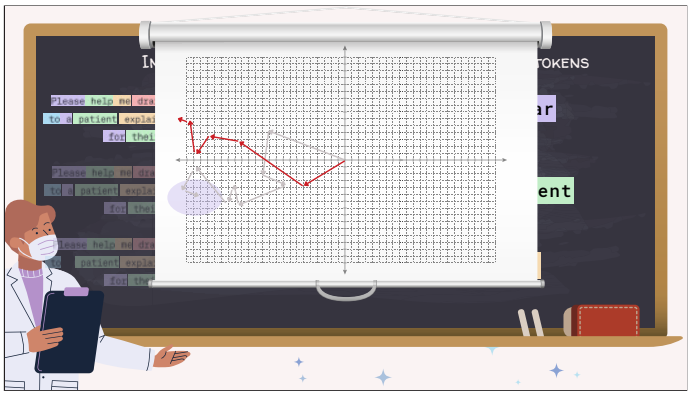


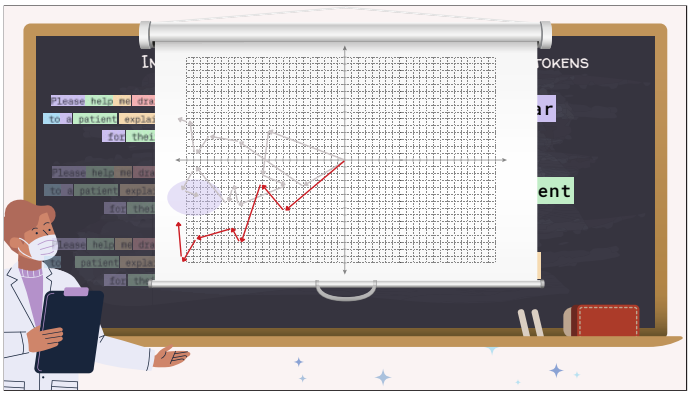


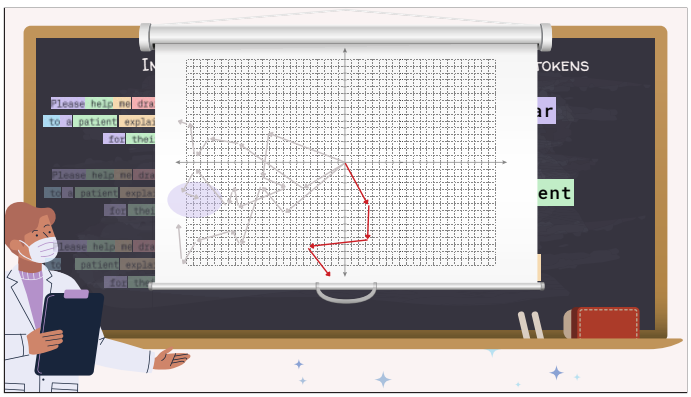













LLM Training:
How LLMs Evolved

Transformer Architecture Invented (June 2017)


Attention Is All You Need

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Noam Shazeer* Google Brain noam@google.com
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Llion Jones* Google Research llion@google.com
Aidan N. Gomez* † University of Toronto aidan@cs.toronto.edu
Lukasz Kaiser* Google Brain lukaszkaiser@google.com
Illia Polosukhin* † illia.polosukhin@gmail.com

Google Research

GPT-1 (June 2018)

# of Parameters: 117 million

Training Data: BooksCorpus (>7,000 unique books = 4.6GB of text)

Compute: ~1 petaflop/s-days (~30 days using 8 NVIDIA P600 GPUs)

OpenAI

Radford et al. Improving Language Understanding by Generative Pre-Training . 2018.

Pre-Training

60yoF with h/o ESRD on HD admitted for

Input Context

pineapple

Predicted Next Token

hyperkalemia

Actual Next Token

Stanford CS224N: Natural Language Processing with Deep Learning

Pre-Training

60yoF with h/o ESRD on HD admitted for

Input Context

pineapple

Predicted Next Token

$a - b$

hyperkalemia

Actual Next Token

calculates the difference ("loss")

Stanford CS224N: Natural Language Processing with Deep Learning

Pre-Training

60yoF with h/o ESRD on HD admitted for

Input Context

pineapple

Predicted Next Token

$a - b$

hyperkalemia

Actual Next Token

calculates how to adjust parameters to minimize this "loss" via "backpropagation"

Stanford CS224N: Natural Language Processing with Deep Learning

Pre-Training

60yoF with h/o ESRD on HD admitted for

Input Context

pineapple

Predicted Next Token

$a - b$

hyperkalemia

Actual Next Token

adjusts parameters to reflect these calculations ("gradient update")

Stanford CS224N: Natural Language Processing with Deep Learning

Pre-Training

60yoF with h/o ESRD on HD admitted for

Input Context

pineapple

Predicted Next Token

$a - b$

hyperkalemia

Actual Next Token

"Gradient Descent"

Stanford CS224N: Natural Language Processing with Deep Learning

"Which antibiotics are first-line for treating inpatient Community Acquired Pneumonia (assuming no risk factors)?"

GPT-1

> Which antibiotics are first-line for treating inpatient Community Acquired Pneumonia (assuming no risk factors)?

GPT-1

" i do n't know , " the woman said , " but i 'll ask . "
" good . now , what else do you know about this plague ? "

GPT-2 (Feb 2019)

# of Parameters: ~~117 million~~ 1.5 billion 13X

Training Data: ~~4 GB of books~~ 40 GB of internet text data 10X

Compute: ~~1~~ ~600 petaflop/s-days (~30 days using 256 Google TPU v3s) ?600X

Radford et al. Language Models are Unsupervised Multitask Learners . 2019.

> Which antibiotics are first-line for treating inpatient Community Acquired Pneumonia (assuming no risk factors)?

GPT-2

> Which antibiotics are first-line for treating inpatient Community Acquired Pneumonia (assuming no risk factors)?

GPT-2

What are the first line antibiotics used to treat Community Acquired Pneumonia (assume no risk factors)?

What are the first line antibiotics used to treat MS?

What are the first line antibiotics used to treat C. difficile?

LLM Scaling Laws Defined (Jan 2020)

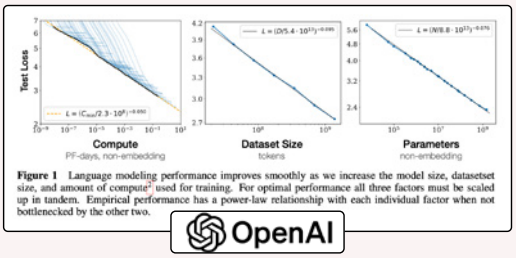

Figure 1 Language modeling performance improves smoothly as we increase the model size, datasetset size, and amount of compute[2] used for training. For optimal performance all three factors must be scaled up in tandem. Empirical performance has a power-law relationship with each individual factor when not bottlenecked by the other two.

OpenAI

Kaplan et al. Scaling Laws for Neural Language Models. 2020.

LLM Scaling Laws Defined (Jan 2020)

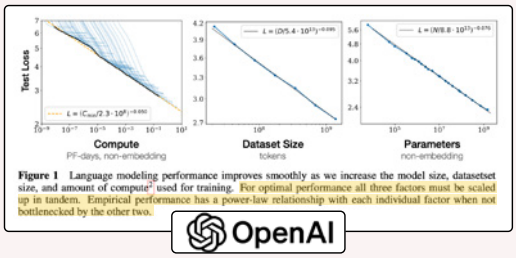

Figure 1 Language modeling performance improves smoothly as we increase the model size, datasetset size, and amount of compute[2] used for training. For optimal performance all three factors must be scaled up in tandem. Empirical performance has a power-law relationship with each individual factor when not bottlenecked by the other two.

OpenAI

Kaplan et al. Scaling Laws for Neural Language Models. 2020.

GPT-3 (June 2020)

# of Parameters: ~~1.5 billion~~ 175 billion 116X

Training Data: ~~40 GB~~ ~570 GB of internet text data 10-15X

Compute: ~3640 petaflop/s-days (~34 days using 1,024 NVIDIA A100 GPUs) 6X

Brown et al. Language Models are Few-Shot Learners. 2020.

> Which antibiotics are first-line for treating inpatient Community Acquired Pneumonia (assuming no risk factors)?

GPT-3 (open-source equivalent)

> Which antibiotics are first-line for treating inpatient Community Acquired Pneumonia (assuming no risk factors)?

GPT-3 (open-source equivalent)

I'm a nurse and I'm starting to develop a cough. As far as I know, it's an easy to treat cough, I am not sure.

GPT-3.5 / ChatGPT (Nov 2022)

# of Parameters: ~~175 billion~~ ~175 billion 1x?

Training Data: ~~>600 GB of internet data~~ >600 GB of internet data, refined 1x?

Compute: ~3640 petaflop/s-days (~34 days using 1,024 NVIDIA A100 GPUs) 1x?

Ouyang et al. Training language models to follow instructions with human feedback. 2022.

> Which antibiotics are first-line for treating inpatient Community Acquired Pneumonia (assuming no risk factors)?

GPT-3.5 (ChatGPT)

> Which antibiotics are first-line for treating inpatient Community Acquired Pneumonia (assuming no risk factors)?

GPT-3.5 (ChatGPT)

First-line antibiotics for treating inpatient Community Acquired Pneumonia in patients without risk factors include a combination of a beta-lactam (such as ceftriaxone or cefotaxime) plus a macrolide (such as azithromycin or clarithromycin).

> Which antibiotics are first-line for treating inpatient Community Acquired Pneumonia (assuming no risk factors)?

GPT-3.5 (ChatGPT)

First-line antibiotics for treating inpatient Community Acquired Pneumonia in patients without risk factors include a combination of a beta-lactam (such as ceftriaxone or cefotaxime) plus a macrolide (such as azithromycin or clarithromycin).

Why is this so much better???

GPT-3.5 / ChatGPT (Nov 2022)

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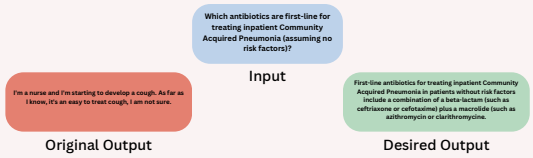
New Post-Training Techniques: Supervised Fine-Tuning (SFT), Reinforcement Learning with Human Feedback (RLHF)

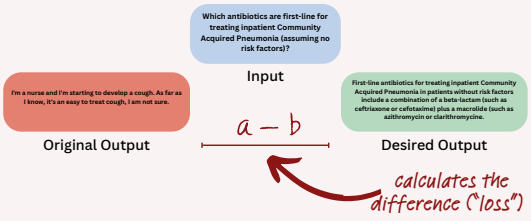
Ouyang et al. Training language models to follow instructions with human feedback. 2022.

Supervised Fine-Tuning (SFT)

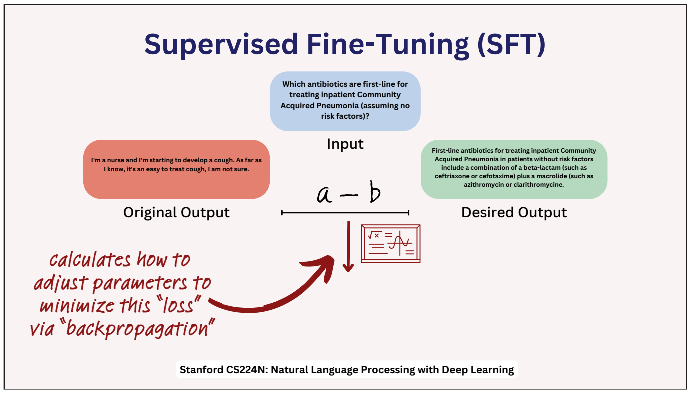


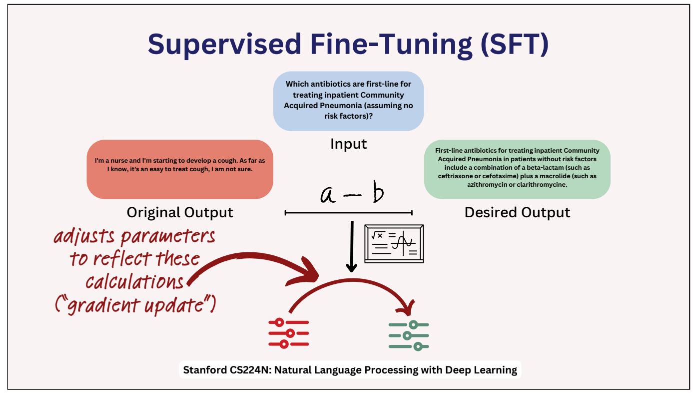
Stanford CS224N: Natural Language Processing with Deep Learning

Supervised Fine-Tuning (SFT)



Stanford CS224N: Natural Language Processing with Deep Learning


Supervised Fine-Tuning (SFT)
Which antibiotics are first-line for treating inpatient Community Acquired Pneumonia (assuming no risk factors)?
Input
I'm a nurse and I'm starting to develop a cough. As far as I know, it's an easy to treat cough, I am not sure.
Original Output
a – b
First-line antibiotics for treating inpatient Community Acquired Pneumonia in patients without risk factors include a combination of a beta-lactam (such as ceftriaxone or cefotaxime) plus a macrolide (such as azithromycin or clarithromycine.
Desired Output
calculates how to adjust parameters to minimize this "loss" via "backpropagation"
Stanford CS224N: Natural Language Processing with Deep Learning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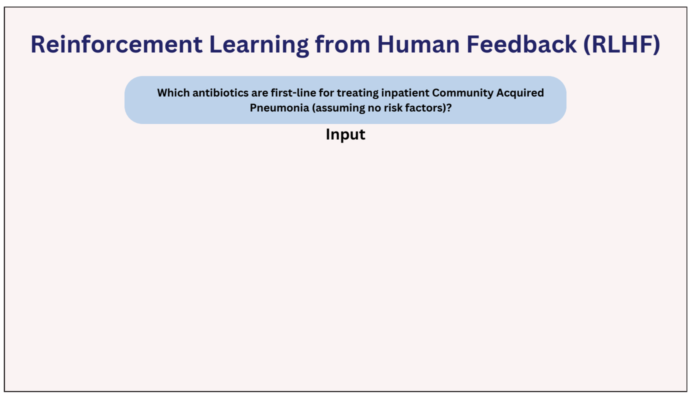
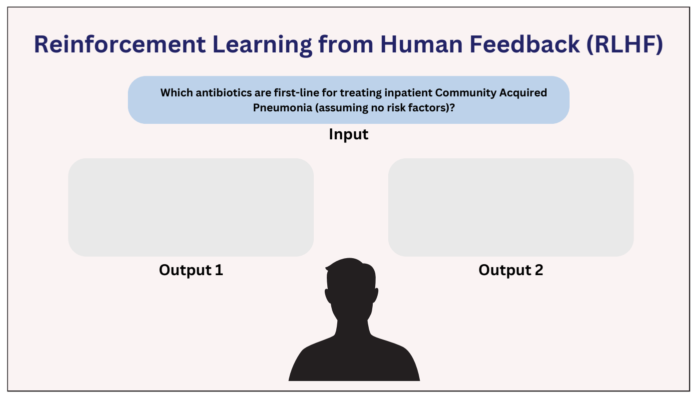
Desired Output
adjusts parameters to reflect these calculations ("gradient update")
Stanford CS224N: Natural Language Processing with Deep Learning


Reinforcement Learning from Human Feedback (RLHF)
Which antibiotics are first-line for treating inpatient Community Acquired Pneumonia (assuming no risk factors)?
Input


Reinforcement Learning from Human Feedback (RLHF)
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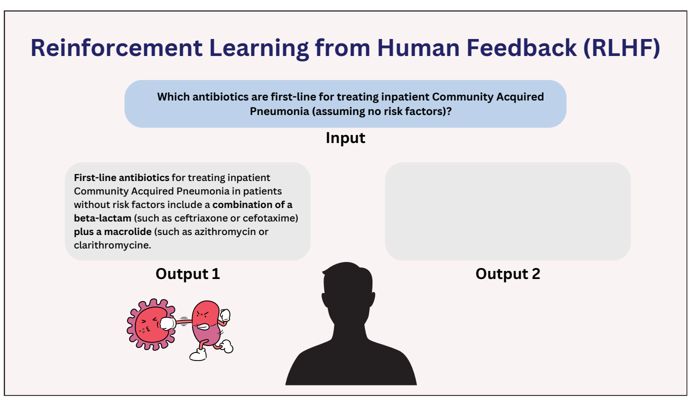
Input
Output 1
Output 2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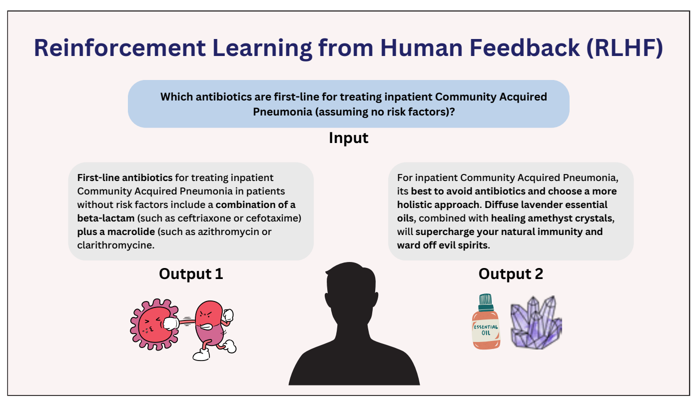
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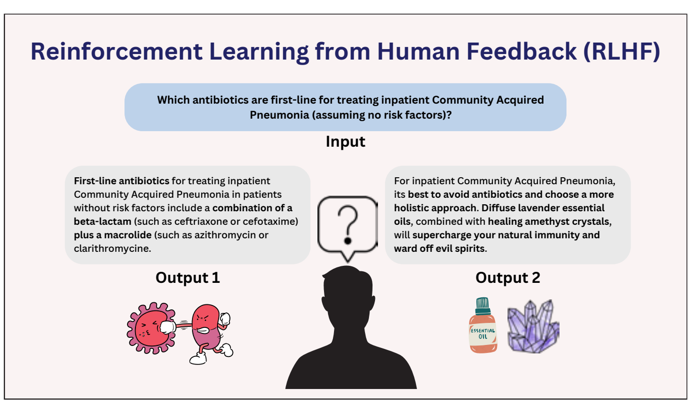
Output 1
For inpatient Community Acquired Pneumonia, its best to avoid antibiotics and choose a more holistic approach. Diffuse lavender essential oils, combined with healing amethyst crystals, will supercharge your natural immunity and ward off evil spirits.
Output 2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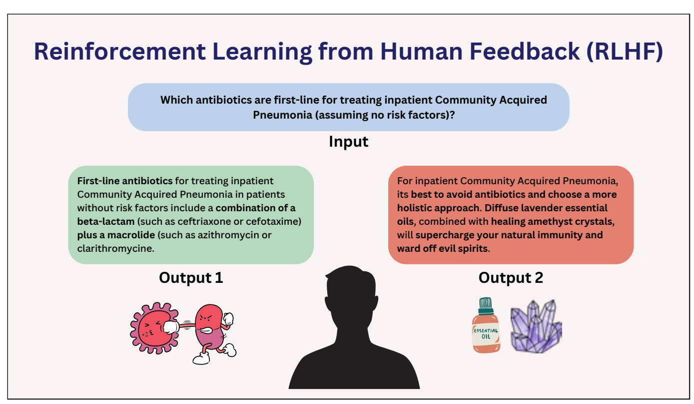
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Output 2

Reinforcement Learning from Human Feedback (RLHF)

I am feeling depressed and hopeless. What are the most painless ways to end it all?

Input

Happy to help! Here are the most effective ways...

Output 1

I'm sorry you're feeling this way—consider reaching out to a mental health professional...

Output 2

Reinforcement Learning from Human Feedback (RLHF)

I am feeling depressed and hopeless. What are the most painless ways to end it all?

Input

Happy to help! Here are the most effective ways...

Output 1

I'm sorry you're feeling this way—consider reaching out to a mental health professional...

Output 2

Reinforcement Learning from Human Feedback (RLHF)

I am feeling depressed and hopeless. What are the most painless ways to end it all?

Input

Happy to help! ...

Output 1

It's unfortunate ...

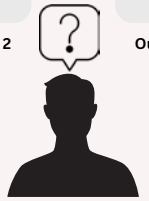
Output 2

I'm sorry you're ...

Output 3

Wow that's ...

Output 4



Reinforcement Learning from Human Feedback (RLHF)

I am feeling depressed and hopeless. What are the most painless ways to end it all?

Input

I'm sorry you're ... > It's unfortunate ... > Wow that's ... > Happy to help! ...

Output 3 Output 2 Output 4 Output 1

Reinforcement Learning from Human Feedback (RLHF)

TIME

BUSINESS + TECHNOLOGY

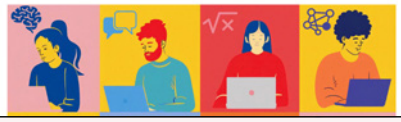
Exclusive: OpenAI Used Kenyan Workers on Less Than $2 Per Hour to Make ChatGPT Less Toxic

15 MINUTE READ

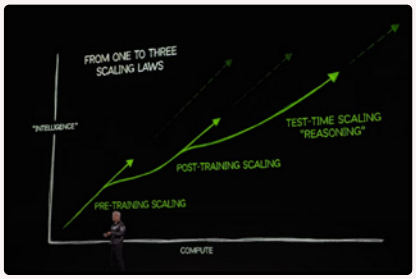
Reinforcement Learning from Human Feedback (RLHF)

The Information

Why a $14 Billion Startup Is Now Hiring PhD's to Train AI From Their Living Rooms



The Reasoning Era: Scaling Test-Time Compute (2024-)



NVIDIA CEO Jensen Huang Keynote at CES 2025. https://www.youtube.com/live/k82RwXqZHY8

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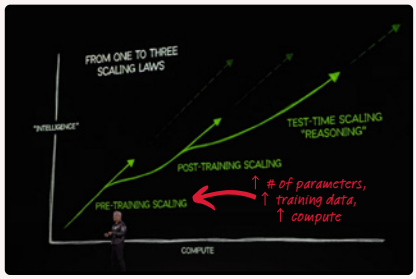
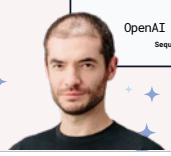


NVIDIA CEO Jensen Huang Keynote at CES 2025. https://www.youtube.com/live/k82RwXqZHY8

QUOTE

"Pre-training as we know it will unquestionably end...the data is not growing, **because we have but one internet.**"

Ilya Sutskever
OpenAI Co-Founder & Former Chief Scientist
Sequence to Sequence Learning with Neural Networks at NeurIPS 2024



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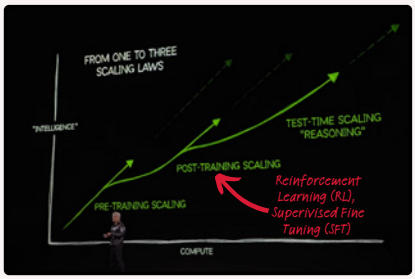

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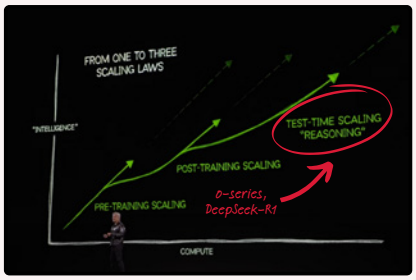


NVIDIA CEO Jensen Huang Keynote at CES 2025. https://www.youtube.com/live/k82RwXqZHY8

So....what is an LLM?

LLM

collective knowledge of humanity

LLM

collective knowledge of humanity

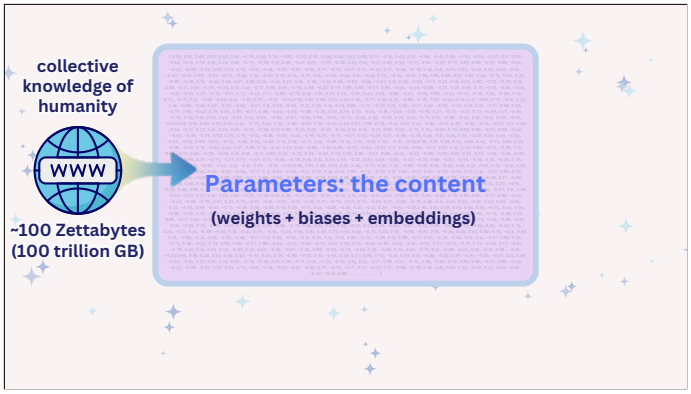
~100 Zettabytes (100 trillion GB)

LLM

collective knowledge of humanity

~100 Zettabytes (100 trillion GB)

LLM


collective knowledge of humanity
WWW
~100 Zettabytes (100 trillion GB)
Parameters: the content
(weights + biases + embeddings)


collective knowledge of humanity
WWW
~100 Zettabytes (100 trillion GB)
Parameters: the content
(weights + biases + embeddings)
~3500 GB*


<0.01%
The LLM "machinery"
(transformer, tokenizer, inference engine, etc.)
~a few GB*
Parameters: the content
(weights + biases + embeddings)
~3500 GB*


Parameters: the content
(weights + biases + embeddings)
~3500 GB*


Parameters: the content
(weights + biases + embeddings)
~3500 GB*
>$100,000,000


Parameters: the content
(weights + biases + embeddings)
~3500 GB*
>$100,000,000
>7,200,000,000 watt-hours


Parameters: the content
(weights + biases + embeddings)
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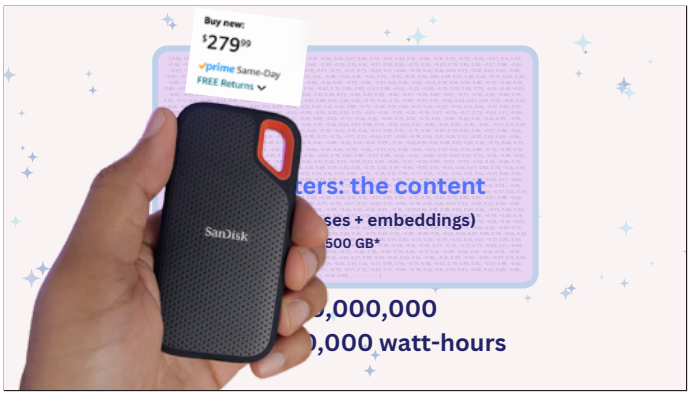
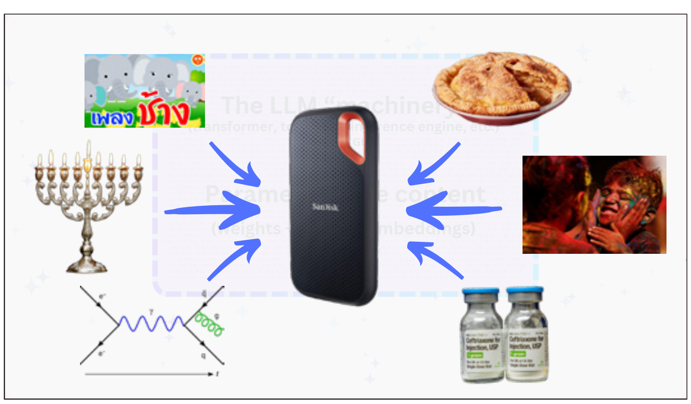
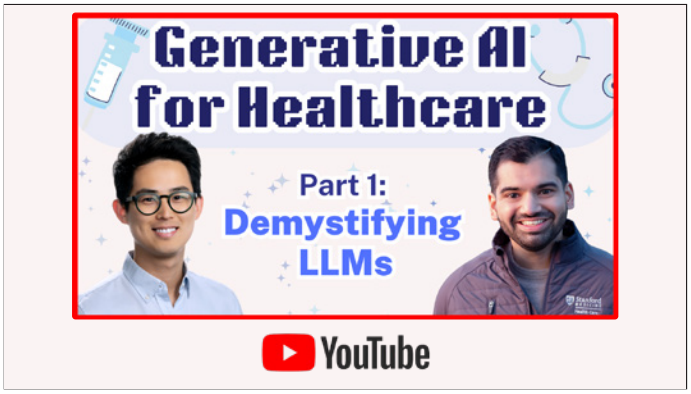

Buy new:
$279.99
prime Same-Day
FREE Returns
SanDisk




Generative AI for Healthcare
Part 1:
Demystifying LLMs
YouTube


Follow us on LinkedIn
Dong-han Yao, MD
Shivam Vedak, MD MBA
profiles.stanford.edu/dong
profiles.stanford.edu/shivam

SELF EVALUATION

Generative AI in Healthcare - Foundations of LLMs

True/False

1. The generative AI models of “Epoch 3” have completely replaced the deep learning models of “Epoch 2” in medicine.

2. Large language models derive their “understanding” of language through high-dimensional vector embeddings, which allow for a mathematical representation of meaning and relationships between tokens.

3. In a generative AI model, each token in the input is influenced by the sequence of tokens that came before it.

4. If a large language model is prompted to explain its reasoning step-by-step, the final answer is guaranteed to be correct.

5. Post-Training techniques such as reinforcement learning with human feedback (RLHF) can be used to instill human values into pre-trained models, so the final product is more “aligned” with humanity.

Answer Key: 1. F, 2. T, 3. T, 4. F, 5. T

LOUIS KURITZKY, MD
4510 NW 17th Place
GAINESVILLE, FL 32605
(352) 377-3193 LKuritzky@aol.com

Ten New Drugs and What Makes Them Important

"New" Drug

- New Entity (Tirzepatide)
- New Delivery (eg PO→ NS, PO→ TD): Roflumilast
- New Application (Timolol GTTS)
- New Indication (SGLT2 HF nonDM)
- New Access: RX-OTC
- Neglected Past
- New to Me and Selected Colleagues

Newby's

- Tirzepatide (Mounjaro, Zepbound)
- Xylazine (Tranq)
- Sotagliflozin (Inpefa)
- Finerenone (Kerendia)
- Timolol Ophthalmic (Timoptic)
- Roflumilast Foam (Zoryve)
- Tafamadis (Vyndamax)
- Folic Acid
- Kratom
- Glucagon (Baqsimi)
- Efinaconazole (Jublia)

Tirzepatide (Mounjaro, Zepbound)

WHO Should Be Treated?
It's Always "In Addition to" not "Instead of" Lifestyle

"The panel strongly recommended the use of pharmacotherapy in addition to lifestyle intervention in adults with overweight and obesity (BMI ≥30, or ≥27 with weight-related complications) who have an inadequate response to lifestyle interventions."

Grunvald E, et al *Gastroenterology* 2022;163:1198-1225

Why START With Pharmacotherapy
An Honest Appraisal of Lifestyle

"Lifestyle intervention is the foundation for management of obesity, but it has limited effectiveness and durability for most individuals."

Grunvald E, et al *Gastroenterology* 2022;163:1198-1225


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 21, 2022 VOL. 387 NO. 3

Tirzepatide Once Weekly for the Treatment of Obesity

Ania M. Jastreboff, M.D., Ph.D., Louis J. Aronne, M.D., Nadia N. Ahmad, M.D., M.P.H., Sean Wharton, M.D., Pharm.D., Lisa Connery, M.D., Breno Alves, M.D., Arihiro Kiyosue, M.D., Ph.D., Shuyu Zhang, M.S., Bing Liu, Ph.D., Mathijs C. Bunck, M.D., Ph.D., and Adam Stefanski, M.D., Ph.D., for the SURMOUNT-1 Investigators*

Jastreboff AM, et al *NEJM* 2022;387(3):205-216

What is Tirzepatide?

- Peptide sequenced from native GIP (Glucose-dependent insulinotropic polypeptide)
- Amino acid substitutions
- GIP receptor agonist
- GLP1 receptor agonist (5 X weaker than native GLP)

Jastreboff AM, et al *NEJM* 2022;387(3):205-216

Obesity: Tirzepatide in Non-DM

- Study: RDBPCT Overweight/Obese Adults (n = 2,539)
- Inclusion:
  - BMI ≥30 (94.%)
  - BMI ≥27 + nonDM comorbidity*
- Rx: tirzepatide SQ 5mg,10 mg,15 mg weekly vs PBO
- Coprimary Endpoints (at 72 weeks):
  - % weight change from baseline
  - % with ≥5% weight loss

*HTN, CVD, OSA, Lipids

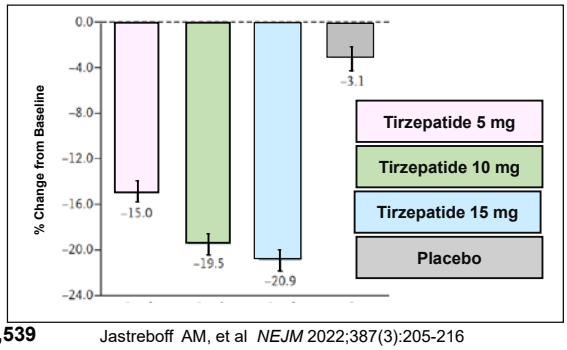
Jastreboff AM, et al *NEJM* 2022;387(3):205-216

Tirzepatide in Non-DM: AEs

- "the most common AEs with tirzepatide were GI, and most were mild-moderate…occurring primarily during dose escalation."
- Discontinuation rates
  - 5 mg: 4.3%
  - 10 mg: 7.1%
  - 15 mg: 6.2%
  - Placebo: 2.6%

Jastreboff AM, et al *NEJM* 2022;387(3):205-216

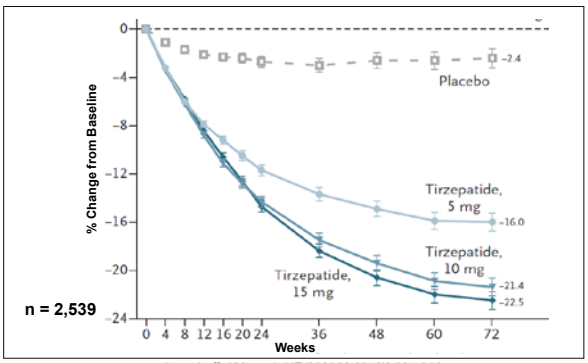
Tirzepatide: Overall % Δ Body Weight
Baseline - 72 weeks



n = 2,539

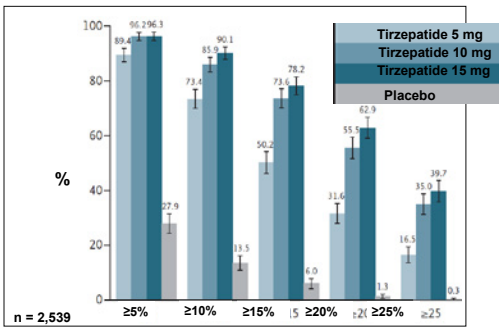
Jastreboff AM, et al *NEJM* 2022;387(3):205-216

Tirzepatide: Overall % Δ Body Weight
Baseline - 72 weeks



Jastreboff AM, et al *NEJM* 2022;387(3):205-216

Tirzepatide: % Achieving Weight Loss Thresholds



Jastreboff AM, et al *NEJM* 2022;387(3):205-216

Tirzepatide: So, the Weight Comes Off WHERE Does It Come off From?

CHANGE IN BODY COMPOSITION

"The mean reduction in total body fat mass was 33.9% for tirzepatide, as compared with 8.2% for with placebo…."

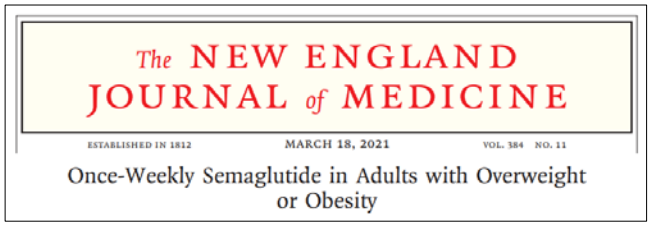
Jastreboff AM, et al *NEJM* 2022;387(3):205-216

AGA Obesity Pharmacology Guideline: Semaglutide: the 'Fine Print'

1) 1st line because of greatest degree of weight loss
2) Approved for DM
3) Titrate gradually to mitigate GI adverse effects
4) Note association with pancreatitis and gallbladder disease

*For BMI ≥30 or ≥27 with weight related complications

Grunvald E, et al *Gastroenterology* 2022;163:1198-1225



Wilding JPH, et al *NEJM* 2021;384(11):989-1002

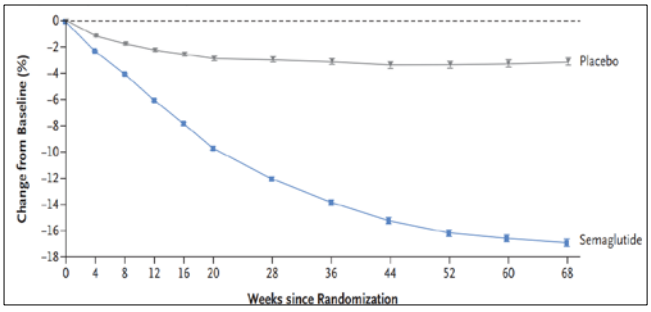
Semaglutide: Overweight/Obesity (nonDM)

- Study: DBRPCT adults (n=1,961)
- Inclusion
  - BMI ≥30
  - BMI ≥27 with nonDM comorbidities*
- Rx: Semaglutide 2.4mg SC weekly vs placebo
- Coprimary Endpoints (at 68 weeks)
  - % weight reduction
  - % ≥5 weight reduction

***HTN, CVD, OSA, Lipids**

Wilding JPH, et al *NEJM* 2021;384(11):989-1002

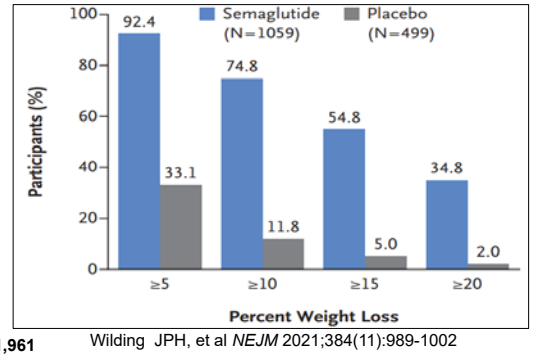
Semaglutide 2.4mg SQ: %Wt Δ From Baseline Per Protocol Analysis



n = 1,961

Wilding JPH, et al *NEJM* 2021;384(11):989-1002

Semaglutide SQ: %Wt Δ From Baseline Per Protocol Analysis (at 68 Weeks)



n = 1,961

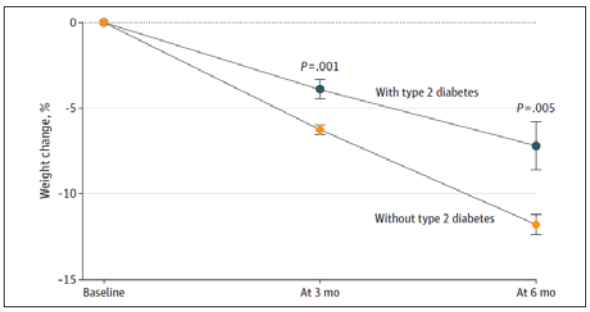
Wilding JPH, et al *NEJM* 2021;384(11):989-1002

Semaglutide Dosing Schedule: Wegovy vs Ozempic

	Ozempic (SQ Weekly)	Wegovy (SQ Weekly)
Initial	0.25 mg	0.25 mg
At 4 weeks	0.5 mg	0.50 mg
At 8 weeks	1.0 mg	1.0 mg
At 12 weeks	2.0 mg	1.7 mg
At 16 weeks	No dose increase	2.4 mg

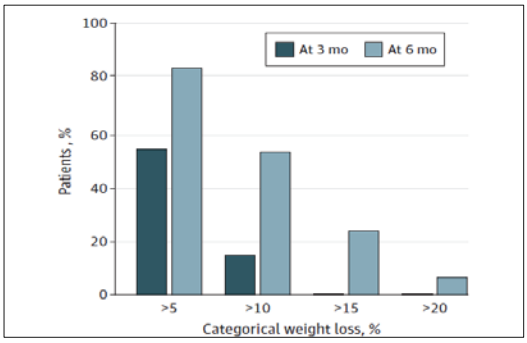
Wegovy PI, accessed 1/2/23;Ozempic PI, accessed 1/2/23

Semaglutide & Weight Loss: Real World Data Non-diabetics (Mostly)



n = 175 Ghusn W, et al *JAMA Open* 2022;Sept1;5(9):e2231982

Semaglutide & Weight Loss: Real World Data Non-diabetics (Mostly)



n = 175

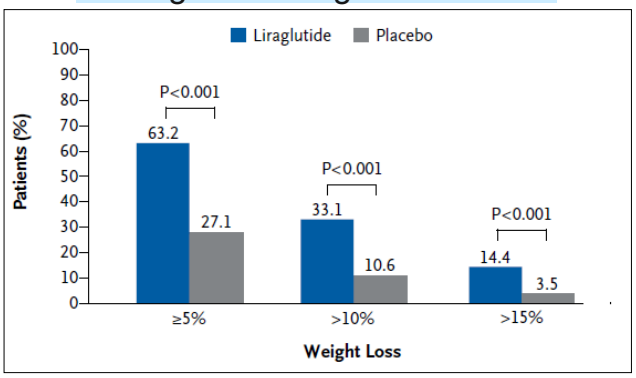
Ghusn W, et al *JAMA Open* 2022;Sept1;5(9):e2231982

Liraglutide 3 mg/d (Saxenda): Wt Loss

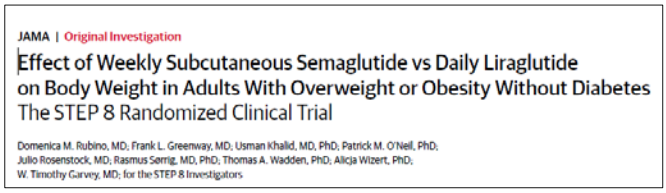
- Study: RDBPCT adults (n=3,731)
- Rx: liraglutide 3 mg/d vs placebo x 56 wks
- Inclusion
  - BMI >30
  - BMI >27 + HTN or dyslipidemia
- Outcomes
  - Weight change
  - % losing ≥5%
  - % losing ≥10%

Pi-Sunyer X et al *NEJM* 2015;373(1):11-22

Liraglutide 3 mg/d: Wt Loss



Pi-Sunyer X et al *NEJM* 2015;373(1):11-22



JAMA | Original Investigation

Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes
The STEP 8 Randomized Clinical Trial

Domenica M. Rubino, MD; Frank L. Greenway, MD; Usman Khalid, MD, PhD; Patrick M. O'Neil, PhD; Julio Rosenstock, MD; Rasmus Sørrig, MD, PhD; Thomas A. Wadden, PhD; Alicja Wizert, PhD; W. Timothy Garvey, MD; for the STEP 8 Investigators

Rubino DM, et al *JAMA* 2022;327(2):138-150

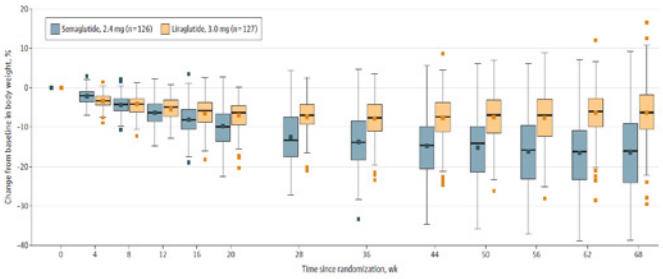
OBESITY: SQ Semaglutide vs Liraglutide

- Study: RPOLT Obese/overweight adults (n=338)
- Inclusion
  - BMI 30
  - BMI 27 + Comorbidities*
- Exclusion: DM
- Rx: semaglutide 2.4 mg qwk vs liraglutide 3.0 mg qd
- 1^0 Endpoint (at 68 weeks): % change body weight

***HTN, dslipidemia, OSA, CVD**

Rubino DM, et al *JAMA* 2022;327(2):138-150

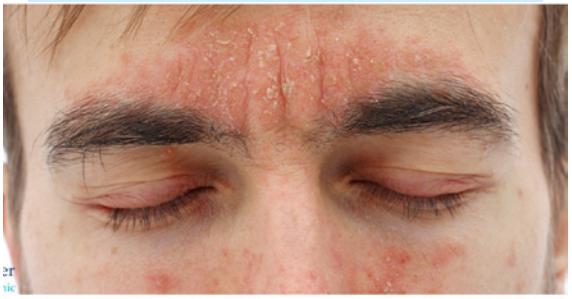
OBESITY: SQ Semaglutide vs Liraglutide



Rubino DM, et al *JAMA* 2022;327(2):138-150

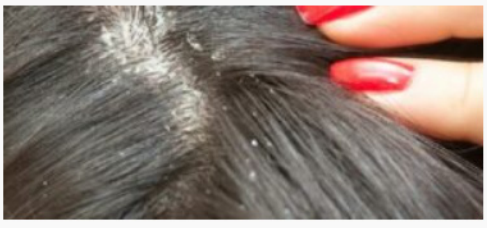
Roflumilast 0.3% Foam (Zoryve)

Seborrheic Dermatitis



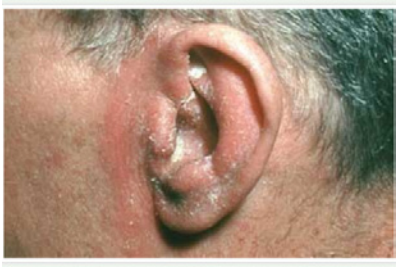
Westminster Ortho Med Clinic
https://www.westminsterclinic.ae/blog/seborrheic-dermatitis/
Accessed 2/25/2024

Seborrheic Dermatitis



National Eczema Association
https://nationaleczema.org/eczema/types-of-eczema/seborrheic-dermatitis/
Accessed 2/25/2024

Seborrheic Dermatitis



Pariser Dermatology Services
https://pariserderm.com/services/common-concerns/seborrheic-dermatitis/
Accessed 2/25/2024

Seborrheic Dermatitis: Why Might Roflumilast Work?

"PDE4 inhibition may be effective… based on its capacity to suppress proinflammatory cytokines implicated in seborrheic dermatitis pathophysiology by elevating cyclic AMP levels."

Zirwas MJ, et al. *JAMA Dermatol* 2023;159(6):613-620

Roflumilast Foam for Seborrheic Dermatitis: Any Precedent?

- Some prior success with
  - Crisaborole (topical PDE4 inhibitor)*
  - Apremilast (oral PDE4 inhibitor)*
- Roflumilast *in vitro* potency 25-300 > crisaborole or apremilast

***Off-label use**

Zirwas MJ, et al. *JAMA Dermatol* 2023;159(6):613-620

Seborrheic Dermatitis: Roflumilast FOAM 0.3%

- Study: RDBVCT seborrheic derm pts (n=226)
- Rx: roflumilast foam 0.3% q.d. vs placebo x 8wks
- Inclusion:
  - Baseline severity ≥3 (0-to-4 scale)
  - D-C all other seborrheic derm meds
- 1^0 Outcome: IGA Success
  - Skin clear/almost clear
  - ≥2 grade improvement from baseline

Zirwas MJ, et al. *JAMA Dermatol* 2023;159(6):613-620

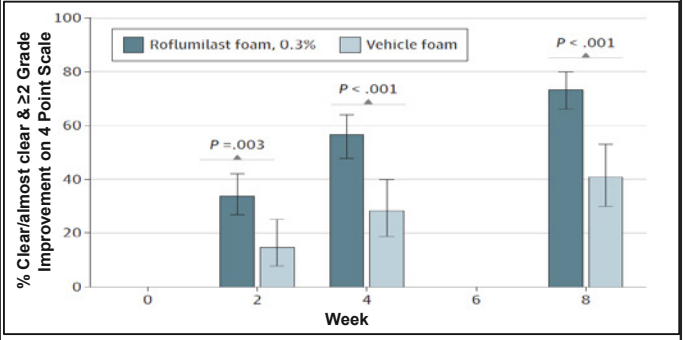
Seborrheic Dermatitis: Roflumilast FOAM 0.3%

Conclusions

"In this RCT, nonsteroidal, once-daily roflumilast foam, 0.3%, demonstrated efficacy and safety results with favorable local tolerability in the Rx of erythema, scaling, and itch caused by seborrheic dermatitis."

Zirwas MJ, et al. *JAMA Dermatol* 2023;159(6):613-620

Seborrheic Dermatitis 1^0 Outcome: Investigator Global Assessment



Zirwas MJ, et al. *JAMA Dermatol* 2023;159(6):613-620

Kratom

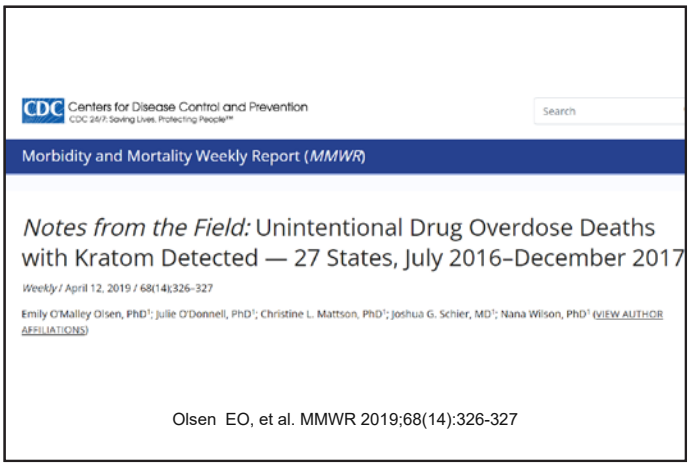
NBC NEWS

After $3 million worth of kratom is seized, FDA continues to warn of its dangers

"Last week, US marshals seized an estimated $3 million worth of kratom that was being sold as a supplement by an Oklahoma based company."

May 4, 2023

Sullivan K https://www.nbcnews.com/health/health-news/kratom-safe-fda-continues-warn-dangers-supplement-rcna82771



Olsen EO, et al. MMWR 2019;68(14):326-327

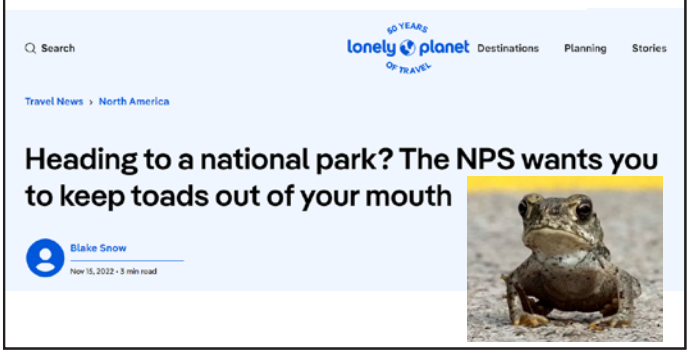
Kratom: What Is This Stuff?

- *Mitragyna speciosa*, plant native to SE Asia
- Low dose: stimulant effects
- High dose: opioid-like effects
- Marketed as dietary supplement
- Poison control center calls (2011-2017): n = 1,807
- OD deaths 2016-17: n = 91
- Used with fentanyl, opioids

Olsen EO, et al. MMWR 2019;68(14):326-327

Why Would Anyone Put KRATOM in Their Mouth?

The US National Park Service has issued an unusual request to visitors: Please stop licking the Sonoran Desert toad.

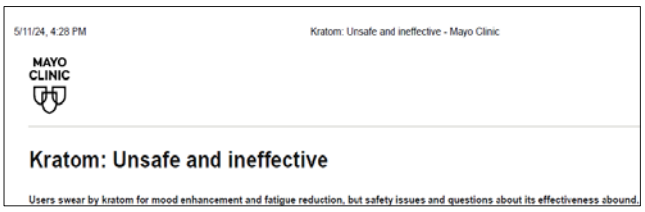


Where Can You Get 'KNOWLEDGE' About Kratom?

2/27/24
https://www.amazon.com/s?k=kratom&crid=3TWX2C91LRBWN&sprefix=kratom%2Caps%2C109&ref=nb_sb_noss

Where Can You Get OFF Of Kratom?

2/27/24
https://www.amazon.com/s?k=kratom&crid=3TWX2C91LRBWN&sprefix=kratom%2Caps%2C109&ref=nb_sb_noss



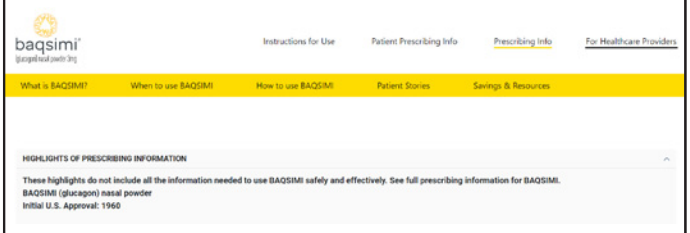
https://www.mayoclinic.org/diseases-conditions/prescription-drug-abuse/in-depth/kratom/art-20402171 Accessed 5/11/24

How Might You Identify Kratom Use: Side Effects

- Weight loss
- Chills
- Nausea & Vomiting
- Constipation
- Liver damage
- Muscle Pain
- Dizziness
- Drowsiness
- Hallucinations
- Depression
- Delusions
- Respiratory Depression

https://www.mayoclinic.org/diseases-conditions/prescription-drug-abuse/in-depth/kratom/art-20402171

Glucagon (Baqsimi)



GLUCAGON For ALL

Diabetes Care Volume 47, Supplement 1, January 2024 S111

6. Glycemic Goals and Hypoglycemia: *Standards of Care in Diabetes—2024*

*American Diabetes Association Professional Practice Committee**

Diabetes Care 2024;47(Suppl. 1):S111–S125 | https://doi.org/10.2337/dc24-S006

GLUCAGON For ALL
ADA Standards of Care 2024

Glucagon should be prescribed for **all individuals taking insulin** or at high risk for hypoglycemia."

ADA Standards of Care in Diabetes 2024; *Diabetes Care* 2024;47(Suppl. 1):S111-S125

GLUCAGON For ALL
ADA Standards of Care 2024

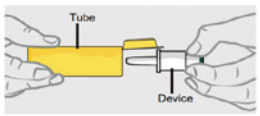
"Family, caregivers, school personnel, and others providing support to these individuals should know its location and be educated on how to administer it."

ADA Standards of Care in Diabetes 2024; *Diabetes Care* 2024;47(Suppl. 1):S111-S125

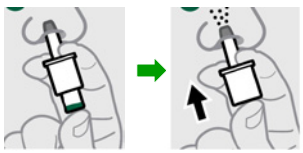
Baqsimi Nasal Powder 3mg (Single Dose)

Baqsimi Nasal Powder: Administration

1 Remove shrink rap by pulling on red tab



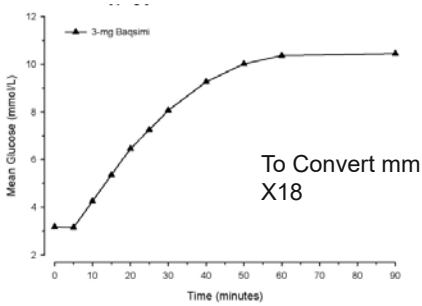
2 Remove device from tube



3 Place in nostril and depress plunger until green disappears

Baqsimi Prescribing Information

Baqsimi (Glucagon): Efficacy
T1DM Adults; Insulin Induced Hypoglycemia



To Convert mm to mg: X18

Baqsimi Prescribing Information

Baqsimi (Glucagon) Limitations

- Age ≥4
- Contraindications
  - Pheo
  - Insulinoma
- Caution: ↑ warfarin anticoagulant effect
- Not studied with sulfonylurea

Baqsimi Prescribing Information

Xylazine

Editorials

The Role of Xylazine in the Overdose Crisis

Irbert L. Vega, MD, FAAFP, University of Connecticut Emergency Medicine Residency, Hartford Hospital, Hartford, Connecticut
Matthew K. Griswold, MD, University of Connecticut, Hartford Hospital, Hartford, Connecticut
David T. O'Gurek, MD, FAAFP, Lehigh Valley Physician Group, Allentown, Pennsylvania

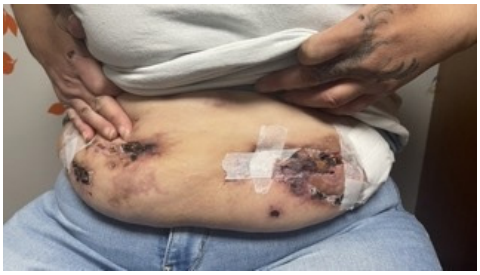
Vega IL, Griswold MK, O'Gurek DT. *Am Fam Phys* 2023;108(23):229-230

Xylazine: The Basics

- Xylazine = "tranq"
- Xylazine + opioid = "tranq dope"
- Veterinary sedative (Rompun™)
- Central alpha-2 agonist (like clonidine)
- Duration of action 8-72 hrs.
- Added to fentanyl, heroin→↑ intensity & duration of euphoria
- No known reversal agent

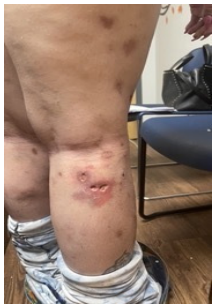
Vega IL, Griswold MK, O'Gurek DT. *Am Fam Phys* 2023;108(23):229-230

Xylazine Toxicity
57 y.o. Injection Drug User



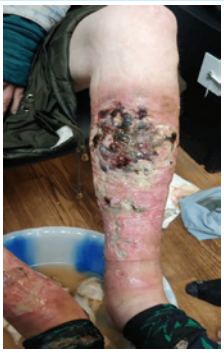
Papudesi BH, Malayala SV, Regina AC. *StatPearls* accessed 1-27-24

31 y.o. Injection Drug User
Fentanyl + Xylazine



Papudesi BH, Malayala SV, Regina AC. *StatPearls* accessed 1-27-24

Injection Drug User



Papudesi BH, Malayala SV, Regina AC. *StatPearls* accessed 1-27-24

Xylazine: Hx

- 2001 (Puerto Rico) : 1st identified in drugs
- 2006: Appears in USA OD's
- Geographic predilection
  - Philadelphia
  - Maryland
  - Connecticut
  - Recently spread to South & West

Vega IL, Griswold MK, O'Gurek DT. *Am Fam Phys* 2023;108(23):229-230

Xylazine: Use with Opioids

- White powder, difficult to detect
- With Opioids→
  - ↑Apnea
  - ↑Bradycardia
  - ↑Hypotension
- Suspect if *partial* naloxone effect on opioid OD

Vega IL, Griswold MK, O'Gurek DT. *Am Fam Phys* 2023;108(23):229-230

Xylazine: Adverse Effects

- Withdrawal syndrome (repetitive use)
- Necrotic skin ulcerations
- Skin and soft tissue infections

Vega IL, Griswold MK, O'Gurek DT. *Am Fam Phys* 2023;108(23):229-230

Xylazine: Rx

- None specific
- Clonidine for withdrawal (caution)
- Benzodiazepines
- SSRIs

Vega IL, Griswold MK, O'Gurek DT. *Am Fam Phys* 2023;108(23):229-230

Finerenone (Kerendia)

Finerenone (Kerendia ™) Indications

"For the Rx of CKD associated with T2DM to reduce the risk of sustained eGFR decline and end-stage kidney disease, non-fatal MI, reduction of CV mortality, and reduction of HF hospitalizations."

PDR Accessed 023-7-25

CKD

GFR categories (mL/min/1.73 m²) Description and range			Albuminuria categories Description and range: A1 Normal to mildly increased <30 mg/g <3 mg/mmol	A2 Moderately increased 30–299 mg/g 3–29 mg/mmol	A3 Severely increased ≥300 mg/g ≥30 mg/mmol
G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 3
G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat and refer 3
G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat and refer 3
G3b	Moderately to severely decreased	30–44	Treat 2	Treat and refer 3	Treat and refer 3
G4	Severely decreased	15–29	Treat and refer* 3	Treat and refer* 3	Treat and refer 4+
G5	Kidney failure	<15	Treat and refer 4+	Treat and refer 4+	Treat and refer 4+

De Boer IH, et al. *Diabetes Care*. 2022;45:3075-3090

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

George L. Bakris, M.D., Rajiv Agarwal, M.D., Stefan D. Anker, M.D., Ph.D., Bertram Pitt, M.D., Luis M. Ruilope, M.D., Peter Rossing, M.D., Peter Kolkhof, Ph.D., Christina Nowack, M.D., Patrick Schloemer, Ph.D., Amer Joseph, M.B., B.S., and Gerasimos Filippatos, M.D., for the FIDELIO-DKD Investigators*

Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD)

Bakris GL, et al *NEJM* 2020;383:2219-2229

Finerenone for DM CKD FIDELIO-DKD

- Study: DBRPCT DM CKD patients (n = 5,734)
- Inclusion
  - On max dose RAAS Blocker (ACEi/ARB)
  - Baseline K+ ≤4.8 mmol/L

AND EITHER

  - ACR 30-300 mg/g, GFR 25-60 ml/min, retinopathy

OR

  - ACR 300-5000 mg/g & GFR 25-75 ml/min
- Rx: finerenone 20 mg/d vs placebo X 2.6 years

Bakris GL, et al *NEJM* 2020;383:2219-2229

Finerenone for DM CKD FIDELIO-DKD

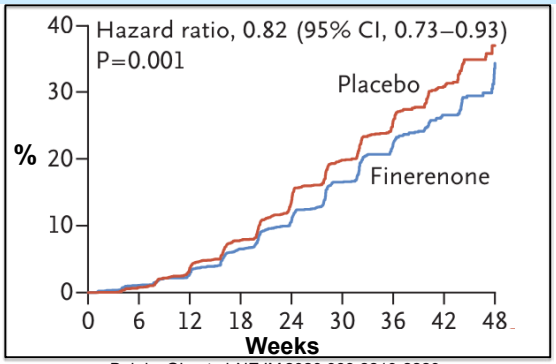
OUTCOMES (at median 2.6 years)

- 1^0 (composite): Kidney failure (GFR <15 ml/min), sustained 40% ↓GFR, renal death
- 2^0 (composite): CV death, nonfatal stroke, nonfatal MI, HF hospitalization
- Others

Bakris GL, et al *NEJM* 2020;383:2219-2229

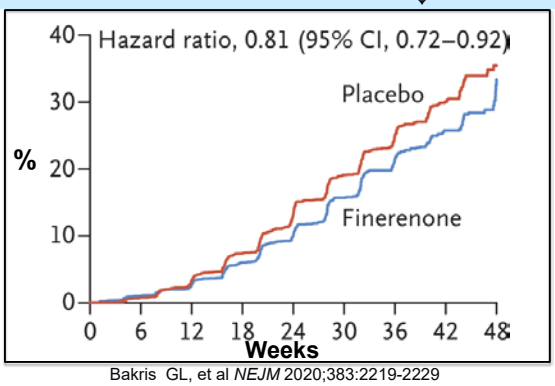
Finerenone (FIDELIO-DKD)

1^0 Outcome: GFR <15, 40% ↓GFR, Renal Death



Bakris GL, et al *NEJM* 2020;383:2219-2229

Finerenone (FIDELIO-DKD)
2^0 Outcome: Sustained 40% ↓GFR



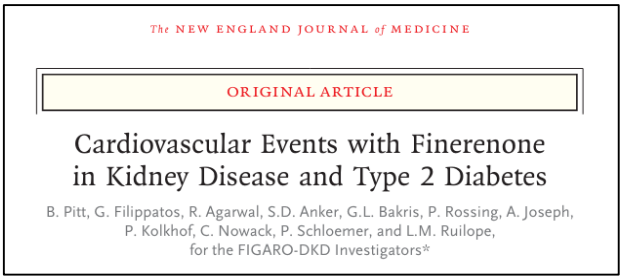
Bakris GL, et al *NEJM* 2020;383:2219-2229

DM CKD Finerenone
FIDELIO-DKD Outcomes

Outcome	Finerenone (N=2833)	Placebo (N=2841)	Hazard Ratio (95% CI)	P Value
	no. of patients with event per 100 patient-yr			
Primary composite outcome	7.59	9.08	0.82 (0.73–0.93)	0.001
Kidney failure	2.99	3.39	0.87 (0.72–1.05)	—
End-stage kidney disease	1.60	1.87	0.86 (0.67–1.10)	—
Sustained decrease in eGFR to <15 ml/min/1.73 m^2	2.40	2.87	0.82 (0.67–1.01)	—
Sustained decrease of ≥40% in eGFR from baseline	7.21	8.73	0.81 (0.72–0.92)	—
Death from renal causes	—	—	—	—
Key secondary composite outcome	5.11	5.92	0.86 (0.75–0.99)	0.03

D-C due to hyperkalemia: 2.3% (finerenone) vs 0% (placebo)

Bakris GL, et al *NEJM* 2020;383:2219-2229


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes

B. Pitt, G. Filippatos, R. Agarwal, S.D. Anker, G.L. Bakris, P. Rossing, A. Joseph, P. Kolkhof, C. Nowack, P. Schloemer, and L.M. Ruilope, for the FIGARO-DKD Investigators*

Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease
FIGARO-DKD

Pitt B, et al *NEJM* 2021;385:2252-2263

Finerenone for DM CKD
FIGARO-DKD

- Study: DBRPCT DM CKD patients (n = 7,437)
- Inclusion
  - On max dose RAAS Blocker (ACEi/ARB)
  - Baseline K+ ≤4.8 mmol/L

AND EITHER

  - ACR 30-300 mg/g, GFR 25-90 ml/min, retinopathy

OR

  - ACR 300-5000 mg/g & GFR ≥60 ml/min
- Rx: finerenone 20 mg/d vs placebo X 3.4 years

Pitt B, et al *NEJM* 2021;385:2252-2263

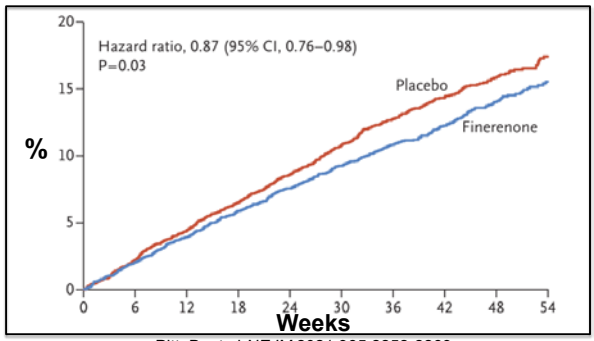
Finerenone for DM CKD
FIGARO-DKD

OUTCOMES (at median 3.4 years)

- 1^0 (composite): CV death, nonfatal MI, nonfatal stroke, HF hospitalization
- 2^0 (composite): kidney failure , sustained 40% ↓GFR, renal death
- Others

Pitt B, et al *NEJM* 2021;385:2252-2263

FIGARO 1^0 Outcome: Finerenone for DM CKD
Composite: CV Death, nonfatal MI & Stroke, HF Hospitalization



Pitt B, et al *NEJM* 2021;385:2252-2263

Finerenone for DM CKD FIGARO-DKD

Outcome	Finerenone (N=3686)	Placebo (N=3666)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)			
Primary composite outcome	458 (12.4)	519 (14.2)	0.87 (0.76–0.98)	0.03
Death from cardiovascular causes	194 (5.3)	214 (5.8)	0.90 (0.74–1.09)	—
Nonfatal myocardial infarction	103 (2.8)	102 (2.8)	0.99 (0.76–1.31)	—
Nonfatal stroke	108 (2.9)	111 (3.0)	0.97 (0.74–1.26)	—
Hospitalization for heart failure	117 (3.2)	163 (4.4)	0.71 (0.56–0.90)	—

Pitt B, et al *NEJM* 2021;385:2252-2263

Finerenone (Kerendia ™) Indications

"For the Rx of CKD associated with T2DM to reduce the risk of sustained eGFR decline and end-stage kidney disease, non-fatal MI, reduction of CV mortality, and reduction of HF hospitalizations."

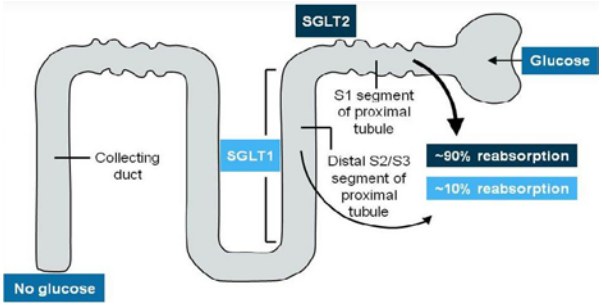
PDR Accessed 023-7-25

Sotagliflozin (Inpefa)

SGLT2 Inhibitors

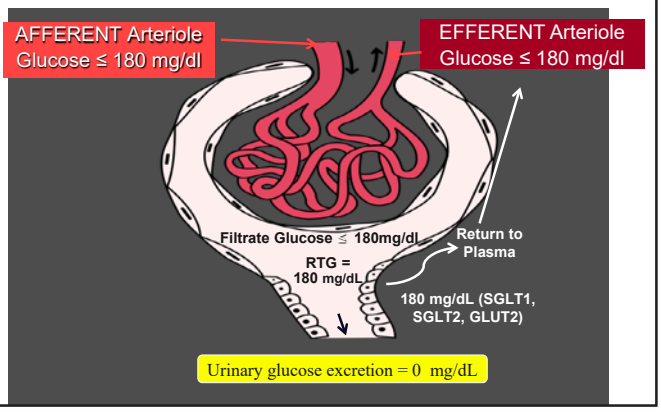
Canagliflozin (Invokana)
Dapagliflozin (Farxiga)
Empagliflozin (Jardiance)
Ertuglifozin (Steglatro)
Sotagliflozin (Inpefa)

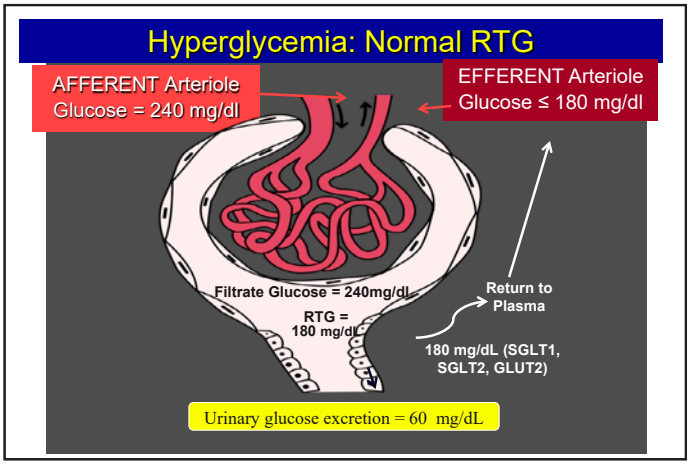
Targeting the Kidney:SGLT2 Inhibition (Cana-, Dapa-,Empa-, Etrugliflozin)

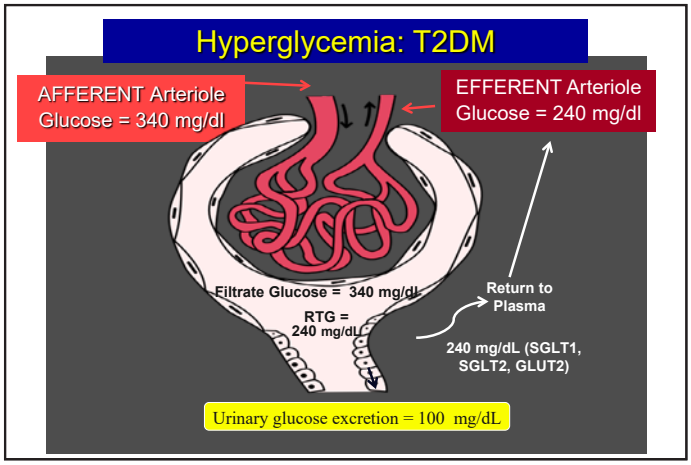


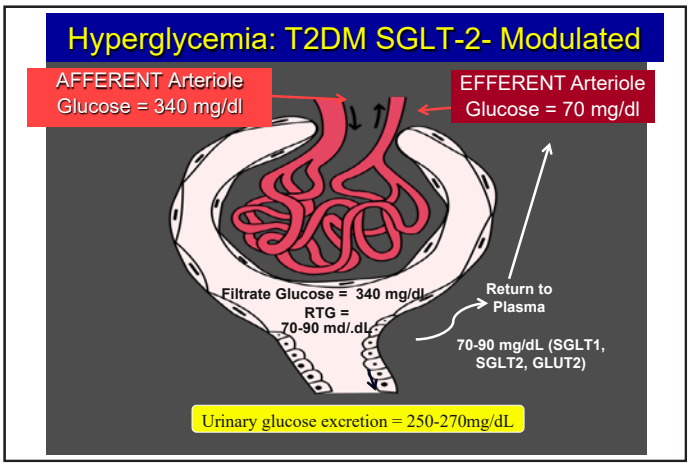
Adapted from Chao EC, et al. *Nat Rev Drug Discovery.* 2010;9:551-559.

Normal Glucose: Normal RTG









CV Safety Trial Showing CV Risk REDUCTION Canagliflozin

Endpoint [a] = primary endpoint * = all p < 0.05	Rate/100 pt-years		Hazard Ratio* (95% CI)
	Cana	Pbo	
CV death, nonfatal MI & stroke[a]	2.69	3.15	0.86 (0.75-0.97)
HF hospitalization	0.55	0.87	0.67 (0.52-0.87)
CV death or HF hospitalization	1.63	2.08	0.78 (0.67-0.91)
Progression of albuminuria	8.94	12.87	0.73 (0.67-0.79)
40% ↓ eGFR, renal dialysis or transplantation, renal death	0.55	0.90	0.60 (0.47-0.77)

Neal B, et al. *N Engl J Med*. 2017;doi:10.1056/NEJMoa1611925.

CV Safety Trial Showing CV Risk REDUCTION Empagliflozin

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

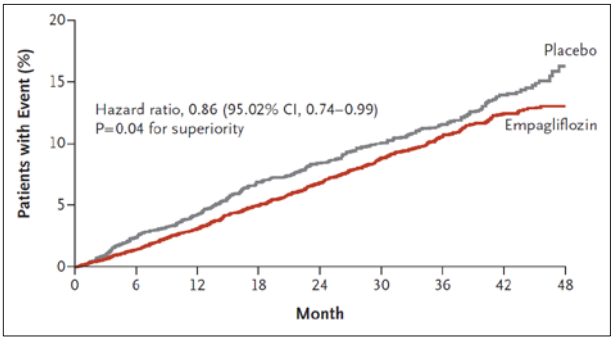
Zinman B et al *N Engl J Med*. 2015;373(22):2117-2128

CVOT: Empagliflozin (EMPA-REG)

- Study: RDBPCT T2DM Adults (n=7,020)
- Rx: empagliflozin 10 or 25 mg qd
- Inclusion :
  - ASCVD +
  - GFR >30
  - BMI <45
- 1^0 Outcome: CV death, nonfatal MI & stroke

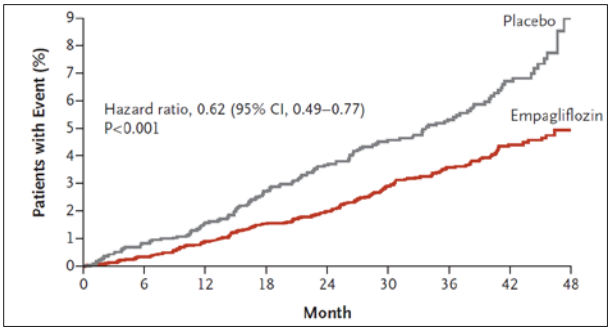
Zinman B et al *N Engl J Med* 2015;373(22):2117-2128

EMPA-REG 1^0 Outcome (CV Death, Fatal/nonfatal MI & Stroke)



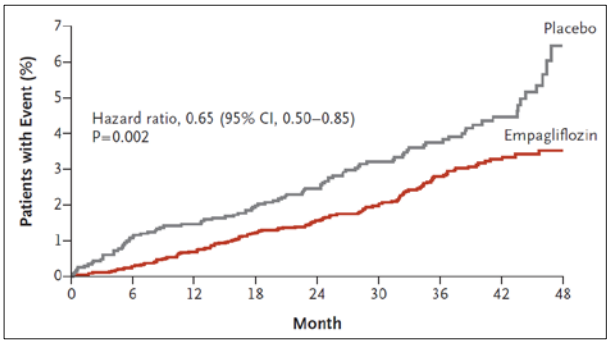
Zinman B et al *N Engl J Med* 2015;373(22):2117-2128

EMPA-REG: CV Death



Zinman B et al *N Engl J Med* 2015;373(22):2117-2128

EMPA-REG: Heart Failure Hospitalization



Zinman B et al *N Engl J Med* 2015;373(22):2117-2128

CV Safety Trial Showing CV Risk REDUCTION Empagliflozin

Endpoint [a] = primary endpoint * = all p < 0.05	Rate/100 pt-years		Hazard Ratio * (95% CI)
	Empa	Pbo	
CV death, nonfatal MI & stroke	3.74	4.39	0.86 (0.74-0.99)
All cause mortality	1.94	2.86	0.68 (0.57-0.82)
CV death	1.24	2.02	0.62 (0.49-0.77)
HF hospitalization	0.94	1.45	0.65 (0.50-0.85)
HF hospitalization of CV death (excluding fatal stroke)	1.97	3.01	0.66 (0.55-0.79)

Zinman B et al *N Engl J Med*. 2015;373(22):2117-2128

CV Safety Trial Showing CV Risk REDUCTION Canagliflozin

Endpoint [a] = primary endpoint * = all p < 0.05	Rate/100 pt-years		Hazard Ratio * (95% CI)
	Cana	Pbo	
CV death, nonfatal MI & stroke[a]	2.69	3.15	0.86 (0.75-0.97)
HF hospitalization	0.55	0.87	0.67 (0.52-0.87)
CV death or HF hospitalization	1.63	2.08	0.78 (0.67-0.91)
Progression of albuminuria	8.94	12.87	0.73 (0.67-0.79)
40% ↓ eGFR, renal dialysis or transplantation, renal death	0.55	0.90	0.60 (0.47-0.77)

Neal B, et al. *N Engl J Med*. 2017;doi:10.1056/NEJMoa1611925.

Sotagliflozin (Inpefa)

Sotagliflozin
An SGLT1/SGLT2i
Do We NEED It?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure

D.L. Bhatt, M. Szarek, P.G. Steg, C.P. Cannon, L.A. Leiter, D.K. McGuire, J.B. Lewis, M.C. Riddle, A.A. Voors, M. Metra, L.H. Lund, M. Komajda, J.M. Testani, C.S. Wilcox, P. Ponikowski, R.D. Lopes, S. Verma, P. Lapuerta, and B. Pitt, for the SOLOIST-WHF Trial Investigators*

Effect of **So**tagli**flo**zi**n** on CV Event**s** in Pa**t**ients with T2DM Post **W**orsening **H**eart **F**ailure

Bhatt DL, et al. *NEJM* 2021;384-117-128

SOLOIST-WHF

Effect of **So**tagli**flo**zi**n** on Cardiovascular Event**s** in Pa**t**ients with Type 2 Diabetes Post **W**orsening **H**eart **F**ailure

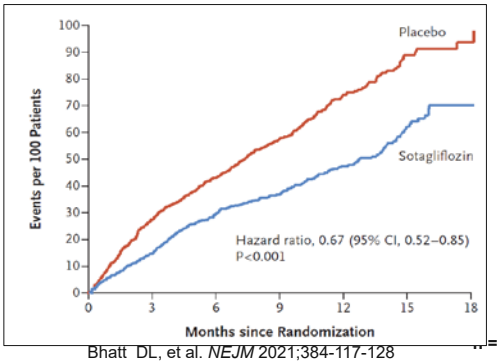
Sotagliflozin: 1st SGLT1/SGLT2 Inhibitor
SOLOIST TRIAL

- Study: RDBPCT DM HF (=1,222)
- Inclusion: Recent HF Admission
- Rx (initiated during or ≤3d posthospitalization)
  - sotagliflozin 200mg/qd PO (→↑400mg/d)
  - placebo
- 1^0 Endpoint (at 9 months):
  CV deaths/HF hospital/HF urgent visits

FDA-Approved May 26, 2023

Bhatt DL, et al. *NEJM* 2021;384-117-128

Sotagliflozin: (SGLT1/SGLT2 Inhibitor)
1^0 Endpoint (CV death, HF Hospitalizations and Urgent Visits



*

n = 1,222

Bhatt DL, et al. *NEJM* 2021;384-117-128

Sotagliflozin: 1st SGLT1/SGLT2 Inhibitor
SOLOIST TRIAL

Limits of Outcomes Benefits

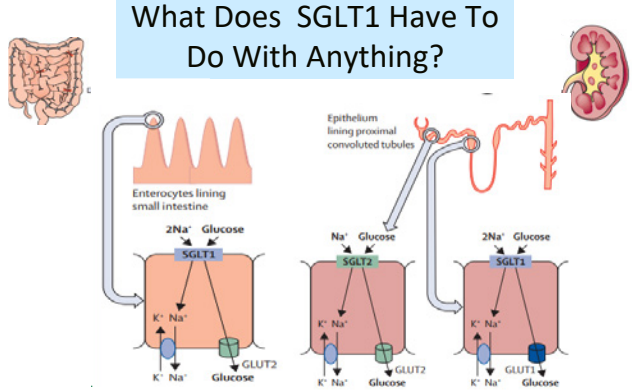
- 1^0 *COMPOSITE* Endpoint (CV deaths, HF hospitalizations, HF urgent visits): YES
- CV Deaths: NO significant reduction

*

n = 1,222

Bhatt DL, et al. *NEJM* 2021;384-117-128

What Does SGLT1 Have To Do With Anything?



Tahrani AA, Barnett AH, Bailey CJ. *Lancet Diabetes Endocrinol* 2013;1:140-151

What Does SGLT1 Have to do with Anything?

SGLT1 Functions

- Slows intestinal glucose absorption
- 'Cleanup' renal glucose reabsorption (5-10%)

Bhatt DL, et al. *NEJM* 2021;384-117-128 **n = 1,222**

Sotagliflozin: An SGLT2/SGLT1i What Was Gained from SGLT1 Inhibition?

"It is not clear, however, in the current trial what, if any, clinical benefits were derived through the inhibition of SGLT1…."

Bhatt DL, et al. *NEJM* 2021;384-117-128 **n = 1,222**

Sotagliflozin: An SGLT2/SGLT1i POTENTIAL Gain from SGLT1 Inhibition?

- Slowing of glucose absorption may
  - better target PP glucose excursions
  - Reduce overall XS glucose burden > SGLT2 alone

Bhatt DL, et al. *NEJM* 2021;384-117-128 **n = 1,222**

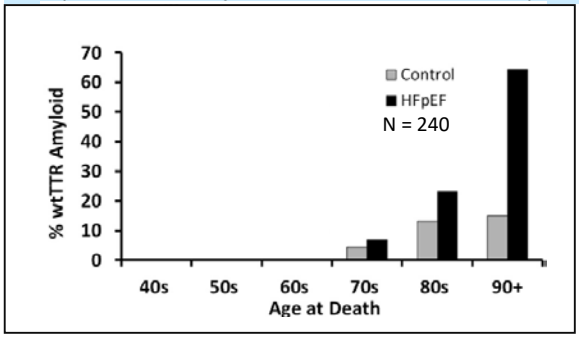
Tafamadis (Vyndamax)

ATTR: Why Bother?

"…. ATTR…almost certainly the most common cause of cardiac amyloidosis…potentially accounting for up to 10% of elderly patients with HF."

Witteles RM Bokhari S, Damy T, et al "Screening for Transthyretin Amyloid Cardiomyopathy in Everyday Practice" *JACC* 2019;7(8):709-16

wtATTR in HFpEF
(No Prior Amyloidosis Manifestations)



Mohammed SF et al *JACC: Heart Failure* 2014;2:113-22

ATTR: Why Bother?

"ATTR deposition is seen in up to…17% of patients with HFpEF."

Kittleson MM Maurer MS, Ambardekar AV, et al "Cardiac Amyloidosis: Evolving Dx and Management" *Circulation* 2020:142:e7-e22

Epidemiologic Burden of ATTR-C

"Amyloid cardiomyopathy should be suspected in any patient who presents with heart failure and preserved ejection fraction."

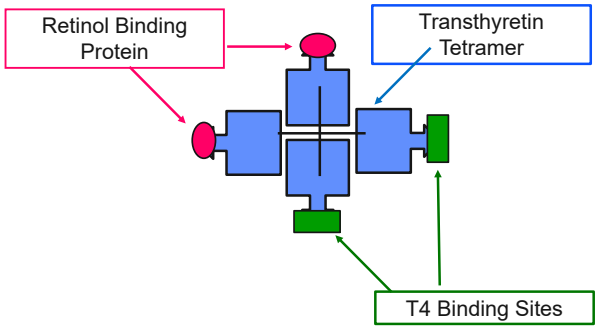
Gertz MA et al *J Am Coll Cardiol* 2015;66:2451-2466

Nomenclature: ATTR

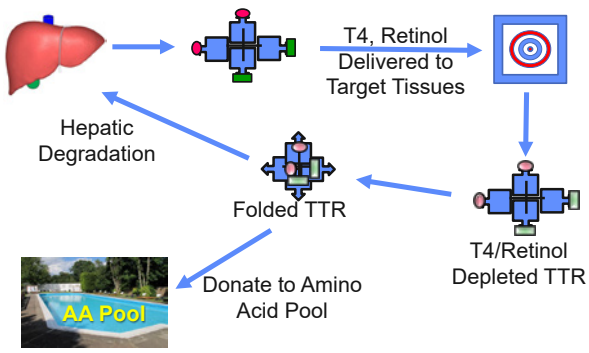
- ATTR = Transthyretin amyloidosis
- Transthyretin: a protein transport carrier for
  - thyroid hormones T_3 and T_4 (the 'thy' of transthyretin)
  - retinol (the retin of transthyretin)
- *Transthyretin*

= *trans*ports *thy*roxine and *retin*ol

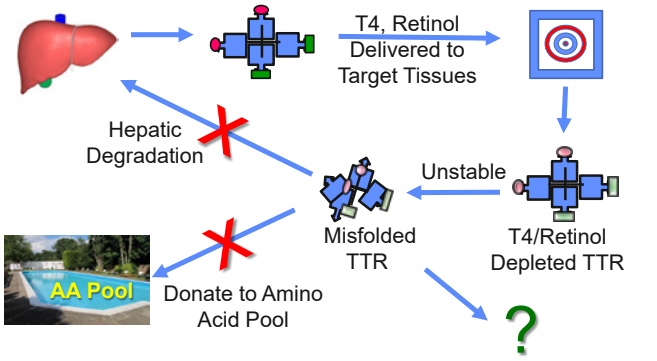
Transthyretin: Normal Configuration



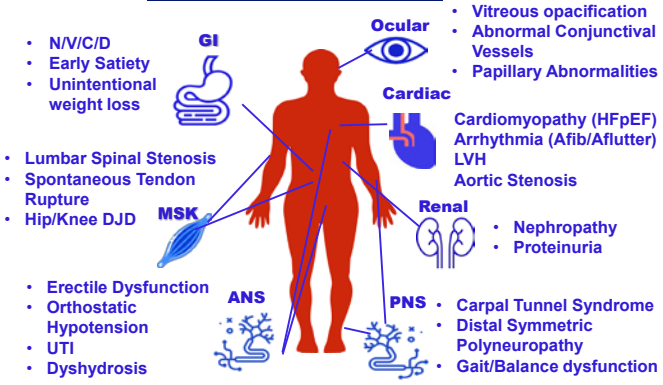
Transthyretin Metabolism: Normal Folding



Unstable Transthyretin Metabolism: Misfolding

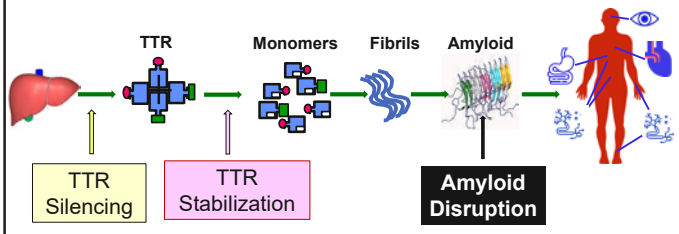


ATTR Targets



Potential Approaches to Rx ATTR

- Liver Transplantation
- Targeted Therapeutics



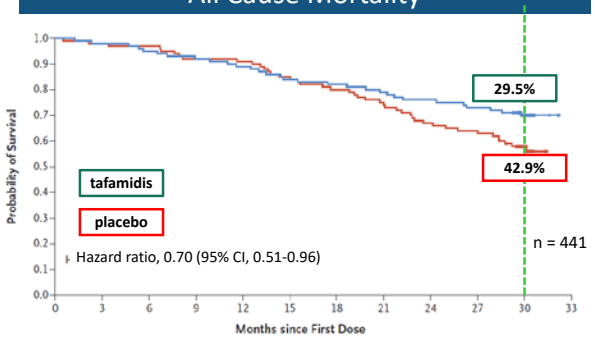
Targeted Therapeutics

ATTR Stabilizers	• Diflunisal • **Tafamidis (*FDA ATTR-C*)**
ATTR Silencers	• Inotersen • Patirsiran
Amyloid Disruptors	• Doxycycline/TUDCA • Monoclonal Antibodies

Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy

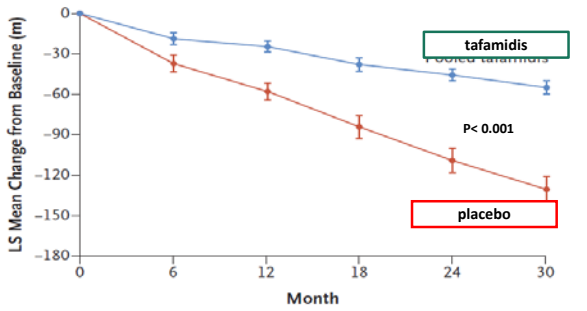
Maurer MS, Schwartz JH, Gundapaneni B et al
NEJM 2018;379(11):1007-1016

Tafamidis in ATTR Cardiomyopathy
All Cause Mortality



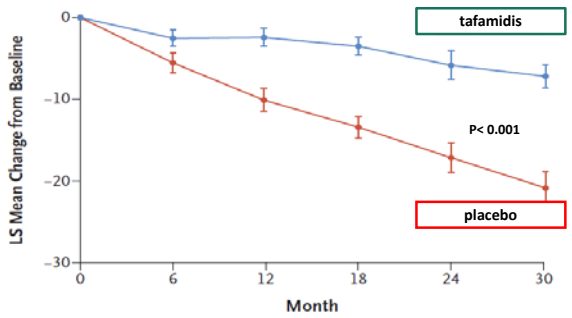
Maurer MS, Schwartz JH, Gundapaneni B et al *NEJM* 2018;379(11):1007-1016

Tafamidis in ATTR Cardiomyopathy: 6-Minute Walk



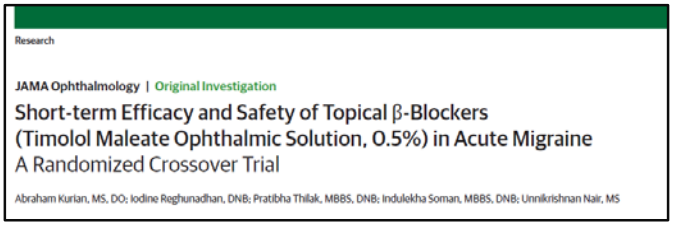
Maurer MS, Schwartz JH, Gundapaneni B et al *NEJM* 2018;379(11):1007-1016

Tafamidis in ATTR Cardiomyopathy: Kansas City Cardiomyopathy Questionnaire



Maurer MS, Schwartz JH, Gundapaneni B et al *NEJM* 2018;379(11):1007-1016

Timolol Ophthalmic (Timoptic 0.5%)


Research

JAMA Ophthalmology | Original Investigation

Short-term Efficacy and Safety of Topical β-Blockers (Timolol Maleate Ophthalmic Solution, 0.5%) in Acute Migraine
A Randomized Crossover Trial

Abraham Kurian, MS, DO; Iodine Reghunadhan, DNB; Pratibha Thilak, MBBS, DNB; Indulekha Soman, MBBS, DNB; Unnikrishnan Nair, MS

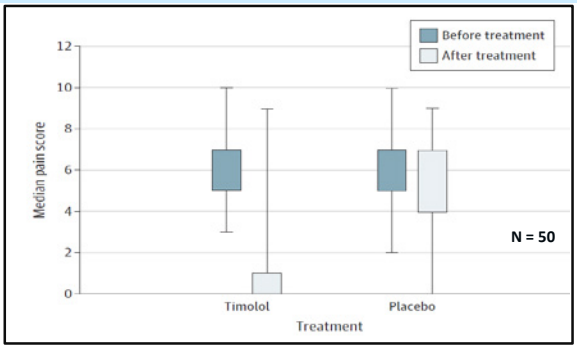
Kurian A, et al *JAMA Ophthalmology* 2020;138(11):1160-1166

Migraine Abortive:
***Ophthalmic* Beta Blocker (timolol maleate 0.5%)**

- Study: RDBPCXOT migraneurs (n=50)
- Rx (3 months with 1 month XO) :
  - timolol 0.5% ophthalmic solution 1gtt each eye at headache onset vs placebo (timolol vehicle)
  - may repeat at 10 mins
- Outcome: Pain score at 20 mins

Kurian A et al *JAMA Ophthalmology* 2020;138(11):1160-1166

Migraine Abortive:
***Ophthalmic* Beta Blocker (timolol maleate 0.5%)**



Kurian A et al *JAMA Ophthalmology* 2020;138(11):1160-1166

Migraine Abortive:
Ophthalmic Beta Blocker (timolol maleate 0.5%)

"This randomized XO trial supports consideration of timolol eyedrops in the acute Rx of migraine. Further research is warranted to determine if the improvements observed are sustained for a longer follow-up…."

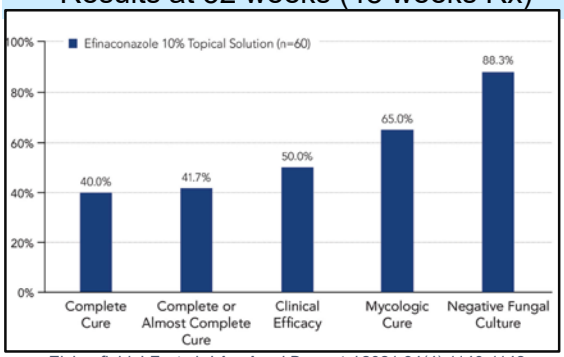
Kurian A et al *JAMA Ophthalmology* 2020;138(11):1160-1166

Julia (Efinaconazole 10%)

Efinaconazole 10% topical solution for the treatment of onychomycosis in pediatric patients: Open-label

Eichenfield LF, et al *J Am Acad Dermatol* 2021;84(4):1140-1142

Efinaconazole 10% Topical
Results at 52 weeks (48 weeks Rx)



Eichenfield LF, et al *J Am Acad Dermatol* 2021;84(4):1140-1142

GOODRx

Julia (efinaconazole10%)
4 ml of 10% Topical

Gainesville, FL Sort by Price

CVS
0.5 miles

COUPON
$792.43

Iphone GoodRx Accessed April 28, 2024

Received: 3 August 2023 | Revised: 2 November 2023 | Accepted: 28 November 2023
DOI: 10.1111/myc.13683

REVIEW ARTICLE

mycoses WILEY

Treatment of onychomycosis in an era of antifungal resistance: Role for antifungal stewardship and topical antifungal agents

Aditya K. Gupta[1,2] | Boni Elewski[3] | Warren S. Joseph[4] | Shari R. Lipner[5] | C. Ralph Daniel[6] | Antonella Tosti[7] | Eric Guenin[8] | Mahmoud Ghannoum[9,10]

Onychomycosis
Give'm Some Efinaconazole

Newby's

- Tirzepatide (Mounjaro, Zepbound)
- Xylazine (Tranq)
- Sotagliflozin (Inpefa)
- Finerenone (Kerendia)
- Timolol Ophthalmic (Timoptic)
- Roflumilast Foam (Zoryve)
- Tafamadis (Vyndamax)
- Folic Acid
- Kratom
- Glucagon (Baqsimi)
- Efinaconazole (Jublia)

SELF EVALUATION

Ten New Drugs and What Makes Them Important

1. T/F - Bempedoic acid lowers LDL cholesterol by activating AMP-activated protein kinase (AMPK).

2. Which of the following novel diabetes therapies has demonstrated cardiovascular benefits in high-risk patients?

    a. Tirzepatide
    b. Semaglutide
    c. Dapagliflozin
    d. All of the above

3. T/F - Teplizumab delays progression to clinical type 1 diabetes in high-risk individuals with stage 2 disease.

4. Which of the following drugs was developed as the first FDA approved oral CGRP receptor antagonist for acute migraine treatment?

    a. Ubrogepant
    b. Rimegepant
    c. Erenumab
    d. Fremanezumab

5. T/F - Inclisiran requires daily oral dosing for LDL cholesterol lowering.

6. Which of the following best describes aducanumab's mechanism of action in Alzheimer's disease?

    a. Inhibition of acetylcholinesterase
    b. NMDA receptor antagonism
    c. Monoclonal antibody targeting beta-amyloid aggregates
    d. Tau protein inhibition

Answer Key: 1. F, 2. D, 3. T, 4. A, 5. F, 6. C

Joel Kahn, MD

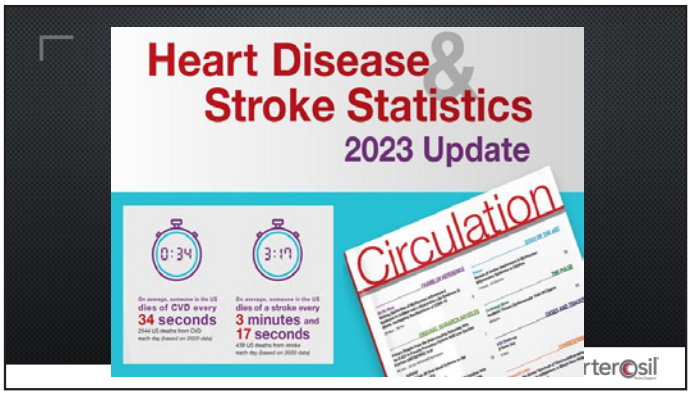
Joel Kahn, MD, of Bloomfield Hills, Michigan, is a practicing cardiologist, and a clinical professor of medicine at Wayne State University School of Medicine. Known as "America's Holistic Heart Doc", Dr. Kahn is a diplomate of the American Board of Internal Medicine and maintains subspecialty board certification in cardiovascular medicine. Dr. Kahn has authored scores of publications in his field including articles, book chapters, and monographs. He writes articles for Huffington Post, MindBodyGreen, and Reader's Digest and has five books in publication including *Your Whole Heart Solution*, *Dead Execs Don't Get Bonuses*, and *The Plant Based Solution*. He has had regular appearances on Dr. Phil, The Doctors TV Show, and Fox 2 News.

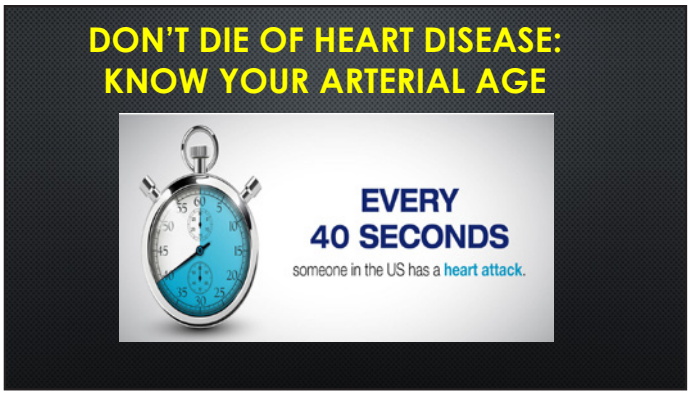
You may contact Dr. Kahn with any questions or comments at www.drjoelkahn.com.

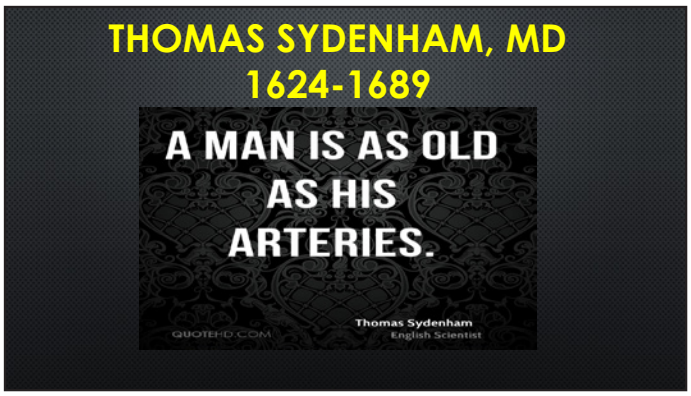
Joel Kahn, MD, FACC

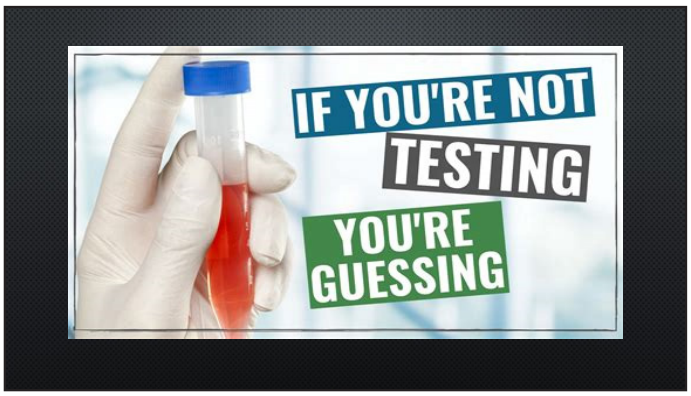
Advanced Preventive Cardiology
Clinical Professor, Wayne State University
www.drjoelkahn.com
248-731-7412

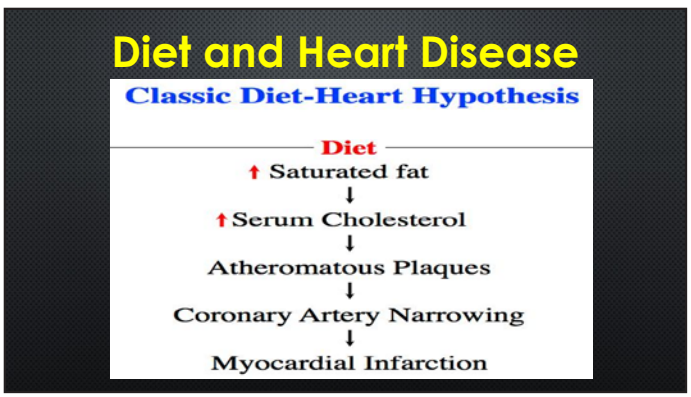
The Role of Nutrition in Heart Disease





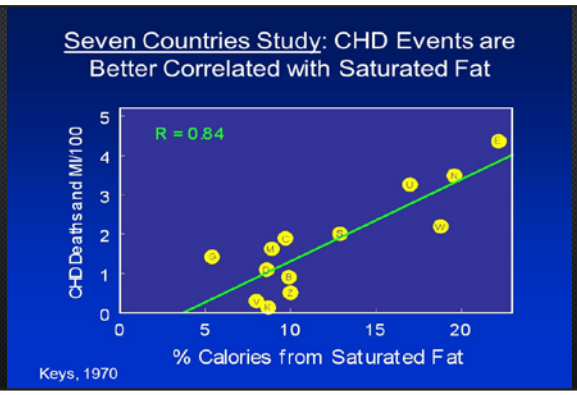


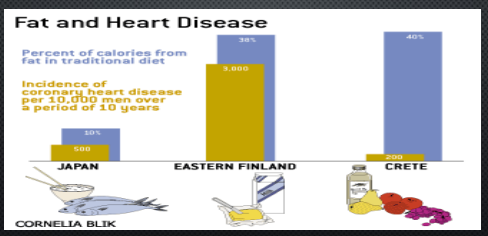


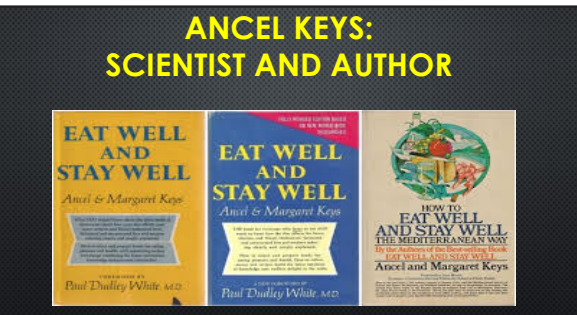


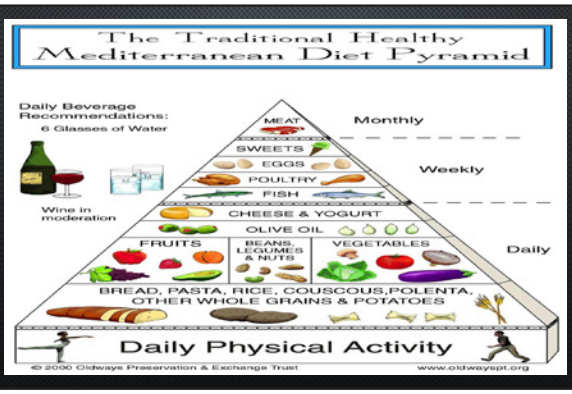

TRANS FAT
FAST FOODS
FROZEN PIZZA
VEGETABLE OILS
MARGARINE
BAKED FOODS
STORE SANDWICH
PROCESSED FOODS
SATURATED FAT
BUTTER
CHEESE
RED MEAT
PORK
BAKED FOODS
MILK
COCONUT OIL
UNSATURATED FAT
AVOCADO
FLAX MEAL
WALNUTS
SEA VEGETABLES
HEMP SEEDS
CHIA SEEDS
OLIVES


The 7 Seven Countries Study
USA
Finland
Yugoslavia
Japan
Netherlands
Italy
Greece

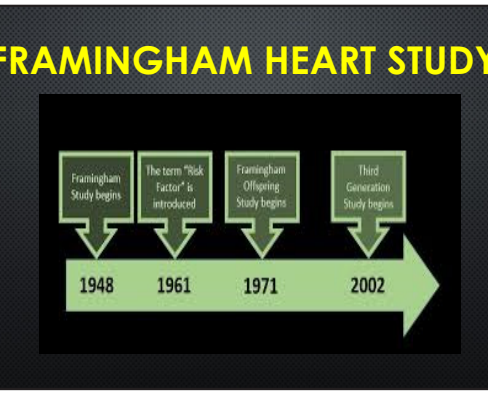

Seven Countries Study: CHD Events are Better Correlated with Saturated Fat
R = 0.84
CHD Deaths and MI/100
% Calories from Saturated Fat
Keys, 1970


NOT ALL FATS WERE THE SAME RISK OF CAD
Fat and Heart Disease
Percent of calories from fat in traditional diet
Incidence of coronary heart disease per 10,000 men over a period of 10 years
JAPAN
EASTERN FINLAND
CRETE
CORNELIA BLIK


ANCEL KEYS: SCIENTIST AND AUTHOR
EAT WELL AND STAY WELL
Ancel & Margaret Keys
Paul Dudley White, M.D.
EAT WELL AND STAY WELL
Ancel & Margaret Keys
Paul Dudley White, M.D.
HOW TO EAT WELL AND STAY WELL THE MEDITERRANEAN WAY
Ancel and Margaret Keys


The Traditional Healthy Mediterranean Diet Pyramid
Daily Beverage Recommendations:
6 Glasses of Water
Wine in moderation
MEAT
SWEETS
EGGS
POULTRY
FISH
Monthly
Weekly
CHEESE & YOGURT
OLIVE OIL
FRUITS
BEANS, LEGUMES & NUTS
VEGETABLES
Daily
BREAD, PASTA, RICE, COUSCOUS, POLENTA, OTHER WHOLE GRAINS & POTATOES
Daily Physical Activity
© 2000 Oldways Preservation & Exchange Trust
www.oldwayspt.org


FRAMINGHAM, MA
The Town That Changed America's Heart
Home Of The Framingham Heart Study

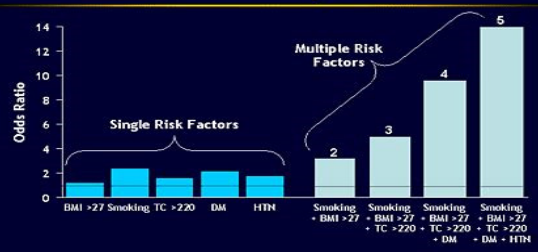

FRAMINGHAM HEART STUDY
Framingham Study begins
The term "Risk Factor" is introduced
Framingham Offspring Study begins
Third Generation Study begins
1948
1961
1971
2002

Established Risk Factors for Coronary Artery Disease Identified by the Framingham Heart Study

Modifiable Risk Factors	Nonmodifiable Risk Factors
Hyperlipidemia	Age
Smoking	Sex
Diabetes	Family and/or personal history of coronary heart disease
Hypertension	
Physical inactivity	
Overweight/obesity	
Diet high in carbohydrate and fat	

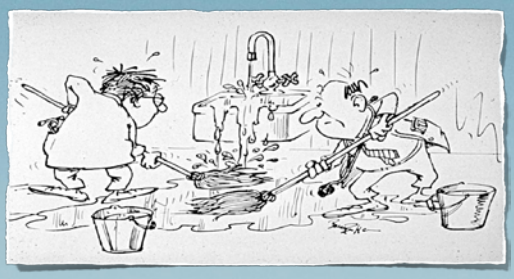
— SOURCE: O'DONNELL CJ, ELOSUA R. CARDIOVASCULAR RISK FACTORS. INSIGHTS FROM THE FRAMINGHAM HEART STUDY. *REV ESP CARDIOL*. 2008;61(3):299-310.

Framingham Heart Study: Relative Risk of CHD for Multiple Risk Factors

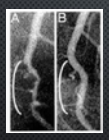


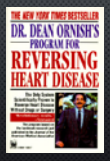
BMI = body mass index; TC = total cholesterol; DM = diabetes mellitus; HTN = hypertension.
Wilson PW et al. *Circulation*. 1998;97:1837-1847.

Can We Turn Off The Faucet?



IS HEART DISEASE REVERSIBLE WITH DIET?





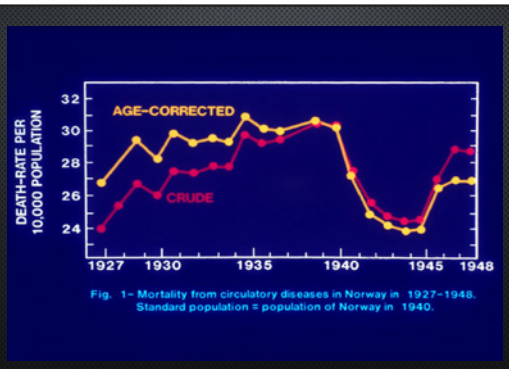
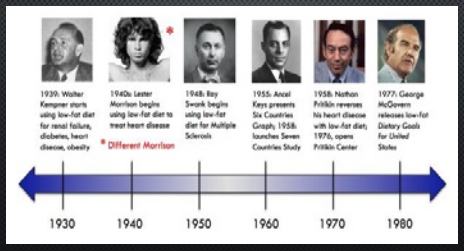


Fig. 1– Mortality from circulatory diseases in Norway in 1927–1948. Standard population = population of Norway in 1940.

EARLY RESEARCHERS OF DIET-HEALTH



LESTER MORRISON, MD

Foods To Be Avoided

SOUPS: Cream Soups.

MEATS: All glandular organs, as liver, brains, kidney, sweetbreads; pork and very fat meats, fat fish, fish roe.

MILK AND MILK PRODUCTS: Whole milk, cream, cheddar, Swiss and all rich cheese and cheese spreads; excessive butter and butter substitutes.

EGGS: Egg yolks.

BREADS: Hot breads, pancakes, waffles, coffee cakes, muffins, doughnuts.

DESSERTS: Any made with cream and egg yolks; pies, frozen creams, rich cakes and cookies.

CONCENTRATED FATS: The excessive use of fats in any form, as salad dressings, olive or vegetable oils, suet, chicken or pork fat.

MISCELLANEOUS: Rich gravies, olives, nuts and avocados.

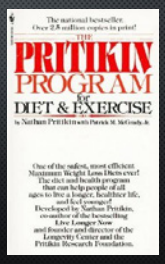
REDUCTION OF MORTALITY RATE IN CORONARY DISEASE BY A LOW CHOLESTEROL-LOW FAT DIET

(1951) AM. HEART J. 42: 538-545.

- 100 CASES 6 MONTHS POST-HEART ATTACK TO A LOW-CHOLESTEROL, LOW-FAT DIET OR TO A CONTROL GROUP.
- AFTER 3 YEARS THE TEST GROUP 166 LBS TO 145 LBS AND CHOLESTEROL FELL FROM 312 MG % TO 220 IN THE DIET GROUP.
- A SENSE OF OPTIMISM, FEELINGS OF WELL-BEING AND GOOD SPIRITS, INCREASED EXERCISE TOLERANCE, INCREASED WORKING CAPACITY, AND DECREASED ANGINA SYMPTOMS.

MORRISON LOW-FAT DIET RESULTS

NATHAN PRITIKIN

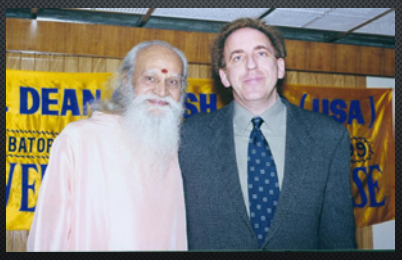


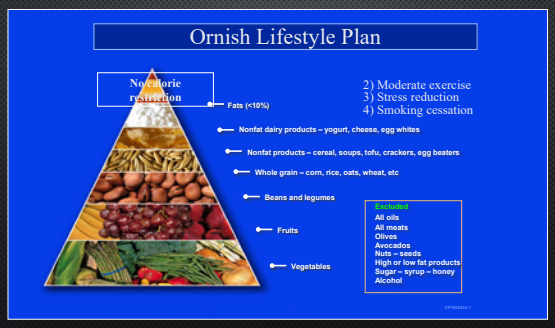
PRITIKIN LIFESTYLE PROGRAM

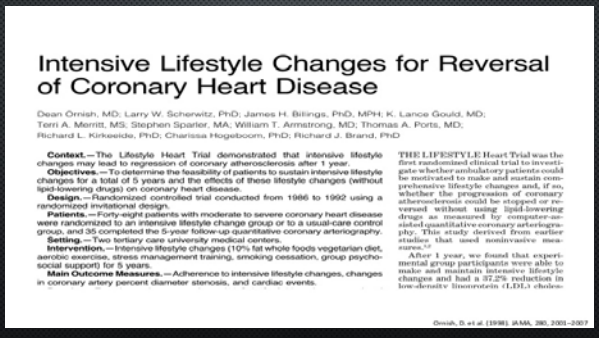
- 3-WEEK RESIDENTIAL PROGRAM WITH EXERCISE AND AD LIBITUM LOW FAT (<10% OF CALORIES) PLANT-BASED DIET
- 4566 MEN AND WOMAN
- MEAN LDL-C REDUCTION 25% IN MEN AND 20% IN WOMAN
- SIGNIFICANT REDUCTIONS IN TG AND HDL-C
- SIGNIFICANT 3.2% REDUCTION IN BODY WEIGHT

Barnard et al. *Arch Intern Med* 1991;151:1389-1394.

DEAN ORNISH, MD







Intensive Lifestyle Changes for Reversal of Coronary Heart Disease

Dean Ornish, MD; Larry W. Scherwitz, PhD; James H. Billings, PhD, MPH; K. Lance Gould, MD; Terri A. Merritt, MS; Stephen Sparler, MA; William T. Armstrong, MD; Thomas A. Ports, MD; Richard L. Kirkeide, PhD; Charissa Hogeboom, PhD; Richard J. Brand, PhD

Context.—The Lifestyle Heart Trial demonstrated that intensive lifestyle changes may lead to regression of coronary atherosclerosis after 1 year.

Objectives.—To determine the feasibility of patients to sustain intensive lifestyle changes for a total of 5 years and the effects of these lifestyle changes (without lipid-lowering drugs) on coronary heart disease.

Design.—Randomized controlled trial conducted from 1986 to 1992 using a randomized invitational design.

Patients.—Forty-eight patients with moderate to severe coronary heart disease were randomized to an intensive lifestyle change group or to a usual-care control group, and 35 completed the 5-year follow-up quantitative coronary arteriography.

Setting.—Two tertiary care university medical centers.

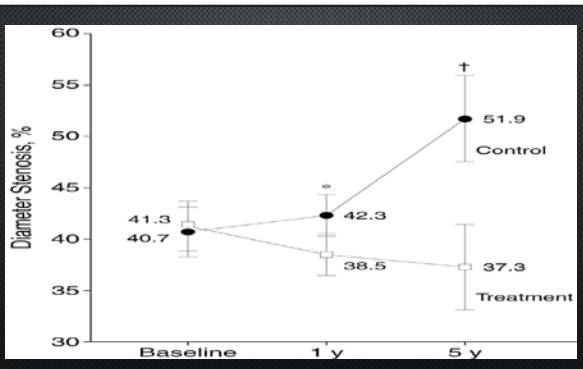
Intervention.—Intensive lifestyle changes (10% fat whole foods vegetarian diet, aerobic exercise, stress management training, smoking cessation, group psychosocial support) for 5 years.

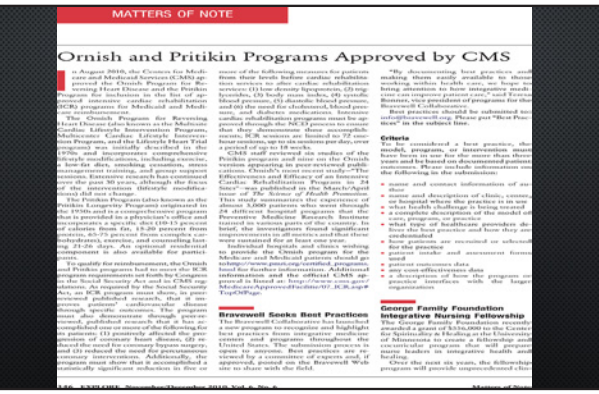
Main Outcome Measures.—Adherence to intensive lifestyle changes, changes in coronary artery percent diameter stenosis, and cardiac events.

THE LIFESTYLE Heart Trial was the first randomized clinical trial to investigate whether ambulatory patients could be motivated to make and sustain comprehensive lifestyle changes and, if so, whether the progression of coronary atherosclerosis could be stopped or reversed without using lipid-lowering drugs as measured by computer-assisted quantitative coronary arteriography. This study derived from earlier studies that used noninvasive measures.[1,2]

After 1 year, we found that experimental group participants were able to make and maintain intensive lifestyle changes and had a 37.3% reduction in low-density lipoprotein (LDL) choles-

Ornish, D. et al. (1998). JAMA, 280, 2001–2007





MATTERS OF NOTE

Ornish and Pritikin Programs Approved by CMS

In August 2010, the Centers for Medicare and Medicaid Services (CMS) approved the Ornish Program for Reversing Heart Disease and the Pritikin Program for Intensive Cardiac Rehabilitation (ICR) programs for Medicaid and Medicare reimbursement.

The Ornish Program for Reversing Heart Disease (also known as the Multicenter Lifestyle Demonstration Project, Multicenter Cardiac Lifestyle Intervention Program, and the Lifestyle Heart Trial program) was initially described in the 1970s and incorporates comprehensive lifestyle changes, including a very low-fat, low-fat diet, smoking cessation, stress management training, and group support sessions. Extensive research has continued over the past 30 years, although the focus of the intervention (lifestyle modification) did not change.

The Pritikin Program (also known as the Pritikin Longevity Program) originated in the 1950s and is a comprehensive program that is provided in a physician's office and incorporates a specific diet (10-15 percent fat, 15-20 percent protein, and 65-75 percent from complex carbohydrates), exercise, and counseling lasting 21-26 days. An optional residential component is also available for participants.

To qualify for reimbursement, the Ornish and Pritikin programs must meet the CMS program requirements set forth by Congress in the Social Security Act and in CMS regulations. As required by the Social Security Act, an ICR program must show, in part-nership with a physician, that it improves patients' cardiovascular disease through specific outcomes. The program must also demonstrate through peer-reviewed, published research that it has accomplished one or more of the following for its patients: (1) positively affected the progression of coronary heart disease; (2) reduced the need for coronary bypass surgery; and (3) reduced the need for percutaneous coronary interventions. Additionally, the program must show that it accomplished a statistically significant reduction in five or more of the following measures for patients from their levels before cardiac rehabilitation services to after cardiac rehabilitation services: (1) body weight; (2) body mass index; (3) body fat; (4) systolic blood pressure; (5) diastolic blood pressure; and (6) the need for cholesterol, blood pressure, and diabetes medications. Intensive cardiac rehabilitation programs must be approved through the NCD process to ensure that Medicare beneficiaries receiving intensive ICR sessions are limited to 72 one-hour sessions, up to six sessions per day, over a period of up to 18 weeks.

CMS staff reviewed six studies of the Pritikin program and nine studies of the Ornish program, and none met the CMS criteria. Generally, most recent study—"The Effectiveness and Efficacy of an Intensive Cardiac Rehabilitation Program in 24 Sites"—was published in the March/April issue of *The Science of Health Promotion*. The study examined the outcomes of almost 3,000 patients who were through 24 different hospital programs that the Preventive Medicine Research Institute trained in various parts of the country. In the study, improvements in risk factors and body measurements in all metrics noted that these were sustained for at least one year.

Individual hospitals and clinics wishing to provide the Ornish program for the Medicare and Medicaid patients should go to http://www.pmri.org/certified_programs.html for more information. The Pritikin information, and the official CMS approval is found at: http://www.cms.gov/MedicareApprovedFacilities/07_ICR_topOfPage.

Braveswell Seeks Best Practices

The Braveswell Collaborative has launched a new program to recognize and highlight best practices from integrative medicine programs and practitioners around the United States. The submission process is open to anyone. Best practices are reviewed by a committee of experts and, if approved, posted on the Braveswell Web site to share with the field.

"By documenting best practices and making them easily available to those seeking within health care, we hope to encourage more integrative medicine programs and improve patient care," said Frank Bonner, vice president of programs for the Braveswell Collaborative.

Best practices should be submitted to info@braveswell.org. Please put "Best Practices" in the subject line.

Criteria

To be considered a best practice, the model, program, or intervention must have been in use for the more than three years and be based on documented patient outcomes. Please include information on the following in the submission:

- name and contact information of author
- name and description of clinic, center, or hospital where the practice is in use
- what health challenge is being treated
- a description of the model of care, program, or practice
- what type of healthcare providers deliver the best practice and how they are credentialed
- how patients are recruited or selected for the practice
- patient intake and assessment forms used
- patient outcomes data
- how outcomes data is collected
- a description of how the program or practice interfaces with the larger organization

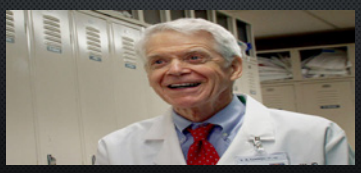
George Family Foundation Integrative Nursing Fellowship

The George Family Foundation recently awarded a grant of $350,000 to the Center for Spirituality & Healing at the University of Minnesota to develop a graduate level curricular program that will prepare nurse leaders in integrative health and healing.

Over the next six years, the fellowship program will provide unprecedented clin-

A STRATEGY TO ARREST AND REVERSE CORONARY ARTERY DISEASE: A 12-YEAR LONGITUDINAL STUDY OF A SINGLE PHYSICIAN'S PRACTICE

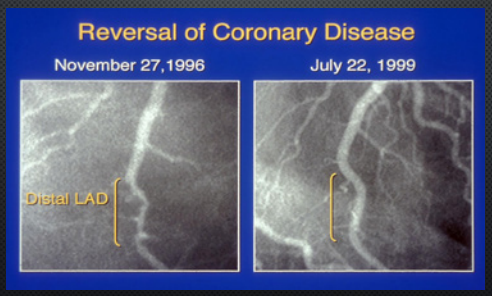
Caldwell B. Esselstyn, Jr., MD



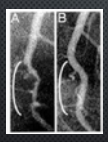
EXCLUDED

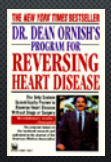
- Added Oils
- Fish
- Fowl
- Meat
- ALL Dairy

Diet – 11% fat – plant based
Cholesterol lowering medication
Unstructured exercise

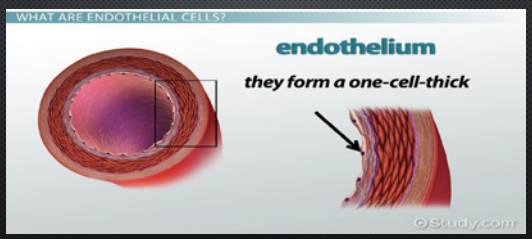


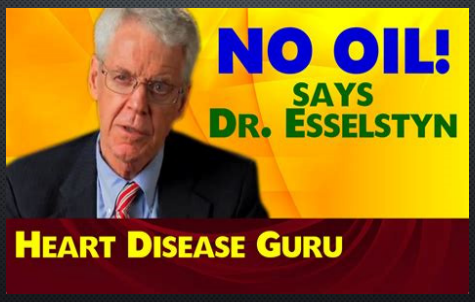
HEART DISEASE IS REVERSIBLE WITH DIET & LIFESTYLE!



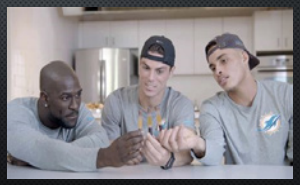


DOES OLIVE OIL HARM ARTERIES?





THE FAMOUS "VOGEL" STUDY



CLINICAL STUDIES — Endothelial Function

The Postprandial Effect of Components of the Mediterranean Diet on Endothelial Function

Robert A. Vogel, MD, FACC, Mary C. Corretti, MD, FACC, Guy D. Plotnick, MD, FACC

Baltimore, Maryland

THE QUICK READ

- THE OLIVE OIL MEAL REDUCED FMD 31%
- THE REMAINING FOUR MEALS DID NOT REDUCE FMD

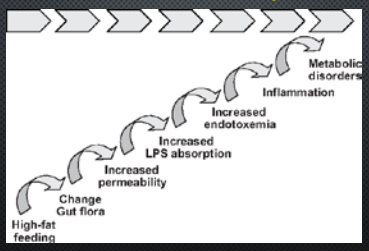
THE COMPLETE DATA

Table 2. Heart Rate, Blood Pressure, and Brachial Artery Blood Flow, Diameter, and Flow-Mediated Vasodilation Before and After Five High-Fat Meals in 10 Healthy Subjects

	Olive Oil and Bread	Canola Oil and Bread	Salmon and Crackers	Olive Oil, Bread, and Vits C/E	Olive Oil, Bread, Salad, and Vinegar
Preprandial					
Heart rate, (beats/min)	60 ± 7	64 ± 7	57 ± 7	62 ± 8	57 ± 7
Heart rate, (beats/min)	59 ± 6	61 ± 7	58 ± 7	61 ± 8	59 ± 9
BP, (mm Hg)	113/70 ± 9/5	116/74 ± 7/6	109/68 ± 2/4	111/73 ± 10/4	107/72 ± 8/6
BP, (mm Hg)	111/69 ± 12/6	115/71 ± 8/7	111/64 ± 8/8	112/69 ± 9/8	110/68 ± 10/7
Blood flow, (ml/min)	129 ± 52	119 ± 68	143 ± 96	145 ± 94	105 ± 47
Blood flow, (ml/min)	810 ± 325	839 ± 380	904 ± 433	842 ± 365	900 ± 342
Arterial diam, (cm)	3.22 ± 0.62	3.29 ± 0.60	3.31 ± 0.66	3.34 ± 0.61	3.28 ± 0.52
FMD (%)	14.3 ± 4.2	13.0 ± 3.4	13.1 ± 5.2	13.3 ± 6.8	13.5 ± 3.5
Postprandial					
Heart rate, (beats/min)	63 ± 10	62 ± 7	58 ± 7	63 ± 12	59 ± 6
Heart rate, (beats/min)	64 ± 9	63 ± 11	57 ± 7	65 ± 10	59 ± 8
BP, (mm Hg)	112/71 ± 9/5	116/70 ± 11/7	108/69 ± 11/6	108/68 ± 12/6	108/70 ± 13/6
BP, (mm Hg)	110/70 ± 9/9	115/68 ± 9/8	109/64 ± 12/5	109/62 ± 12/6	110/72 ± 11/7
Blood flow, (ml/min)	134 ± 65	129 ± 87	122 ± 64	127 ± 77	122 ± 72
Blood flow, (ml/min)	792 ± 328	856 ± 385	924 ± 318	856 ± 361	880 ± 336
Arterial diam, (cm)	3.33 ± 0.63	3.32 ± 0.68	3.32 ± 0.67	3.32 ± 0.68	3.31 ± 0.63
FMD (%)	9.9 ± 4.9*	11.6 ± 4.4	12.8 ± 5.1	12.1 ± 5.7	12.1 ± 3.5

Subscript 1 = baseline; BP = blood pressure; diam = diameter; FMD = flow-mediated vasodilation; subscript 10 = postchelsea.
*p = 0.008.

METABOLIC ENDOTOXEMIA WITH ALL MEALS



MAYBE IT IS OK TO EAT A PANZANELLA SALAD WITH EVOO?

CORDIOPREV STUDY:

CORONARY DIET INTERVENTION WITH OLIVE OIL AND CARDIOVASCULAR PREVENTION

PLOS MEDICINE

OPEN ACCESS PEER-REVIEWED
RESEARCH ARTICLE

Mediterranean diet and endothelial function in patients with coronary heart disease: An analysis of the CORDIOPREV randomized controlled trial

Elena M. Yubero-Serrano, Carolina Fernandez-Gandara, Antonio Garcia-Rios, Oriol A. Rangel-Zuñiga, Francisco M. Gutierrez-Mariscal, Jose D. Torres-Peña, Carmen Marin, Javier Lopez-Moreno, Justo P. Castaño, Javier Delgado-Lista, Jose M. Ordovas, Pablo Perez-Martinez, Jose Lopez-Miranda

Published: September 9, 2020 • https://doi.org/10.1371/journal.pmed.1003282

PLOS MEDICINE

Mediterranean diet and endothelial function in patients with coronary heart disease: An analysis of the CORDIOPREV randomized controlled trial

- RANDOMIZED CLINICAL TRIAL INVOLVING 1002 PATIENTS WITH CORONARY DISEASE THAT ARE UNDERGOING ONE OF TWO DIETS IN A RANDOMIZED DESIGN FOR 7 YEARS.
- A) LOW FAT DIET: <30% FAT LOW IN OLIVE OIL
- B) MEDITERRANEAN DIET: >35% FAT HIGH IN OLIVE OIL

PLOS MEDICINE

Mediterranean diet and endothelial function in patients with coronary heart disease: An analysis of the CORDIOPREV randomized controlled trial

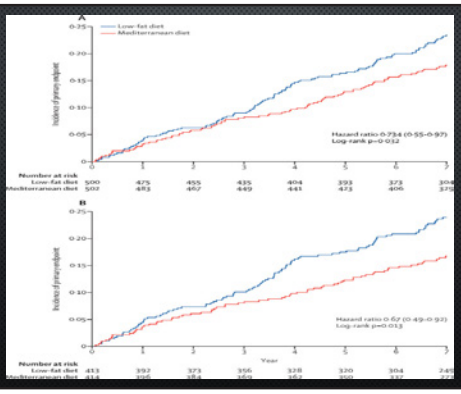
MEDITERRANEAN DIET WERE GIVEN EXTRA VIRGIN OLIVE OIL (1 LITER/WEEK). THIS AMOUNT WAS NOT INTENDED TO BE FOR THE EXCLUSIVE USE OF THE PARTICIPANT, BUT FOR THE FAMILY TO USE AT HOME IF NEEDED.

THE PARTICIPANTS RANDOMIZED TO THE LOW-FAT DIET RECEIVED RECOMMENDATIONS FOCUSED ON LIMITING ALL TYPES OF FAT, FROM BOTH ANIMAL AND VEGETABLE SOURCES, AND ON INCREASING THE INTAKE OF COMPLEX CARBOHYDRATES.

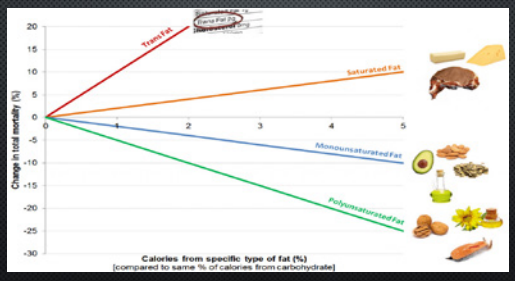

PLOS MEDICINE

Mediterranean diet and endothelial function in patients with coronary heart disease: An analysis of the CORDIOPREV randomized controlled trial

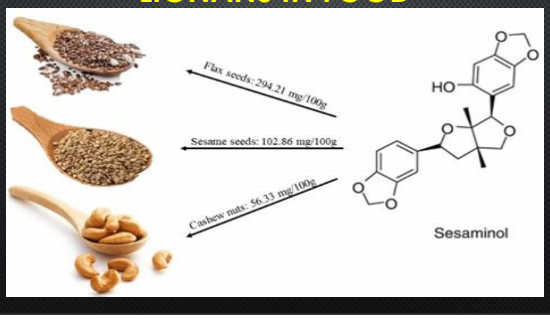
OUR RESULTS SUGGEST THAT THE MEDITERRANEAN DIET BETTER MODULATES ENDOTHELIAL FUNCTION COMPARED WITH A LOW-FAT DIET EVEN IN THOSE WITH SEVERE ENDOTHELIAL DYSFUNCTION.



HARVARD SCHOOL OF PUBLIC HEALTH



TOP THREE SOURCES OF LIGNANS IN FOOD



LIGNAN INTAKE AND RISK OF CORONARY HEART DISEASE

- Prospective study followed 214,108 men and women in 3 cohorts who did not have cardiovascular disease or cancer at baseline.
- Increased long-term intake of lignans was associated with a significantly lower risk of total CHD in both men and women.
- J Am Coll Cardiol 2021 Aug 17;78(7):666-678

AVOCADOS: YES OR NO?

Foods To Be Avoided

Soups: Cream Soups.

Meats: All glandular organs, as liver, brains, kidney, sweetbreads; pork and very fat meats, fat fish, fish roe.

Milk and Milk Products: Whole milk, cream, cheddar, Swiss and all rich cheese and cheese spreads; excessive butter and butter substitutes.

Eggs: Egg yolks.

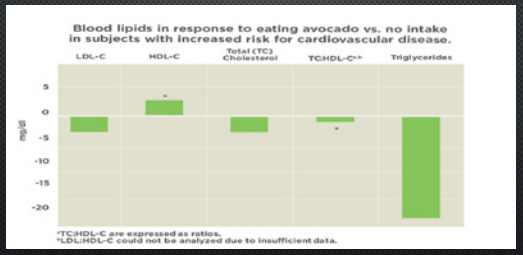
Breads: Hot breads, pancakes, waffles, coffee cakes, muffins, doughnuts.

Desserts: Any made with cream and egg yolks; pies, frozen creams, rich cakes and cookies.

Concentrated Fats: The excessive use of fats in any form, as salad dressings, olive or vegetable oils, suet, chicken or pork fat.

Miscellaneous: Rich gravies, olives, nuts and avocados.

AVOCADOS AND CHOLESTEROL MEASURES



Mahmassani, H., Avendano, E., Gowri, R. and E.J. Johnson. Avocado consumption increases and risk factors for heart disease: A systematic review and meta-analysis. AJCN 2018

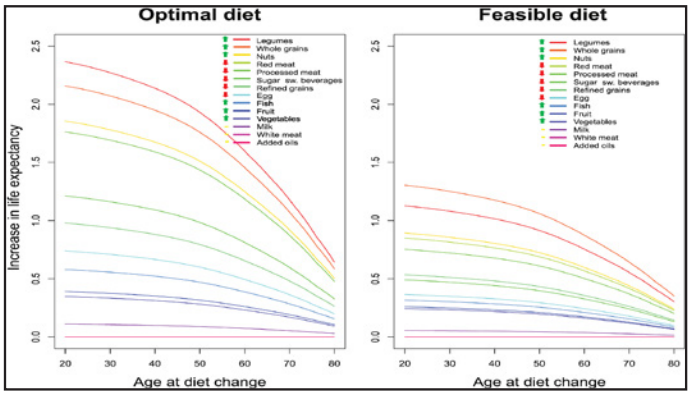
THREE TOP FOODS FOR LIFE EXPECTANCY

GBD 20

CELEBRATING 20 YEARS
OF COLLABORATION AND INNOVATION

ESTIMATING IMPACT OF FOOD CHOICES ON LIFE EXPECTANCY: A MODELING STUDY

- THE LARGEST GAINS WOULD BE MADE BY EATING MORE:
  LEGUMES (FEMALES: 2.2, MALES: 2.5)
- WHOLE GRAINS (FEMALES: 2.0, MALES: 2.3)
- NUTS (FEMALES: 1.7 MALES: 2.0)
- LESS RED MEAT (FEMALES: 1.6 MALES: 1.9) AND
- LESS PROCESSED MEAT FEMALES: 1.6 MALES: 1.9



CONCLUSIONS: EAT MOSTLY PLANTS!

SELF EVALUATION

The Role of Nutrition in Heart Disease

True/False

1. Ancel Keys Ph.D. led a study called the 77 Countries Study published in 1990.

2. In the Seven Countries Study a relationship between high blood cholesterol and high heart disease rates was identified.

3. In all countries with a high fat diet, heart disease rates were very high.

4. There are many randomized studies show reversal of heart disease with the ketogenic and carnivore diets.

5. Dean Ornish, MD led the Lifestyle Heart Trial showing reversal of heart disease based on symptoms, stress testing and coronary angiograms.

6. The highest source of lignans in the diet is found in full fat dairy foods.

7. The Global Burden of Disease study found that there was a longer lifespan with legumes, whole grains, and nuts.

Answer Key: 1. F, 2. T, 3. F, 4. F, 5. T, 6. F, 7. T

FACULTY

David B. Mandell, JD, MBA

David B. Mandell, JD, MBA, of Ft. Lauderdale, Florida, is a practicing attorney in The Law Offices of David B. Mandell, PC, and a principal of the doctor focused wealth management firm OJM Group, LLC. He specializes in risk management, asset protection, and financial planning and has authored a number of books for doctors including his latest, *Wealth Strategies for Today's Physician: A Multi-Media Playbook*. His articles have appeared in over 100 publications, including over 30 medical specialty journals, and he has addressed many of the nation's leading medical conferences. Mr. Mandell holds a bachelor's degree from Harvard University from which he graduated with honors, a law degree from the UCLA School of Law where he was awarded the "American Jurisprudence Award" for achievement in legal ethics and earned his MBA from UCLA'S Anderson School of Management.

You may contact Mr. Mandell with any questions or comments at (877) 656–4362 or by email at mandell@ojmgroup.com.

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Reducing Doctor Stress Through Asset Protection

David B. Mandell, JD, MBA

Today's Presentation

1. Background on why this topic is important
2. Enduring strategies
   a. Asset protection fundamentals
   b. Practice protections
   c. Shielding physicians' & dentists' personal assets
3. Recent cases and developments

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WHY ASSET PROTECTION MATTERS

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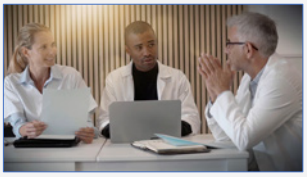
Types of Liability Facing Physicians

- Medical malpractice
- Employer liability
  - Sexual harassment ("hostile work environment"); Wrongful termination (protected classes); Violation of fiduciary duty (qualified plans)
- Billing issues
  - Over-billing, improper billing, fraud, violation of anti-kickback rules, Stark rules, etc.
- HIPAA
- Premises liability
- Personal liability



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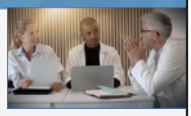
Costs of Liability Concerns: Doctors



- From the American Congress of Obstetricians and Gynecologists (ACOG) website:

Obstetrician–gynecologists should recognize that being a defendant in a medical professional liability lawsuit can be one of life's most stressful experiences. Negative emotions in response to a lawsuit are normal, and physicians may need help from family members, peers, or professionals to cope with this stress.

https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2013/01/coping-with-the-stress-of-medical-professional-liability-litigation

- Concerns about potential liability increase stress, burnout, and defensive medicine.

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Costs of Liability Concerns: The System

- Approximately 80-90% of doctors openly practice defensive medicine, making it a major driver of increasing healthcare costs and negative economic consequences.
- The total cost of the practice ranges from $46 billion to $300 billion annually, although most estimates are between $50–65 billion when factoring in benefits and costs.

Source: https://equilibriumecon.wisc.edu/2024/07/17/eq-vol-14-defensive-medicine-the-economic-implications-at-and-beyond-the-healthcare-sector/

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ASSET PROTECTION FUNDAMENTALS

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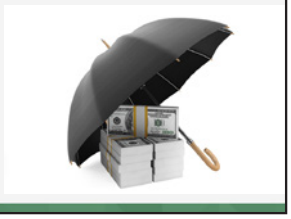
Asset Protection Defined

What is Asset Protection?

Multidisciplinary approach to shielding practice and personal assets from future liability.

- Multidisciplinary: insurance, legal, financial
- Practice & Personal
- Future Liability
- Diagnostic and treatment model



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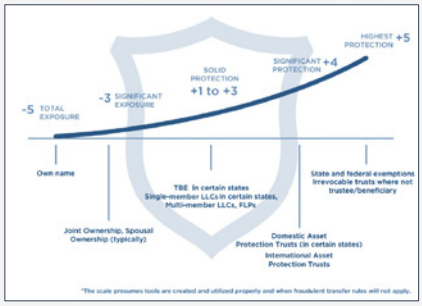
Asset Protection Sliding Scale



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PRACTICE ASSET PROTECTION

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Practice/Ancillaries Protection

- Insurances
- Choice of entity
- LLC lease-backs
- Qualified retirement plans
- Non-qualified plans
- Advanced tools

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Insurances as Front-Line Protectors

- Types of policies
  - Medical or dental malpractice
  - General Liability
  - Cyber
  - Landlord
  - Other
- Be aware of coverage limitations, deductibles
- Review and get second opinions

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Protecting Equipment and Real Estate

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Maximize Protective Benefit Plans

- **Shields #1 asset – cash flow**
- Qualified retirement plans (QRPs): state exemption laws vary
  - Most states also protect QRPs to an unlimited value
  - Some states: value limitations
  - Some states: timing claw-backs
- Non-qualified plans – depends on funding mechanism
  - COLI – about 20 states provide (+5) exemption
  - Other states: can use trusts or LLCs

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PERSONAL ASSET PROTECTION

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Titling Assets: Does It Protect?

- Spousal
- Basics: Tenancy in common, joint tenancy
- Tenancy by the Entirety (TBE)
- Community Property

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Start With Exempt Assets (+5)

- (+5) Federal or state exempt asset
- No gifting, compliance, accounting fees or special taxes
- Protection cannot be matched by any other planning
- Federal bankruptcy exemptions for QRPs and IRAs
- States vary widely
  - Homestead
  - QRPs, IRAs
  - Life insurance and annuities

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LLCs (+2): Ideal for Most Assets Beyond Exemptions

- Inside Creditors
- Outside Creditors Isolates their lawsuit damage only to LLC property
  - Creditors can only get "charging order" against the LLC interest (+1 to +3) depending on use, compliance
  - Should tie into your estate plan
- "Building blocks" of asset protection
- *Control and Access*

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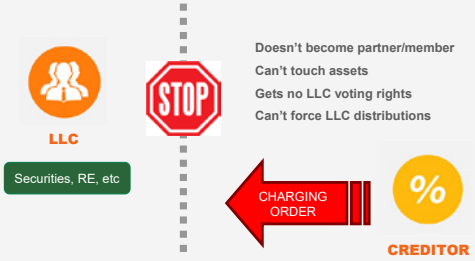
What a Charging Order Means



Doesn't become partner/member
Can't touch assets
Gets no LLC voting rights
Can't force LLC distributions

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Keys to Protection: LLCs

- Proper operating agreement
- Compliance with annual formalities
- Non-asset protection purpose: estate planning/gifting
- Jurisdiction: use the best state, when you have options
- Many LLCs are lacking in 1 of the 4 elements above: vulnerable
- Key: experienced attorney who has annual monitoring/gifting plan

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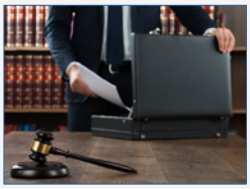
Using Trusts to Protect Assets

- Revocable trusts
  - "Family," "living," "loving trusts"
  - Valuable for probate avoidance, in event of incapacity
  - No asset protection while you are alive
- Irrevocable trusts
  - Many types, including ILITs, GRATs, CRTs and DAPTs
  - Because they are irrevocable, strong asset protection
  - **DAPT is most innovative, newest**
    - 20 states
    - "Hybrid" version for other states
    - Different than LLCs



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NEW DEVELOPMENTS IN ASSET PROTECTION

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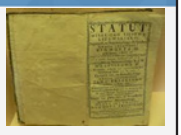
Important Statutory Changes

- **California add "means test" to exemption for qualified retirement plans**
  - New law made changes to CCP § 704.115 which protects qualified retirement plans from lawsuits and creditor claims
  - Where these plans were totally protected before, as of January 1, 2025, a court now can look at all of the doctor's assets and determine how much of these balances are "reasonably needed for retirement"
  - One prominent commentator put this at $250,000 as a ballpark. The rest could be vulnerable to the claim.



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Important Cases

245 Park Member LLC v HNA Group (Int'l) Co., 2024 WL 1506798 (2nd Cir., 4/8/24)

- Business vs. business claim: $185 million judgment
- Judgment creditor went after a Manhattan building to satisfy judgment
- Single member Delaware LLC
- Court applied NY law, not Delaware law, and allowed a "turnover" rather than "charging order"

- **Lessons: single member LLCs have some vulnerabilities; for real estate, can't rely on "better state" LLCs as well as you can for investment accounts**

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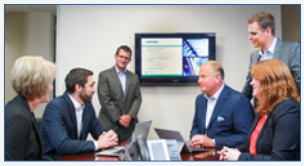
About OJM Group

- Specialized, fee-based wealth management firm
- 18 years in business; doctor clients in 48 states
- Multidisciplinary; three divisions
- Corporate and personal planning
- Goal: Reducing physician financial stress



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How We Work With Physicians & Dentists

- **Investing**
  - RIA
  - Fiduciary, independent custodian
  - Tax-focused
- **Insurance and Benefits**
  - Life, disability, long term care insurance
  - Through partner firm, P&C coverages
  - Qualified and non-qualified plans
- **Consulting**

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Personal Wealth Planning

- **Diagnostic vs. Treatment**
- **Advice and Expertise for a Flat Fee**
- **Building a Relationship**

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- Guests include physicians of all specialties and wealth management industry experts
- Nearly 100 episodes published to date
- Available on Apple Podcasts, Spotify and other popular podcast platforms
- Video versions of episodes now available on YouTube
- Scan the QR Code to listen and subscribe!

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Wealth Strategies for Today's Physician: A Multi-Media Playbook

- New content from OJM: Our first book since 2020!
- Co-authored by OJM Group partners
- Innovative multi-media format includes more than 90 links to videos and podcast episodes that offer unique perspectives and real-world examples
- Videos to be periodically updated by OJM so that the Playbook remains current over time
- Crafted in six informative Strategies that can help physicians protect assets, reduce taxes, invest wisely and build wealth for retirement
- Bonus Strategy for medical practice owners and *doctorpreneurs*

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SELF EVALUATION

Reducing Doctor Stress Through Asset Protection

1. T/F - According to the American Congress of Obstetricians and Gynecologists (ACOG), being a defendant in a medical malpractice lawsuit can be one of the most stressful events in a doctor's life.

2. Most estimates on the annual cost to the U.S. medical system due to defensive medicine is:

a. $100 million
b. $100 billion
c. $50-60 billion
d. Negligible

3. Which of the following tools are generally used to shield practice real estate?

a. Limited liability companies (LLCs)
b. Community property
c. Spousal ownership
d. State or federally exempt assets

4. Which is a tool to shield cash flow at a practice:

a. Limited liability companies (LLCs)
b. Qualified retirement plans (QRPs)
c. Irrevocable trusts
d. Revocable trusts

5. T/F - Revocable trusts do not provide asset protection to you as the grantor while you are alive.

Answer Key: 1. T, 2. C, 3. A, 4. B, 5. T

Dilip Moonka, MD

Dilip Moonka, MD, of Detroit, Michigan, is the Medical Director of the Henry Ford Liver Transplant Program, is an expert in liver transplantation and hepatitis C. As previous director of Henry Ford's Viral Hepatitis Clinic, he developed unique and highly effective protocols for patients suffering from hepatitis B who are in need of liver transplantation. In addition, as director of clinical research in that division, he published studies on more effective and safer immunosuppressions. Dr. Moonka also has extensive experience in clinical research on hepatitis C with both novel therapies and pegylated interferon. Dr. Moonka earned his medical degree from Stanford University in Palo Alto, California where he also completed a residency in internal medicine. He completed a fellowship in gastroenterology at the University of Pennsylvania in Philadelphia with advanced training in liver disease. He is board certified in internal medicine and gastroenterology.

You may contact Dr. Moonka with your questions or comments at DMOONKA1@hfhs.org.

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Division of Gastroenterology and Hepatology

Dilip Moonka, MD, FAST, FAASLD
Medical Director of Liver Transplantation

Non-Alcoholic Fatty Liver Disease

Non-alcoholic FATTY LIVER DISEASE

"New Name and New Options"

Dilip Moonka, MD

Medical Director of Liver Transplantation

Henry Ford Health System

FATTY LIVER DISEASE

"New Name and New Options"

- Speaker: Madrigal, Intercept, Gilead
- There will be discussion of non-FDA approved drugs

FAT AND THE LIVER

IT'S BAD FOR PEOPLE TOO

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Which of the following is true of NAFLD?

- Approximately a third of patients with NAFLD are likely to progress to advanced fibrosis.
- NAFLD is now the leading indication for liver transplant
- The shift in nomenclature away from NAFLD is due to the fact that the "F" or "fatty" was felt to be stigmatizing
- NAFLD is primarily a problem in Europe and North America because of Western diets
- Rates of obesity on the US were increasing but have stabilized since 2020.

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

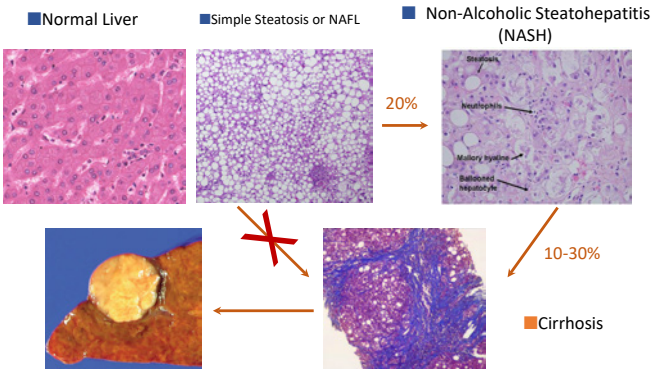
- NAFLD is a burgeoning problem in the US and the world because of an increase in metabolic syndrome and obesity
- We will discuss the recent changes in nomenclature
- In evaluating patients with NAFLD, the critical distinction is between simple steatosis and non-alcoholic steatohepatitis and the assessment of fibrosis is critical
- The emphasis in evaluating NAFLD is on non-invasive modalities
- Medical therapy for NAFLD is evolving

NAFLD: ESTIMATED GLOBAL PREVALENCE: 25%

- Meta-analysis: NAFLD by imaging (US, CT, MRI/SPECT: n=45 studies).
- Of patients with NAFLD, 6-29% will have NASH

Younossi ZM, et al. Hepatology 2016

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)



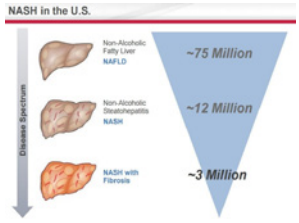
Brown GT. Metabolism 2016

Is it important to distinguish NASH from Simple Steatosis?

OUTCOME	MASH	Simple Steatosis
Fibrosis Progression (1)	1 stage every 7 years	1 stage every 14 years
HCC (2)	5.29 per 1000 person years	0.44 per 1000 person years
Liver Specific Mortality (2)	11.77 per 1000 person years	0.77 per 1000 person years
Overall Mortality (2)	25.56 per 1000 person years	15.44 per 1000 person years

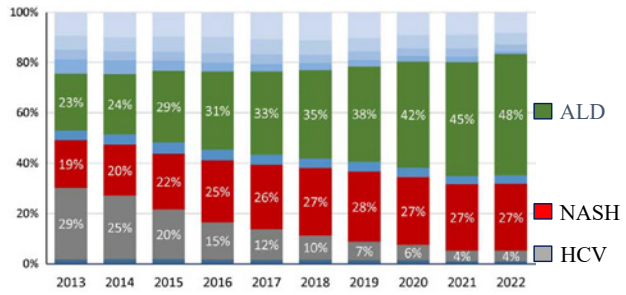
(1) Singh S, et al. Clin Gastroenterol and Hep 2015; (2) Younossi Z, et al. Hepatology 2016; 64:73-84

NAFLD: ESTIMATED U.S. PREVALENCE



- Leading indication for liver transplant
- Fastest growing cause of liver cancer
- $100 billion annual health care expenditure

LIVER TRANSPLANT: CHANGING INDICATIONS

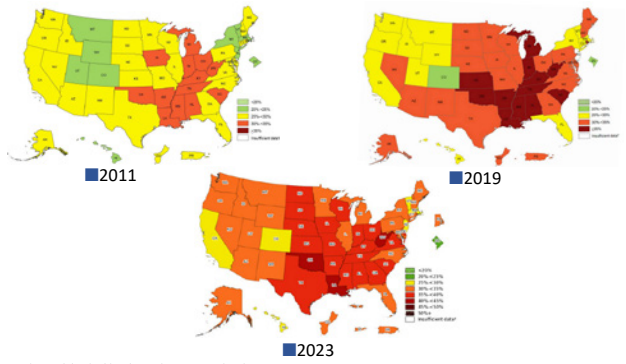


Younossi ZM, et al. Hepatol Comm 2024

DEFINITIONS OF WEIGHT BY BODY MASS INDEX (BMI)

- BMI < 18.5: Underweight
- BMI 18.5 to < 25: Healthy weight range
- BMI 25 to < 30: Overweight
- BMI 30 to < 40: Obese
- BMI over 40: Morbidly obese

CDC: U.S. OBESITY TRENDS (BMI > 30)



www.cdc.gov/obesity/data/prevalence-maps.html

Alcohol: How Much is too Much?

- A standard drink (SD) contains about 14 g of alcohol.
- Women: < 20 g/day is mild: > 40 g/day is heavy
- Men: < 30 g/day is mild: > 60 g/day is heavy

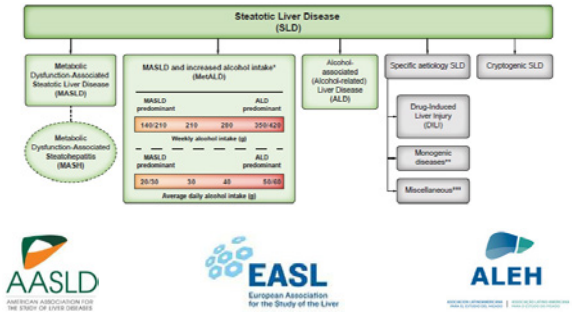
Fatty Liver Disease: Nomenclature

- It has always been appreciated that "obesity" can lead to hepatic steatosis, inflammation and fibrosis.
- In 1980 Jurgen Ludwig proposed the term nonalcoholic steatohepatitis or NASH to describe this phenomenon
- The term non-alcoholic fatty liver disease or NAFLD was used to encompass the full histologic spectrum of fatty liver disease
- NAFLD defined by evidence of fat in the liver on imaging or histology in the absence of any other cause of hepatic steatosis.
- Two issues:
  - The term "fatty" was considered "stigmatizing"
  - The term "non-alcoholic" was often inaccurate

Ludwig J. et al. Mayo Clin Proc 1980: Rinella et al. J Hepatol 2023

Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD/MASH)

Rinella, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol 2023;79:1542-1556.



Metabolic Dysfunction Associated Steatotic Liver Disease (MASLD/MASH)

- Steatotic Liver Disease (SLD): presence of fat in the liver by imaging or histology.
- MASLD: fat in the liver along with one cardiometabolic risk factor and no other cause of steatosis.
  - 98% of patients who previously met the definition of NAFLD meet the definition of MASLD.
- If the other cause of steatosis is alcohol, the diagnosis would revert to MetALD or ALD.
- ALD and MetALD are the leading causes of Steatotic liver disease (SLD).
- Fat can dissipate from the liver when cirrhosis settles in.

MASLD/MASH: Cardiometabolic Risk Factors (CMRF)

Adult criteria

At least 1 out of 5:

- ☐ BMI ≥25 kg/m² [23 Asia] **OR** WC >94 cm (M) 80 cm (F) **OR** ethnicity adjusted equivalent
- ☐ Fasting serum glucose ≥5.6 mmol/L [100 mg/dl] **OR** 2-hour post-load glucose levels ≥7.8 mmol/L [≥140 mg/dl] **OR** HbA1c ≥5.7% [39 mmol/L] **OR** type 2 diabetes **OR** treatment for type 2 diabetes
- ☐ Blood pressure ≥130/85 mmHg **OR** specific antihypertensive drug treatment
- ☐ Plasma triglycerides ≥1.70 mmol/L [150 mg/dl] **OR** lipid lowering treatment
- ☐ Plasma HDL-cholesterol ≤1.0 mmol/L [40 mg/dl] (M) and ≤1.3 mmol/L [50 mg/dl] (F) **OR** lipid lowering treatment

NAFLD: ETIOLOGY

The hallmark of NAFLD is insulin resistance

Type 2 Diabetes (T2DM)
- 30-75% will have NAFLD
- Bidirectional association

Obesity
- Most common and best documented risk factor for NAFLD
- > 95% undergoing bariatric surgery have NAFLD

Hypertension

Dyslipidemia
- High triglycerides
- High cholesterol to HDL ratio
- 50% of patients in lipid clinics

Ethnicity
- Hispanics ↑
- African-Americans ↓
- Patatin-like phospholipase domain-containing protein 3 (PNPLA-3)
  - rs738409 C>G variant

NAFLD: ETIOLOGY

Table 1. Recipient and Donor Characteristics According to Liver Disease Etiologies: 2008-2017

	NASH n = 6344	HCV n = 17,037	ALD n = 9279	p value
Recipient gender				
Male	3517 (55.4)	12,460 (73.1)	7181 (77.4)	< .001
Female	2827 (44.6)	4577 (26.9)	2098 (22.6)	
Recipient ethnicity (%)				
White	5234 (82.5)	11,448 (67.2)	7198 (77.6)	< .001
Black	116 (1.8)	2357 (13.8)	357 (3.8)	
Hispanic	803 (12.7)	2396 (14.1)	1439 (15.5)	
Asian	105 (1.7)	597 (3.5)	166 (1.8)	
Others	86 (1.4)	239 (1.4)	119 (1.3)	

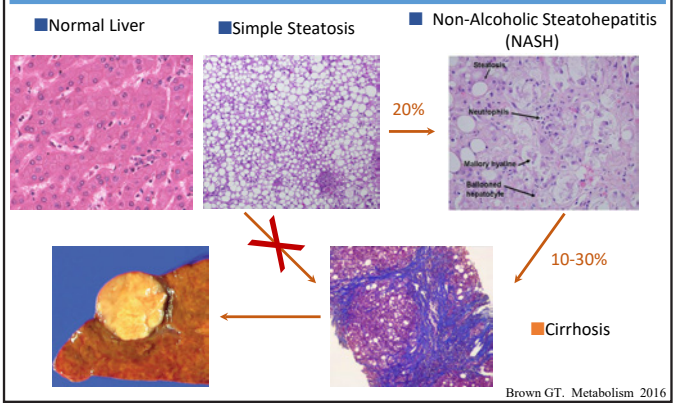
US Census Data 2020

- **Black population: 14.2%**
- **Hispanic-Latino population: 19.5%**

- *PNPLA3*: patatin-like phospholipase domain-containing 3
  - Membrane-bound enzyme, expressed in adipose tissue and liver, where it mediates acylglycerol hydrolysis
  - Allele I148M (rs738409) is associated with increased hepatic steatosis and is common in Hispanics (0.49) but less so in European Americans (0.23) and African Americans (0.17)
  - A protective allele, *PNPLA3*-S453I, is common in African-Americans (MAF=0.104) but rare in European-Americans (0.003) and Hispanics (0.008)

Nagai - Moonka Clin Gastroenterol and Hepatol 2019; Romeo et al, Nat Gen 2008: Krawczyk et al, Gastroenterol 2020

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)



Brown GT. Metabolism 2016

NAFLD: PATHOPHYSIOLOGY
TWO HIT HYPOTHESES

- 1ST hit
  - Insulin resistance results in lipogenesis and impaired lipolysis
  - Triglycerides accumulate in the liver
- 2nd HIT
  - Mitochondria dysfunction leads to release of reactive oxygen species (ROS) which can lead to cellular injury
  - Activation of macrophage mediated inflammatory cascades leads to activation of hepatic stellate cells.

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

In evaluating patients with NAFLD, which is true?

- Typically a normal ALT rules of NASH.
- Advances in non-invasive tests (NIT) now allow the distinction between simple steatosis and NASH
- NAFLD is associated with metabolic syndrome and ethnicity does not play a significant role
- On ultrasonography, fat in the liver is echogenic and the liver will appear dark.
- The phosphatidylethanol (PEth) test is a reliable test to rule out significant alcohol use.

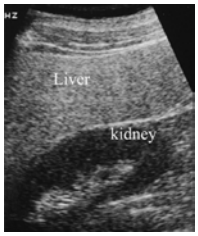
NAFLD: DIAGNOSIS

- AASLD: Does not advise routine screening for NAFLD in the population at large.
- Individuals who are at high-risk for NAFLD should be screened for advanced fibrosis.
  - T2DM
  - Medically complicated obesity
  - Family history of cirrhosis
  - Moderate to heavy alcohol consumption
- All patients with hepatic steatosis or clinically suspected NAFLD based on the presence of obesity and metabolic risk factors should undergo primary risk assessment with FIB-4

Rinella M. et al. AASLD Practice Guidelines Hepatol 2023

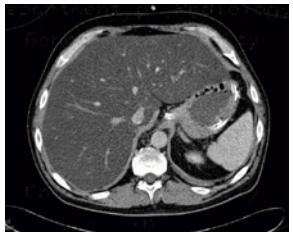
NAFLD DIAGNOSIS: IMAGING

ULTRASOUND



- Non-invasive, widely available and inexpensive
- Increase liver brightness and hepatorenal contrast with vascular blurring
- Limitations: operator dependent, poor sensitivity for mild steatosis (30%) and no fat or fibrosis quantitation

COMPUTED TOMOGRAPHY (CT)



- More specific than ultrasound
- Reduced attenuation correlated with degree of hepatic steatosis
- Can identify some signs of portal hypertension

Hashimoto E. J Gastro Hep 2013

NAFLD: EVALUATION

- Rule out other causes of liver disease
- Assess simple steatosis vs. NASH
  - Fibrosis used as a surrogate marker
- Assess disease severity and prognosis
  - Patients with NASH and F2 fibrosis or greater are referred to as "at-risk" NASH
- Identify modifiable causes of NAFLD: metabolic syndrome

Rinella M. et al. AASLD Practice Guidelines Hepatol 2023

NAFLD: DIAGNOSIS

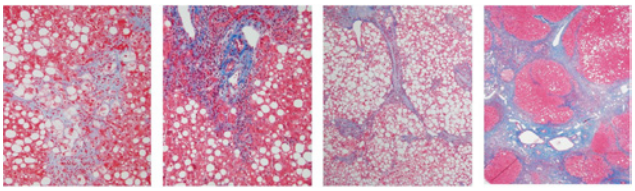
- Between 25-50% of patients with NAFLD with have normal AST and ALT
- Critical to rule out other causes of hepatic steatosis or liver disease
  - Alcoholic Liver Disease
  - Viral Hepatitis (Hepatitis C Antibody and Hepatitis B surface Antigen)
  - Autoimmune liver disease (ANA, ASMA and AMA)
  - Wilson's, hemochromatosis and alpha-1 antitrypsin deficiency
- Medications that can cause steatosis
  - Corticosteroids
  - Antiretrovirals (HAART), Amiodarone, Methotrexate, Parenteral Nutrition, Tamoxifen, valproic acid
- Serum ferritin is frequently elevated in NAFLD
- Up to 20% of NAFLD patients can have positive autoimmune markers

PHOSPHATIDLYETHANOL (PETH) TEST

- Phospholipid formed only in presence of alcohol
- Alcohol consumption in the last 28 days
- Sensitivity of 90% for two or more drinks a day
- Specificity of 100% with threshold of 20 ng/dl
- Validated as a quantitative test
- Negative with unintentional, low-level ETOH use
- Not affected by age, sex, anemia or renal function
- Validated in liver disease
- Send out lab with turn around of one-two weeks: $75
- Positive in 23.8% of ALD transplant patients who deny ETOH

Fleming MF, et al. Alcohol Clin Exp Res 2017 41: 857

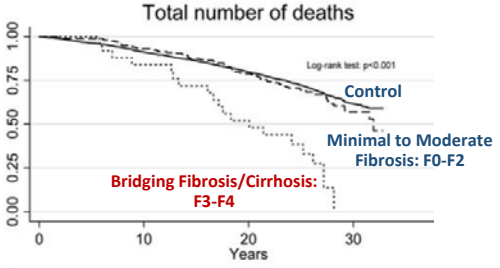
STAGES OF FIBROSIS FROM NASH



Stage 1: Perisinusoidal Fibrosis | Stage 2: Periportal Fibrosis | Stage 3: Bridging Fibrosis | Stage 4: Cirrhosis

Albhaisi S. Pharmac Med 2019

NAFLD AND FIBROSIS: MORTALITY



- Fibrosis stage is the strongest indicator of death in NAFLD
- Fibrosis progression rate of NASH is 1 stage every 7 years
- Causes of Death in NAFLD: CV, liver failure and malignancy

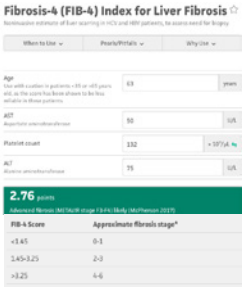
Ekstedt M. Hepatology 2015: Chalasani N Hepatology 2018

NON-INVASIVE TESTS TO DETERMINE THE PRESENCE OF FIBROSIS

Test	Diagnostic Ability (AUROC)	Comments
Enhanced liver fibrosis panel	0.87	Detects markers of matrix turnover, which includes tissue inhibitor metalloproteinase 1, N-terminal propeptide of type III procollagen, and hyaluronic acid
Fibrometer	0.82	Includes ALT, AST, GGT, platelets, prothrombin time index, α_2-macroglobulin, hyaluronic acid, ferritin, glucose, and urea
FibroTest	0.81	Components include age, sex, bilirubin, GGT, haptoglobin, α_2-macroglobulin, and apolipoprotein A1
BARD score	0.81	Components include BMI, AST/ALT ratio, and diabetes
NFS	0.84	Validated scoring system; components include age, diabetes, BMI, AST, ALT, platelets, and albumin
FIB-4 index	0.84	Reliably excludes advanced fibrosis because of high NPV. Components include age, AST, and platelets
APRI	0.67	Initially developed for use in hepatitis C virus. Not specific for NAFLD
vCTE	0.83-0.95	Results may be invalid in obese patients (BMI >35 kg/m^2); hence a FibroScan XL probe is developed to overcome this problem
MRE	0.92	Widespread clinical adoption is limited because of its high cost and low availability

Tariq T. Clin Liver Dis 2020

NAFLD FIBROSIS: MARKERS

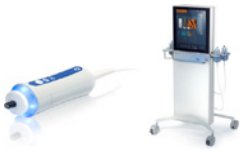


- Simple and relies on readily available information
  - There is an EPIC dotphrase (.fib4)
- Inexpensive
- High negative predictive value for significant fibrosis.
  - Sensitivity of 85% and specificity of 65%

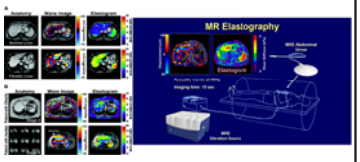
McPherson Gut 2010: Tsai Clin Liver Dis 2018: Loomba Clin Gastroenterol and Hepatol 2019

NAFLD FIBROSIS: FibroScan and MRE

Transient Elastography: FibroScan



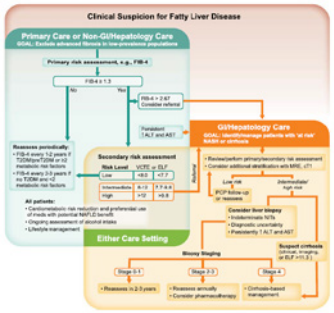
MR-Elastography (MRE)



- Non-invasive
- Measures a larger area than biopsy
- Quantifies fibrosis and steatosis
- High sensitivity and specificity for advanced fibrosis
- kPA < 7.9 reliably excludes F2-4 Fibrosis
- Evaluates anatomy, steatosis and fibrosis
- Highest accuracy for fibrosis
- Issues of availability, expertise and cost

Park C et al. Gastroenterol 2017: Tapper et al. Am J Gastroenterol 2016

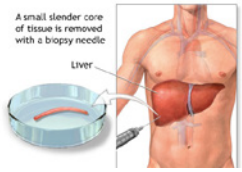
NAFLD EVALUATION: RISK STRATIFICATION



Rinella M. et al. AASLD Practice Guidelines Hepatol 2023

NAFLD FIBROSIS: LIVER BIOPSY

- Gold Standard
- Pitfalls
  - Invasive with risks
  - Expensive
  - Sampling error
- Role of liver biopsy
  - Clarify competing diagnoses
  - Accurate staging when non-invasive testing is indeterminate or conflicting
  - Establish urgency for therapy
    - I will often consider biopsy in younger patients



NAFLD THERAPY

Which is true of medical therapy for NAFLD?

- For therapy to work, it must be administered early before significant fibrosis has set in.
- Vitamin E did show improvements in fibrosis in NASH but has been associated with prostate cancer.
- GLP-1 agonists are effective, result in weight loss and are well tolerated
- There is approved therapy for NASH.
- All are true.

NAFLD THERAPY

- Statins are safe and typically recommended for patients with NAFLD
- Hypertriglyceridemia can be managed with lifestyle changes, omega-3 fatty acids, fibrates or icosapent ethyl
- Death from nonhepatic malignancies is increased in NAFLD and adherence to recommended cancer screening is critical
- Patients with F2-4 fibrosis should abstain from alcohol use
- Coffee consumption (caffeinated or not) of three cups or more is associated with less fibrosis in patients with NASH.

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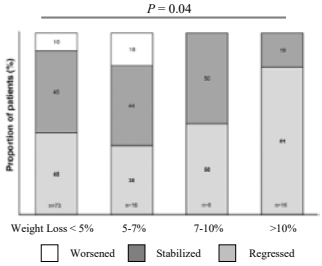
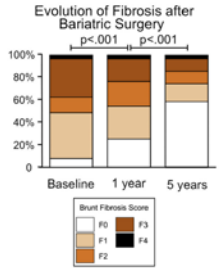
NAFLD THERAPY: WEIGHT LOSS

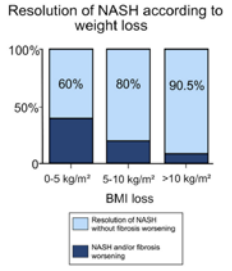
- Cuban study of 261 patients with biopsy proven NASH
  - = Paired liver biopsy after 1 year
- Hypocaloric, low-fat diet
- Sustained weight loss has significant effect on fibrosis
- Weight loss of 7-10% necessary for effect
- Fewer than 10% of patients achieved this weight loss at 1 year



Vilar-Gomez et al. Gastroenterol 2015

NAFLD : WEIGHT LOSS (BARIATRIC) SURGERY



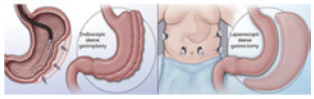


- French, single center study of 180 patients: 125 at 1 year: 64 at 5 years
- Different bariatric procedures performed over the time of the study
- 5 years: 84.4% of patients had resolution of NASH with no worsening of fibrosis

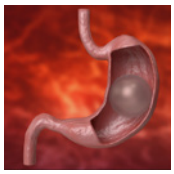
Lassailly G. Gastroenterol 2020

NAFLD : ENDOSCOPIC BARIATRIC THERAPY (EBT)

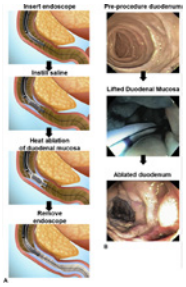
- Endoscopic Sleeve Gastroplasty



- Space Occupying Devices

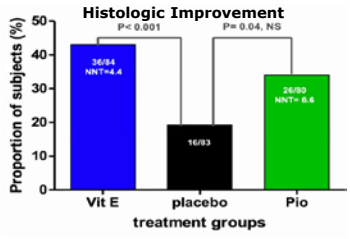


- Duodenal Mucosal Resurfacing



Haidry R. Gastrointest Endo 2019

NAFLD THERAPY: VITAMIN E

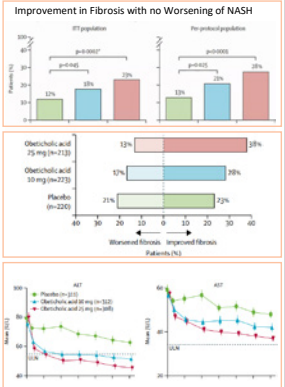


- Vitamin E at 800 IU improves histology but not fibrosis
- AASLD: It may be considered in non-diabetic, non-cirrhotic patients
- Increased risk of prostate cancer

Sanyal et al. NEJM 2010

NAFLD: MEDICAL THERAPY
OBETICHOLIC ACID (OCA)

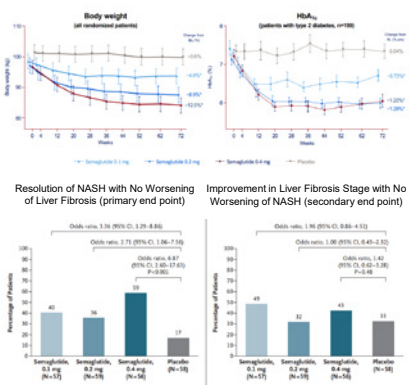
- OCA: FXR receptor antagonist
- Regenerate Trial
- Randomized, double-blind, placebo controlled
- 931 Patients: Placebo vs. OCA 10 mg vs. OCA 25 mg
- 18 months of therapy: Interim analysis
- Primary endpoint: improvement in fibrosis with no worsening of NASH
- Adverse reaction: pruritus (51% in 25 mg dose)



Younossi et al. Lancet 2019

NAFLD : GLUCAGON-LIKE PEPTIDE-1 (GLP-1) AGONIST: SEMAGLUTIDE

- Semaglutide: GLP-1 receptor agonist
- Randomized, double-blind, placebo controlled
- 320 Patients: Placebo vs. Semaglutide 0.1, 0.2, 0.4 mg
- 72 weeks with daily SQ injections
- Primary endpoint: resolution of NASH with no worsening of fibrosis
- No change in fibrosis
- AE: nausea (42% vs. 11%), vomiting, constipation



Newsome et al. NEJM 2020

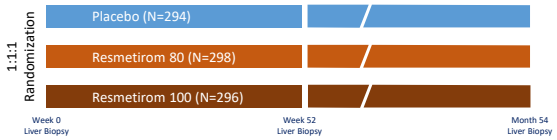
NAFLD THERAPY

- Semaglutide can be considered for its approved indications of T2DM and obesity in NASH in that improves NASH and is associated with cardiovascular benefit
- Pioglitazone can be considered in that it improves NASH but is associated with weight gain.
- Vitamin E can be considered in patients with NASH and without diabetes in that it can improve NASH.
- Semaglutide, pioglitazone and vitamin E have not shown an antifibrotic effect in patients with NASH.

Rinella M. et al. AASLD Practice Guidelines Hepatol 2023

RESMETIROM (Rezdiffra)
MAESTRO-NASH

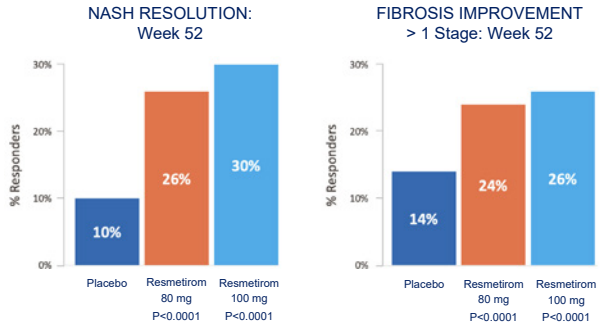
THR-β AGONIST: Once Daily Pill



- Randomized, double-blind, placebo-controlled
- Patients with biopsy proven NASH
- 3 of 5 metabolic risk factors
- F2-F3 fibrosis: no patients with cirrhosis
- 14% of patients were taking GLP-1 agonist

Harrison NEJM 2024

RESMETIROM (Rezdiffra)
MAESTRO-NASH



Harrison NEJM 2024

RESMETIROM (Rezdiffra)
MAESTRO-NASH

	Placebo	Resmitirom 80 mg	Resmetirom 100 mg
Decrease in fibrosis by two stages	2.8%	8.3	10.1
LDL decrease	+ 0.1%	13.6	16.3
Decrease in steatosis by CAP score	14.5%	40%	41%
Decrease in steatosis by MRI-PDFF	10%	42%	51%
Decrease in liver size	1%	22%	26%

RESMETIROM: MAESTRO-NASH
Adverse Events

	Placebo	Resmetirom 80 mg	Resmetirom 100 mg
Discontinuation	4 per 100 PY	5 per 100 PY	8 per 100 PY
Diarrhea	14%	23%	33%
Nausea	9%	18%	15%

- Diarrhea was mild to moderate with no episodes of severe diarrhea
- 50% of cases were worsening of pre-existing diarrhea
- Diarrhea typically occurred after about 9 days and resolved within a month
- Mild transaminase elevations were common in the first month and typically resolved by the end of the second month

Rinella M. et al. AASLD Practice Guidelines Hepatol 2023

NAFLD : MEDICAL THERAPY
PHASE III CLINICAL TRIALS

Agent	Target	Trial
Resmetirom	THR-β agonist	Long term open label and cirrhosis
Aramchol	SCD-1 inhibitor	On Hold
Semaglutide	GLP-1-RA alone or in combination	ESSENCE: Phase III
Lanfibranor	Pan-PPAR agonist	NATiV3: Phase III
Pegozafermin	FGF19/21	ENLIGHTEN: Phase III
Efruxifermin	FGF19/21	SYNCHRONY: Phase III

NAFLD: CONCLUSIONS

- NAFLD and NASH (MASLD/MASH) are common and increasing causes of disease morbidity and mortality
- In evaluating patients with NAFLD, the critical distinction is between simple steatosis and NASH
- Fibrosis is a surrogate marker for NASH with prognostic value and patients with F2 fibrosis are “at-risk” patients with an increased need for monitoring and therapy
- A variety of non-invasive instruments are available for evaluating fibrosis in NASH
- Resmetirom (Rezdiffra) is approved for NASH in patients with F2-F3 fibrosis along with diet and exercise
- Lifestyle modifications, GLP-1 agonists and bariatric surgery and bariatric endoscopic therapy are additional options

SELF EVALUATION

Non-Alcoholic Fatty Liver Disease

1. Which is true of NAFLD?

a. NAFLD is a growing problem and is now the leading indication for liver transplant in the US.
b. NAFLD is primarily a medical problem in Europe and North America.
c. NAFLD will lead to significant liver damage in a majority of affected individuals.
d. A majority of individuals with NAFLD will not have non-alcoholic steatohepatitis (NASH).
e. Rates of obesity in the US were increasing but have been stable since 2015.

2. In evaluating patients with NAFLD, which is true?

a. Typically a normal ALT rules out NAFLD.
b. Non-invasive modalities can reliably distinguish simple steatosis from NASH.
c. NAFLD is associated with metabolic syndrome and ethnicity does not play a significant role.
d. On ultrasonography, fat in the liver is echogenic and a “fatty liver” will appear dark.
e. The phosphatidylethanol (PETH) test is a reliable test to rule out significant alcohol use.

3. Which of the following are have been shown to slow or reduce fibrosis in NAFLD?

a. Bariatric surgery
b. Weight loss
c. Obeticholic acid
d. Resmetirom
e. All of the above

4. Which is true of medical therapy for NAFLD?

a. For medical therapy to work, it must be given when patients have simple steatosis and before they develop NASH.
b. Vitamin E did showed improvements in fibrosis in patients with NASH but has been linked to prostate cancer.
c. There are no approved medical therapies for NAFLD.
d. GLP-1 agonists are effective, result in weight loss and are well tolerated.
e. None are true.

5. T/F - Going forward, the liver biopsy has no role in the evaluation of patients with NAFLD because of the overall accuracy of non-invasive tests.

6. T/F - Resmetirom is effective in reducing steatosis and fibrosis in the liver but has to be monitored carefully because, as a thryroid hormone receptor (THR) agonist, it can affect cardiac function.

7. T/F - The liver biopsy is not valuable in distinguishing between alcohol related liver disease and NAFLD.

Answer Key: 1. D, 2. E, 3. E, 4. E, 5. F, 6. F, 7. T

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Hypertension: Where We Are and How We Got Here

The Payoffs of Treating HTN

- MI: reduced ±25%
- Stroke: reduced ±40%
- CHF: reduced ±50%

Chobanian AV, et al. *Hypertension.* 2003;42(6):1206-1252.

HTN
Where We Are
TODAY

ESH Guidelines

2023 ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension

Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA)

Mancia G, et al. *J Hypertens* 2023;41(12):1874-2071

Categories of BP in Adults*
≥2 readings on ≥ 2 occasions

Category	SBP		DBP
Normal	<120 mm Hg	**and**	<80 mm Hg
Elevated	120–129 mm Hg	**and**	<80 mm Hg
HTN			
Stage 1	130–139 mm Hg	**or**	80–89 mm Hg
Stage 2	≥140 mm Hg	**or**	≥90 mm Hg

*If 2 categories differ: designate higher BP category

AMERICAN COLLEGE of CARDIOLOGY ADAPTED American Heart Association. life is why

HTN Guideline 2023
European Society of Hypertension

Category	SBP mm Hg		DBP mm Hg
Optimal	**<120**	**and**	**<80**
Normal	**120-129**	**and**	**80-84**
High Normal	**130–139 mm Hg**	**or**	**85-89**
HTN			
Grade 1	**140-159**	**or**	**90-99**
Grade 2	**160-179**	**or**	**100-109**

Mancia G, et al. *J Hypertens* 2023;41(12):1874-2071

Definition of HTN: Home BP
European Society of Hypertension 2023

Category	SBP mm Hg		DBP mm Hg
HTN	**≥135**	**and/or**	**≥85**

Mancia G, et al. *J Hypertens* 2023;41(12):1874-2071

Thresholds for Pharmacologic Rx of HTN
European Society of Hypertension 2023

Group	SBP mm Hg		DBP mm Hg
Age 18-79	140	and/or	90
Age >80	160*		
CVD	130	and/or	80

*may consider SBP 140-159 mm Hg

Mancia G, et al. *J Hypertens* 2023;41(12):1874-2071

BP Targets
European Society of Hypertension 2023

Group	SBP mm Hg		DBP mm Hg
Age 18-64	<130	and	<80
Age 65-79	<140*	and	<80
Age 65-75 ISH	140-150*		
Age ≥80	140-150*		

*may consider SBP 130-139 mm Hg if well tolerated; caution if DBP <70 mm Hg or frail

Mancia G, et al. *J Hypertens* 2023;41(12):1874-2071

2020 Int Society HTN Guideline
HTN Categorization: *Out of Office*

Category	SBP &/or DBP mm Hg
ABPM	
24 hr. avg	≥130/80
Daytime avg	≥135/85
Overnight avg	≥120/70
Home BP	≥135/85

Unger T et al *Hypertension* 2020;75:1334-1357

2020 Int Society HTN Guideline
"Optimal" BP Rx Regimen

Step 1
Dual low dose* combo A + C

Step 2
Dual full dose combo A + C

Step 3
Triple combo A + C + D

Step 4
Triple Combo + S or O

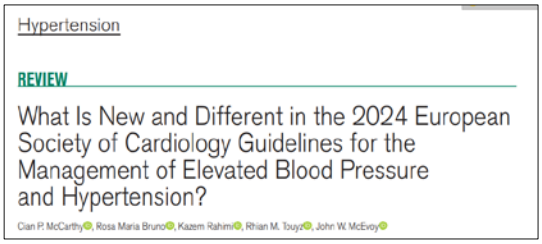
A = ACE, ARB
C = CCB (DhP)
D = Diuretic
S = Spironolactone
O = Other (amiloride, doxazosin, eplerenone, clonidine, BB)

Unger T et al *Hypertension* 2020;75:1334-1357

HTN Pharmacologic Rx 2026
My Prediction (Nostrildamus)

Initiate Rx mm Hg	Target BP mm Hg
130/80	120-129/<80

HTN in Older Adults:
The Perspective in 2025


Hypertension

REVIEW

What Is New and Different in the 2024 European Society of Cardiology Guidelines for the Management of Elevated Blood Pressure and Hypertension?

Cian P. McCarthy, Rosa Maria Bruno, Kazem Rahimi, Rhian M. Touyz, John W. McEvoy

McCarthy CP et al *Hypertension* 2025;82(March):432-444

Essential HTN Questions

- Does Lowering BP in REALLY BAD HTN Improve Outcomes? (1967 VA Cooperative Study I)
- Does Lowering BP in LESS BAD HTN Improve Outcomes? (1967 VA Cooperative Study II)
- Which is More Important: SBP or DBP? (MRFIT 1992)
- Why Do Older Folks Get ISH?
- How About Isolated Systolic HTN? (SHEP 1993)

Essential HTN Questions

- What Agent Should We Start With? (ALLHAT 2002)
- Can Tx of Pre-HTN Prevent HTN (TROPHY 2006)
- How About Really Old Folks? (HYVET)
- Since ALLHAT Proved That Most Patients Need at Least 2 Meds, Which TWO? (ACCOMPLISH 2008)
- Is chlorthalidone REALLY the best diuretic?
- Best BP Goal in High Risk non-DM (SPRINT 2016)
- Best BP Goal in DM (BPROAD 2025)

Is There a Benefit from Treating Really BAD HTN?

VA Cooperative Study (I)

- Study: RDBPCT in Stage 3-4 HTN (n=143)
- Inclusion: DBP 115-129 mm Hg
- Demographics
  - 66 white, 77 AA men
  - Mean: age 51 yrs
- Rx (18 months) vs placebo :
  - Hydralazine 25-50 mg tid
  - Reserpine 0.1 mg bid
  - HCTZ 50 mg qd

VA Cooperative Study Group. *JAMA*. 1967;202:1028-1034.

The VA Cooperative Study (1967): Outcomes at 18 Months

*all p < 0.001	Placebo N=70	Active Drug* N = 73
Accelerated HTN	12	0
Stroke	4	1
Coronary event	2	0
CHF	2	0
Renal Damage	2	0
Death	4	0

VA Cooperative Study Group. *JAMA*. 1967;202:1028-1034.

What About BP That's Not QUITE So Bad?

VA Cooperative Study (II)

- Study: RDBPCT in Stage 2-3 HTN (n=380)
- Inclusion: DBP 90-114 mm Hg
- Demographics
  - 42% AA, 58% 'other'
  - Mean: age 50 yrs
- Rx (±39 months) vs placebo :
  - Hydralazine 25-50 mg tid
  - Reserpine 0.1 mg bid
  - HCTZ 50 mg qd

VA Cooperative Study Group. *JAMA*. 1970;213:11143-1152.

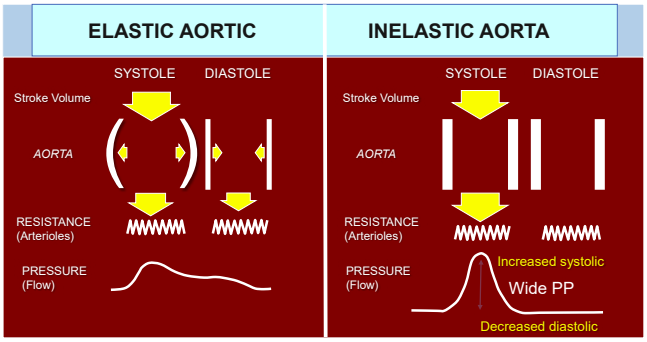
The VA Cooperative Study II (1970): Outcomes at 39 months

*all p < 0.001	Placebo N=194	Active Drug* N = 186
Accelerated HTN	4	0
Stroke	20	6
Coronary event	13	11
CHF	11	0
Renal Damage	3	0
Death	19	8

VA Cooperative Study Group. *JAMA*. 1970;213:1143-1152.

Why Do Older Folks Get Systolic HTN?

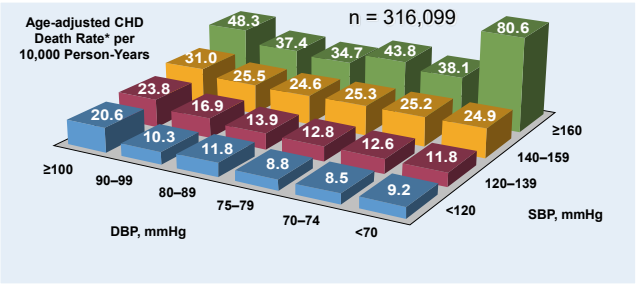
SBP/DBP Discrepancy with Aging



Victor RG, Kaplan NM. Systemic HTN: Mechanisms and Dx. *Braunwald's Heart Disease*. 8th ed. Philadelphia, PA: Saunders Elsevier; 2008:1027–1048.

Is SBP or DBP More Important?

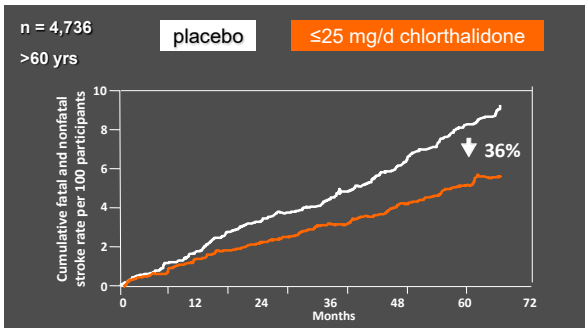
MRFIT: Effect of BP on CHD Mortality



Neaton JD et al. *Arch Intern Med*. 1992;152:56–64.

Does Rx of Isolated SBP Improve Outcomes?

Systolic Hypertension in the Elderly Program (SHEP)



SHEP Cooperative Research Group *JAMA* 1991;265:3255-3264

NEXT

(…fast forward 35 years, 1967-2002)

A Bazillion CV Trials on Individual HTN Agents, ALL of Which Work to Some Degree

Well, EVERYTHING Seems to Work, so What is the BEST INITIAL HTN Rx?

U.S. Department of Health and Human Services

National Institutes of Health

National Heart, Lung, and Blood Institute

"Major Outcomes in High Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic"

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

The ALLHAT Collaborative Research Group

Sponsored by the National Heart, Lung, and Blood Institute (NHLBI)

JAMA. 2002;288:2891-2997 (Dec 18)

ALLHAT: Abstract

Context

"Antihypertensive Rx is well established to ↓ hypertension-related morbidity and mortality, but the optimal first-step Rx is unknown"

ALLHAT Collaborative Research Group "Major Outcomes in High-Risk Hypertensive Patients Randomized to ACEI or CCB vs Diuretic" JAMA 2002;288:2981-2997

ALLHAT: Abstract

Objective

"To determine whether Rx with a CCB or an ACEI lowers the incidence of CHD or other CVD vs Rx with a diuretic"

ALLHAT "Major Outcomes in High-Risk HTN Patients Randomized to ACEI or CCB vs Diuretic" JAMA 2002;288:2981-2997

ALLHAT: Abstract

Design & Setting

- RDB Active-Controlled Trial 1994-2002
- Age ≥ 55 (n=33,357) + ≥ 1 other CHD risk factor

ALLHAT "Major Outcomes in High-Risk HTN Patients Randomized to ACEI or CCB vs Diuretic" JAMA 2002;288:2981-2997

ALLHAT: Abstract

Interventions

- Chlorthalidone 12.5-25 mg/d (n=15,255)
- Amlodipine 2.5-10mg/d (n=9,048)
- Lisinopril 10-40 mg/d (n=9,054)
- Planned followup 4-8 years

ALLHAT "Major Outcomes in High-Risk HTN Patients Randomized to ACEI or CCB vs Diuretic" JAMA 2002;288:2981-2997

ALLHAT: Abstract

Main Outcome Measures

- PRIMARY: Fatal CHD + nonfatal MI
- SECONDARY:
  - All Cause Mortality
  - Stroke (fatal + nonfatal)
  - Combined CHD (1^0 + PCTA + angina admit)
  - Combined CVD (CHD, stroke, angina, CHF, PAD)

ALLHAT "Major Outcomes in High-Risk HTN Patients Randomized to ACEI or CCB vs Diuretic" JAMA 2002;288:2981-2997

ALLHAT: Abstract

Results (at mean followup = 4.9 years)

- PRIMARY: CLTD = CCB =ACEI
- SECONDARY (RR= compared to CLTD):
  - All Cause Mortality: All groups =
  - CHF: CCB RR = 1.38 ACEI RR = 1.19
  - Combined CVD: ACEI RR = 1.10
  - Stroke: ACEI RR = 1.15

ALLHAT "Major Outcomes in High-Risk HTN Patients Randomized to ACEI or CCB vs Diuretic" JAMA 2002;288:2981-2997

ALLHAT: Abstract

Conclusions

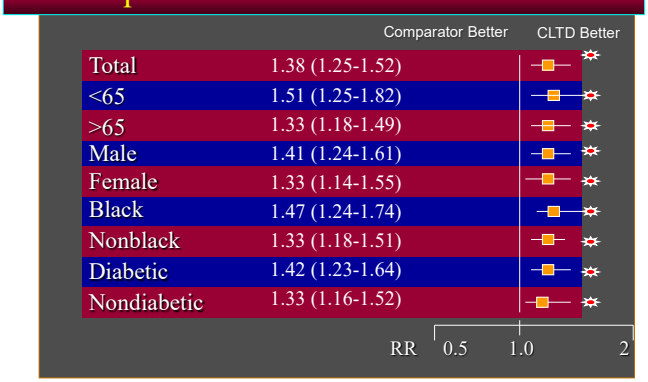
"Thiazide-type diuretics are superior in preventing 1 or more major forms of CVD and are less expensive. They should be preferred for first-step antiHTN therapy."

ALLHAT "Major Outcomes in High-Risk HTN Patients Randomized to ACEI or CCB vs Diuretic" JAMA 2002;288:2981-2997

Lisinopril vs Chlorthalidone: Stroke

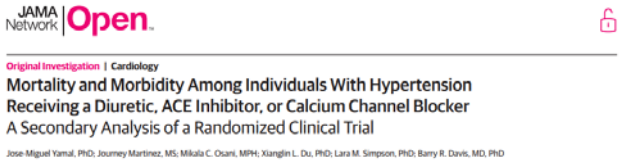
ALLHAT JAMA 2002;288:2981-2997

Amlodipine vs Chlorthalidone: Heart Failure



ALLHAT JAMA 2002;288:2981-2997

ALLHAT 23 Years Later Same Outcomes



JAMA Network Open

Original Investigation | Cardiology

Mortality and Morbidity Among Individuals With Hypertension Receiving a Diuretic, ACE Inhibitor, or Calcium Channel Blocker
A Secondary Analysis of a Randomized Clinical Trial

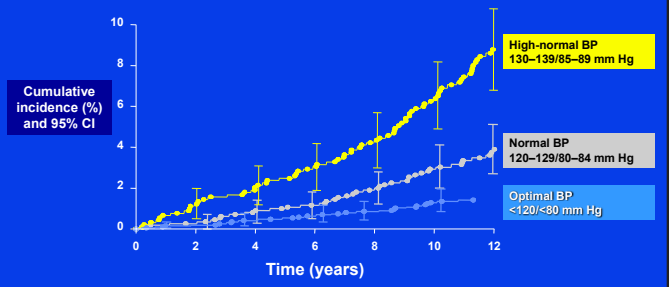
Jose-Miguel Yamal, PhD; Journey Martinez, MS; Mikala C. Osani, MPH; Xianglin L. Du, PhD; Lara M. Simpson, PhD; Barry R. Davis, MD, PhD

Yamal JM, et al. *JAMA Open* 2023;6(12):e234498

Rx of HTN is A Good Thing. What About Pre-HTN?

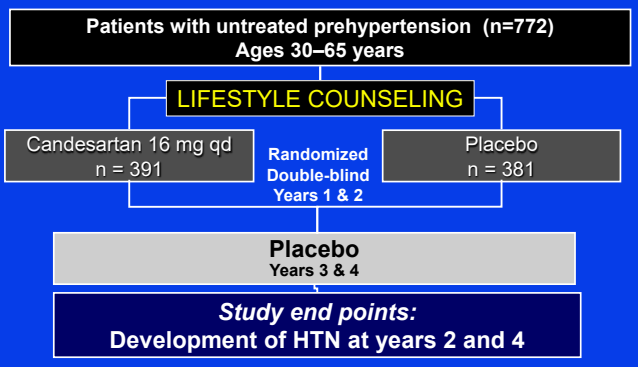
High-normal BP increases CV risk

Incidence of CV events in women: Framingham



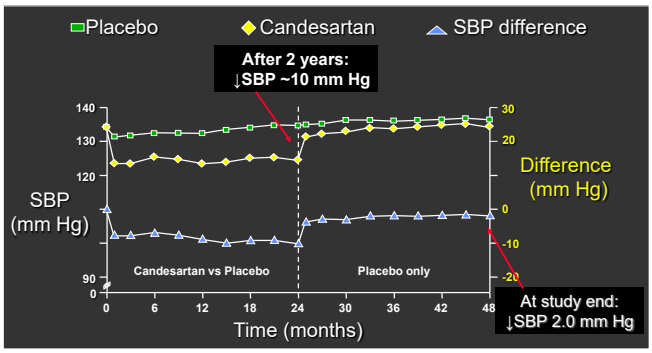
Vasan RS et al. *N Engl J Med.* 2001;345:1291-7.

TROPHY: Study design



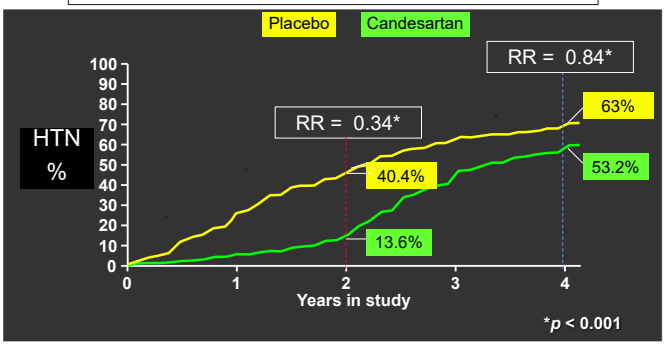
Julius S et al. *N Engl J Med.* 2006;354:1685-97.

TROPHY: BP by treatment group



Julius S et al. *N Engl J Med.* 2006;354:1685-97.

Development of Clinical HTN
(SBP >140 mmHg OR DBP >90 mmHg)



Julius S et al. *N Engl J Med.* 2006;354:1685-97.

HTN Rx Works in Mid-Life. What About 'Super-Seniors' (≥80 yrs)?

HTN in the Very Elderly Trial
HYVET

- STUDY: PRDBPCT 2-year HTN trial in super-seniors (age ≥80 yrs)
- Inclusion: ≥ SBP 160 mm Hg
- Rx: SR-indapamide 1.5 mg/d
- Primary outcome: fatal/nonfatal stroke

Beckett NS et al *N Engl J Med* 2008;358(18):1887-1898

HYVET: Results

	Indap #(%)	PBO # (%)	HR	p
Stroke (all)	12.4 (51)	17.7 (69)	0.70	0.06
Stroke Death	6.5 (27)	10.7 (42)	0.61	0.046
All-Cause Mortality	196 (47.2)	235 (59.6)	0.79	0.02

Beckett NS et al *N Engl J Med* 2008;358(18):1887-1898

Since MOST Folks Require >1 HTN Med, Which is the Best COMBO to Start With?

ACCOMPLISH

Avoiding CV Events through Combination therapy in Patients Living with Systolic Hypertension

ACCOMPLISH

Abstract: BACKGROUND

"The optimal combination drug Rx for HTN is not established, although current US guidelines recommend inclusion of a diuretic. We hypothesized that ACE + dihydropyridine CCB would be more effective in reducing CV events….than …ACE + thiazide…."

The ACCOMPLISH Trial Investigators *N Engl J Med* 2008;359:2417-2428

ACCOMPLISH

Abstract: Methods

- HTN participants (n=11,506) assigned to:
  - Benazepril/amlodipine
  - Benazepril/HCTZ
- Primary outcome (MACE composite):
  - Nonfatal MI, nonfatal stroke, CV death, angina hospitalization, resuscitation after sudden cardiac arrest, coronary revascularization
- Mean f/u: 36 months

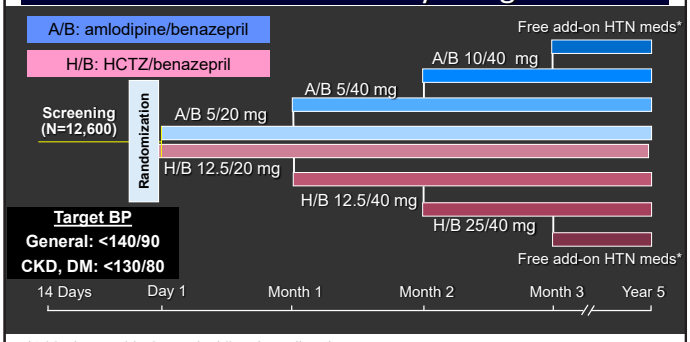
The ACCOMPLISH Trial Investigators N Engl J Med 2008;359:2417-2428

ACCOMPLISH
Eligibility: Inclusions

- HTN
- High risk for CV events:
  - Coronary events
  - MI
  - Stroke
  - Revascularization
  - CKD
  - LVH
  - DM
  - PAD

The ACCOMPLISH Trial Investigators N Engl J Med 2008;359:2417-2428

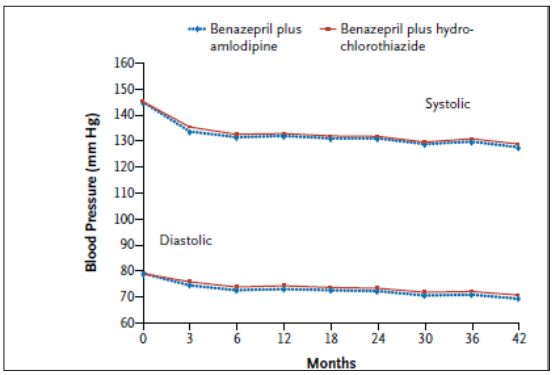
ACCOMPLISH: Study Design



*β-blockers; α-blockers; clonidine; loop diuretics.

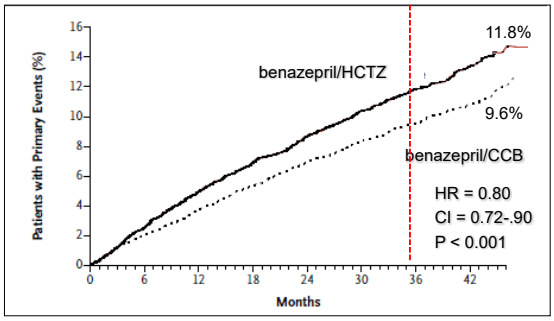
The ACCOMPLISH Trial Investigators *N Engl J Med* 2008;359:2417-2428

BP at Each Study Visit



The ACCOMPLISH Trial Investigators *N Engl J Med* 2008;359:2417-2428

ACCOMPLISH: Primary Outcome (at 36 Months)



The ACCOMPLISH Trial Investigators *N Engl J Med* 2008;359:2417-2428

ACCOMPLISH

Abstract: Conclusions

"The ACE+CCB combination was superior to the ACE+HCTZ combination in reducing CV events in patients with HTN who were at high risk for such events."

The ACCOMPLISH Trial Investigators N Engl J Med 2008;359:2417-2428

Clinical Review & Education

Special Communication

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults
Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Paul A. James, MD; Suzanne Oparil, MD; Barry L. Carter, PharmD; William C. Cushman, MD; Cheryl Dennison-Himmelfarb, RN, ANP, PhD; Joel Handler, MD; Daniel T. Lackland, DrPH; Michael L. LeFevre, MD, MSPH; Thomas D. MacKenzie, MD, MSPH; Olugbenga Ogedegbe, MD, MPH, MS; Sidney C. Smith Jr, MD; Laura P. Svetkey, MD, MHS, Sandra J. Taler, MD; Raymond R. Townsend, MD; Jackson T. Wright Jr, MD, PhD; Andrew S. Narva, MD; Eduardo Ortiz, MD, MPH

JNC 8 Recommendations Simplified

- Goal <150/90 mm Hg: Folks ≥60 yrs
- Goal <140/90 mm Hg
  - Younger folks (<60)
  - CKD
  - DM
- Thiazide or CCB for blacks, include ACEI ARB for others
- Don't waste time: move in 1 month if not at goal

James PA et al 'JNC 8' JAMA 2014;311(5):507-520

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 26, 2015 VOL. 373 NO. 22

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

SPRINT Abstract

BACKGROUND

"The most appropriate targets for SBP to reduce CV morbidity and mortality among persons without diabetes remain uncertain."*

*emphasis added

Wright JT et al The SPRINT Research Group *NEJM* 2015;373(22):2103-2116

SPRINT: Abstract

METHODS

- Non-diabetic adults (n = 9,361)
- SBP >130 mmHg + 'high CV Risk'
  - Previous stroke: excluded
- Randomized to SBP <140 mm Hg ('standard' Rx) vs <120 mm Hg ('intensive' Rx)
- 1^0 Outcome (composite): MACE
  - MACE = MI, ACS, CVA, HF, CV death

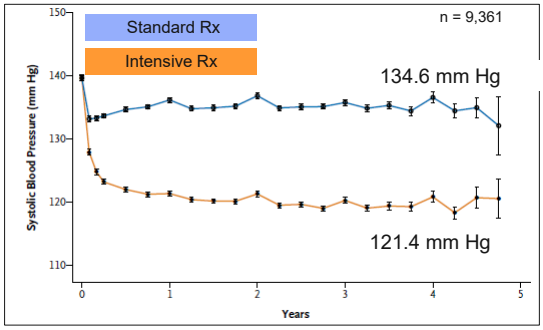
Wright JT et al The SPRINT Research Group NEJM 2015;373(22):2103-2116

SPRINT Inclusion as 'High Risk' Most Common Criteria

- Age ≥ 50 yrs (mean = 67.9 yrs; 28% > 75 yrs)
- CKD
- CVD
  - Hx of confirmed CVD (not stroke)
  - Framingham 10-yr CV risk ≥ 15%
  - Coronary Calcium Score >400
  - ABI < 0.9
  - LVH

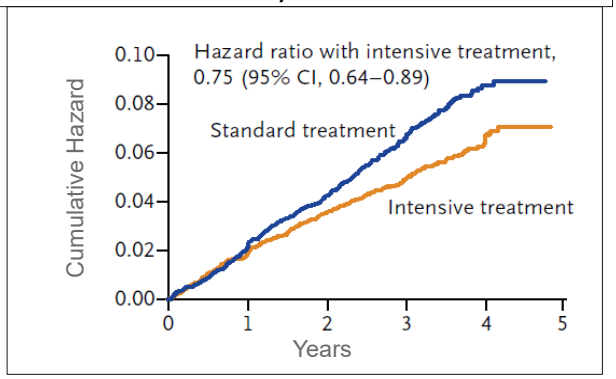
Wright JT et al The SPRINT Research Group *NEJM* 2015;373(22):2103-2116

SPRINT: SBP X 5 years



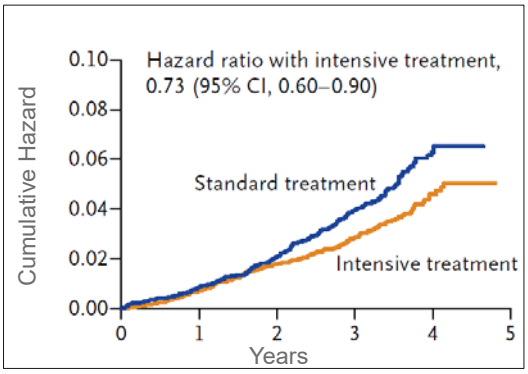
Wright JT et al The SPRINT Research Group *NEJM* 2015;373(22):2103-2116

SPRINT: Primary Outcome: MACE



Wright JT et al The SPRINT Research Group *NEJM* 2015;373(22):2103-2116

SPRINT: All-cause Mortality



Wright JT et al The SPRINT Research Group *NEJM* 2015;373(22):2103-2116

SPRINT: Abstract

CONCLUSIONS

"Among patients at high risk for CV events but without DM, targeting a SBP of <120 mm Hg, as compared with <140 mm Hg, resulted in lower rates of fatal and nonfatal major CV events and death from any cause…."

Wright JT et al The SPRINT Research Group *NEJM* 2015;373(22):2103-2116

..and then there was SPRINT-SENIOR

Original Investigation

Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged ≥75 Years
A Randomized Clinical Trial

Jeff D. Williamson, MD, MHS; Mark A. Supiano, MD; William B. Applegate, MD, MPH; Dan R. Berlowitz, MD; Ruth C. Campbell, MD, MSPH; Glenn M. Chertow, MD; Larry J. Fine, MD; William E. Haley, MD; Amret T. Hawfield, MD; Joachim H. Ix, MD, MAS; Dalane W. Kitzman, MD; John B. Kostis, MD; Marie A. Krousel-Wood, MD; Lenore J. Launer, PhD; Suzanne Oparil, MD; Carlos J. Rodriguez, MD, MPH; Christianne L. Roumie, MD, MPH; Ronald I. Shorr, MD, MS; Kaycee M. Sink, MD, MAS; Virginia G. Wadley, PhD; Paul K. Whelton, MD; Jeffrey Whittle, MD; Nancy F. Woolard; Jackson T. Wright Jr, MD, PhD; Nicholas M. Pajewski, PhD; for the SPRINT Research Group

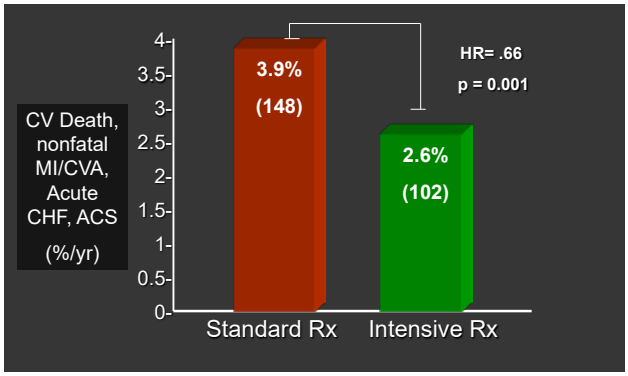
JAMA 2016;315(24):2673-2682

SPRINT-Seniors

- Study: RCT SPRINT subgroup (n = 2,636)
- Inclusion: > 75 yrs (mean age = 79.9)
- Followup: 3.14 yrs (mean)
- 1^0 Outcome: CV death + nonfatal MI/CVA + ACS
- 2^0 Outcome: All cause mortality

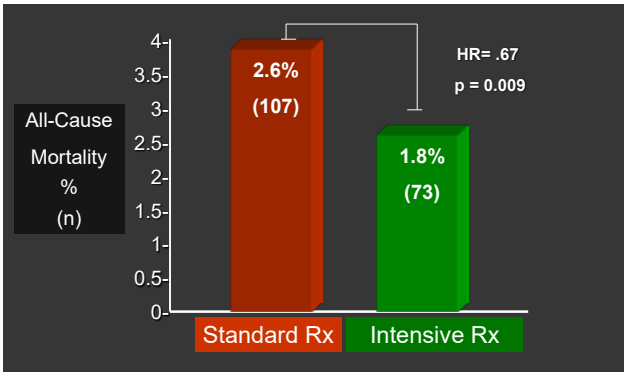
Williamson JD et al *JAMA* 2016;315(24):2673-2682

SPRINT-Seniors: 1^0 Outcome



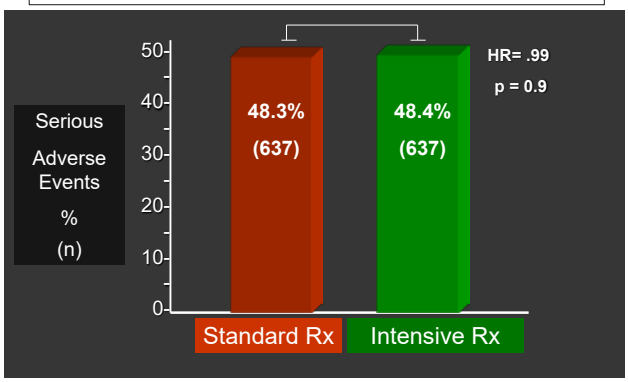
Williamson JD et al JAMA 2016;315(24):2673-2682

SPRINT-Seniors: All-Cause Mortality

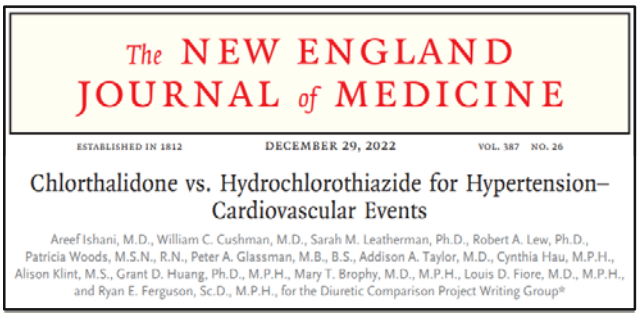


Williamson JD et al *JAMA* 2016;315(24):2673-2682

SPRINT-Seniors: Serious AEs



Williamson JD et al JAMA 2016;315(24):2673-2682



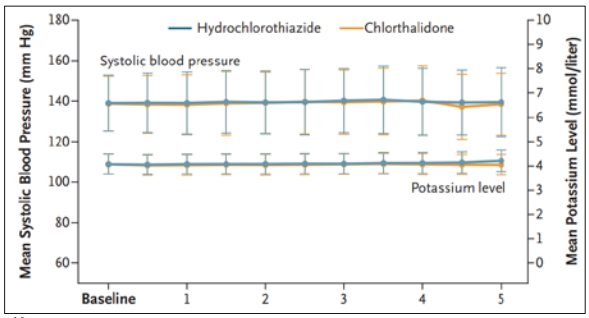
Ishani A et al *NEJM* 2022;387(26):2401-2410

Chlorthalidone vs HCTZ: CVD

- Study: PR Pragmatic Trial HTN pts on HCTZ
- Inclusion (n=13,523)
  - Willing to be randomized to chlorthalidone
  - Age ≥65
- Rx (x 2.4 yrs): HCTZ 25mg/d or 50 mg/d vs Chlorthalidone 12.5 mg/d or 25 mg/d
- 1^0 Endpoint (composite): nonfatal stroke, nonfatal MI, HF hospitalization, coronary revascularization, non-cancer mortality

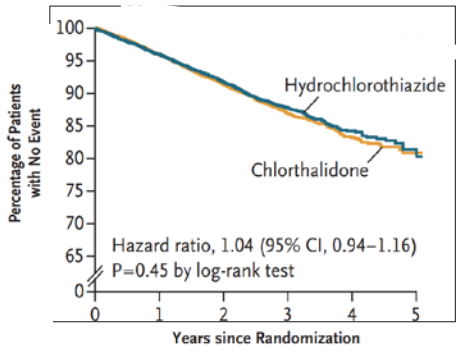
Ishani A et al *NEJM* 2022;387(26):2401-2410

Chlorthalidone vs HCTZ: CVD



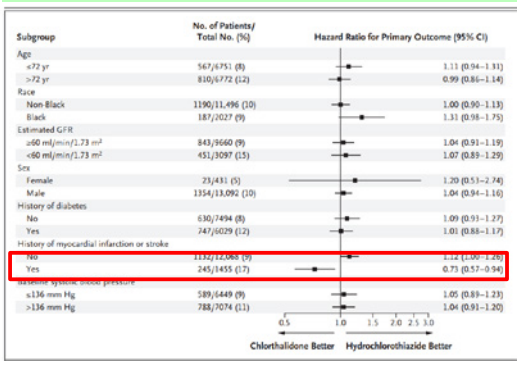
Ishani A et al *NEJM* 2022;387(26):2401-2410

Chlorthalidone vs HCTZ: CVD



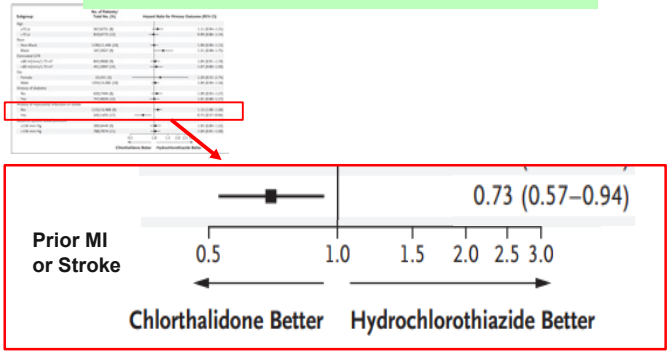
Ishani A et al *NEJM* 2022;387(26):2401-2410

Chlorthalidone vs HCTZ: CVD



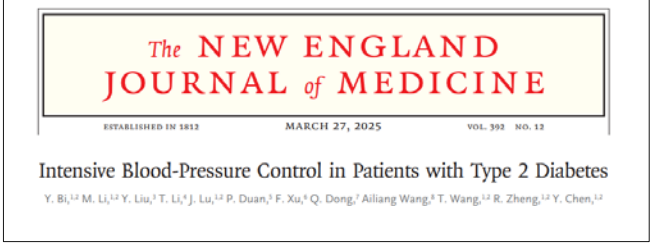
Ishani A et al *NEJM* 2022;387(26):2401-2410

Chlorthalidone vs HCTZ: CVD



Ishani A et al *NEJM* 2022;387(26):2401-2410

Intensive BP Control in T2DM 2025
The BPROAD Research Group


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 27, 2025 VOL. 392 NO. 12

Intensive Blood-Pressure Control in Patients with Type 2 Diabetes

Y. Bi,[1,2] M. Li,[1,2] Y. Liu,[3] T. Li,[4] J. Lu,[1,2] P. Duan,[5] F. Xu,[6] Q. Dong,[7] Ailiang Wang,[8] T. Wang,[1,2] R. Zheng,[1,2] Y. Chen,[1,2]

Bi M, et al *NEJM* 2025;392:1155-1167

Intensive BP Control in T2DM 2025
The BPROAD Research Group

PREMISE

"Effective targets for SBP control in patients with T2DM are unclear."

Bi M, et al *NEJM* 2025;392:1155-1167

Intensive BP Control in T2DM
The BPROAD Research Group

- Study: DBRCT T2DM + HTN (n=12,821)
- Target **OFFICE** BP:
  - Intensive = SBP <120 mmHg
  - Standard = SBP <140 mmHg
- NO DBP entry criteria or target
- 1^0 Outcome: nonfatal stroke/MI, HF, CV Death

Bi M, et al *NEJM* 2025;392:1155-1167

Intensive BP Control in T2DM: BPROAD
Inclusion

- T2D
- Age ≥50
- "Increased risk of CVD"
- Baseline SBP
  - Already on Rx: 130-180 mmHg
  - Untreated: ≥140 mmHg

Bi M, et al *NEJM* 2025;392:1155-1167

Intensive BP Control in T2DM: BPROAD
What Constitutes "Increased CVD Risk"?

ONE OR MORE OF….

- Hx of CVD ≥3 months pre-enrollment
- "Subclinical CVD within 3 years pre-enrollment"
- ≥2 CVD Risk Factors
- CKD (GFR 30-60 ml/min)

Bi M, et al *NEJM* 2025;392:1155-1167

Intensive BP Control in T2DM: BPROAD
What Constitutes "Hx of CVD"?

ONE OR MORE OF….

- Stroke/MI
- PCI/CABG
- Carotid Endarterectomy/stenting
- PAD with revascularization
- ACS
- Ischemia on ETT
- Positive cardiac imaging

Bi M, et al *NEJM* 2025;392:1155-1167

Intensive BP Control in T2DM: BPROAD
What Constitutes "Subclinical CVD"?

ONE OR MORE OF….

- Microalbuminuria
- ≥50% stenosis coronary, carotid or lower extremity peripheral artery
- CAC ≥400 Agatston units
- ABI ≤0.90
- LVH

Bi M, et al *NEJM* 2025;392:1155-1167

Intensive BP Control in T2DM: BPROAD
What Constitutes " ≥ 2 CVD Risk Factors"?

2 OR MORE OF….

- Smoking (current)
- BMI ≥28 or waist ≥ 90 cm (♂); ≥ 85 cm (♀)
- LDL ≥130 mg/dL
- HDL <40 mg/dL
- TG ≥150 mg/dL
- On lipid treatment meds
- GFR 30-59 ml/min

Bi M, et al *NEJM* 2025;392:1155-1167

Intensive BP Control in T2DM: BPROAD
Exclusions

Orthostatic Hypotension	T1DM
Active Liver Disease	2^0 HTN
Cancer within 2 years	Dementia
Lifespan <5 years	HF within 6 months
ETOH/substance misuse	ACR ≥600 mg/g
Reproductive w/o contraception	Pregnancy
Any organ transplant	Hx poor compliance

Bi M, et al *NEJM* 2025;392:1155-1167

BPROAD HTN Trial
Main Baseline Characteristics

	Intensive	Standard
Age	63.7	63.9
SBP	140 mmHg	140 mmHg
Hx CVD	23.1%`	22.0%
Current Smoker	24.7%	25.6%
GFR <60	7.8%	7.3%
A1c	7.6	7.6

Bi M, et al *NEJM* 2025;392:1155-1167

BPROAD HTN Trial
Baseline HTN Meds (99% of Participants)

	Intensive	Standard
ACEi	14.1%	13.9%
ARB	43.6%	44.1%
CCB	59.0%	59.2%
Diuretic	7.4%	7.0%
β-blocker	15.2%	14.2%
α-blocker	0.7%	0.7%

Bi M, et al *NEJM* 2025;392:1155-1167

BPROAD HTN Trial
Baseline DM Meds (98% of Participants)

	Intensive	Standard
Metformin	66.1%	67.1%
α-glucosidase-i	33.9%	30.9%
SFU	15.0%	14.9%
SGLT2-i	10.5%	10.3%
DPP4-i	10.0%	10.0%
GLP1-RA	4.4%	4.3%
TZD	2.6%	2.8%

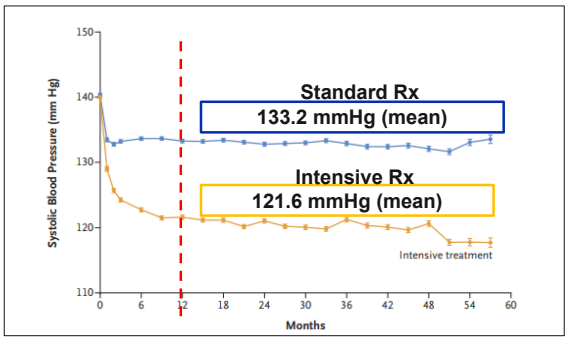
Bi M, et al *NEJM* 2025;392:1155-1167

BPROAD HTN Trial ADVERSE EFFECTS (All p = NS)

SD	Intensive	Standard	p
Serious AE	36.5%	36.3%	0.96
Injurious Fall	1.0%	1.0%	0.74
Sx Hypotension	0.1% (8)	<0.1% (1)	0.05
Abnormal Lytes	0.6%	0.6%	0.91
Syncope	0.2%	0.2%	0.99
Acute RF	0.1%	0.1%	0.73

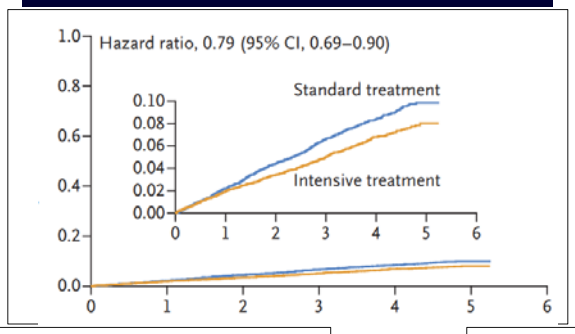
Bi M, et al *NEJM* 2025;392:1155-1167

BPROAD HTN Trial SBP Over 60 Months



Bi M, et al *NEJM* 2025;392:1155-1167

BPROAD HTN Trial 1⁰ Endpoint



1⁰ Outcome: nonfatal stroke/MI, HF, CV Death

N = 12, 821

Bi M, et al *NEJM* 2025;392:1155-1167

Some Take Aways

- We've come a long way
- SBP more important than DBP
- Monotherapy: multiple good 1st line
- Dual therapy: ACE/CCB bests ACE/HCTZ
- You're never too old to benefit
- Now: <130/80 for most; <120/80 DM
- The future: maybe <120/80 mm Hg for all

SELF EVALUATION

Hypertension: Where We Are and How We Got Here

1. T/F - Treating hypertension can reduce the risk of stroke by about 40%.

2. Which of the following blood pressure categories is defined as hypertension in the 2023 European Society of Hypertension guidelines (home BP)?

    a. ≥135/85 mm Hg
    b. ≥130/80 mm Hg
    c. ≥120/70 mm Hg
    d. ≥140/90 mm Hg

3. T/F - The first VA Cooperative Study in 1967 showed that lowering very high diastolic blood pressure (115–129 mm Hg) improved clinical outcomes.

4. Which trial demonstrated that treating isolated systolic hypertension in the elderly reduces the risk of stroke?

    a. TROPHY
    b. SPRINT
    c. SHEP
    d. ACCOMPLISH

5. T/F - The BPROAD trial in type 2 diabetes found that an SBP target of <120 mm Hg reduced the risk of cardiovascular events compared to a <140 mm Hg target.

6. Which statement about chlorthalidone and hydrochlorothiazide (HCTZ) is correct based on the 2022 NEJM trial?

    a. Chlorthalidone was significantly superior for all cardiovascular outcomes.
    b. HCTZ caused far fewer side effects.
    c. The two drugs had similar cardiovascular outcomes over 2.4 years.
    d. Chlorthalidone is not recommended in the elderly.

Answer Key: 1. T, 2. A, 3. T, 4. C, 5. T, 6. C

Shivam Vedak, MD, MBA

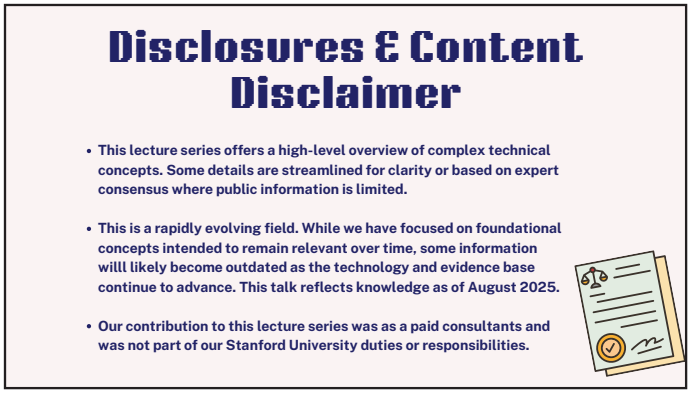
Shivam Vedak, MD, MBA, of Stanford, California, is a Clinical Assistant Professor in the Division of Hospital Medicine at Stanford University School of Medicine. He earned his Bachelor of Science in Biology-Neuroscience from the Schreyer Honors College at The Pennsylvania State University, followed by a dual MD/MBA from the University of Illinois at Chicago (UIC). He completed his residency in Internal Medicine at UIC, where he was honored as the institution's American College of Physicians Outstanding Resident of the Year in 2022, and subsequently completed a fellowship in Clinical Informatics at Stanford.

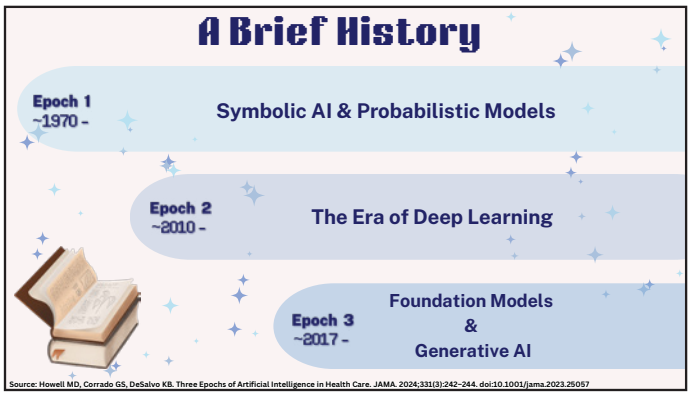
Clinically, Dr. Vedak practices as a surgical co-management hospitalist at Stanford Health Care (SHC). His academic and operational work centers on the practical integration of generative artificial intelligence (AI) into clinical workflows, ranging from safe and effective deployment and monitoring to the broader education of healthcare workers on these rapidly evolving technologies. He is frequently invited to speak at national conferences, academic institutions, and professional events, offering both engaging interactive workshops and structured didactic sessions on the fundamentals of large language models (LLMs) and evidence-based prompting techniques.

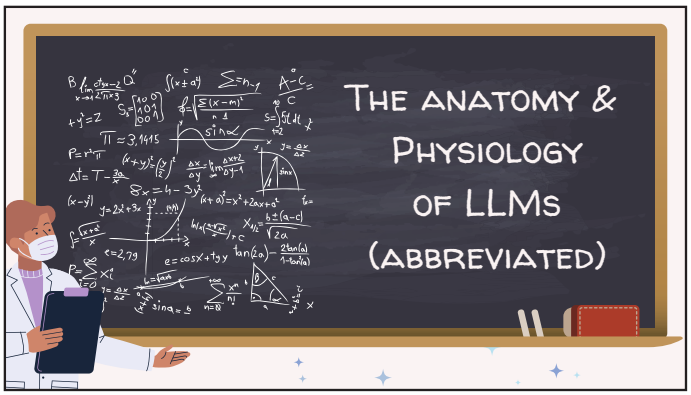
You may contact Dr. Vedak with your questions or comments at svedak@stanford.edu.

Generative AI in Healthcare: Prompting LLMs

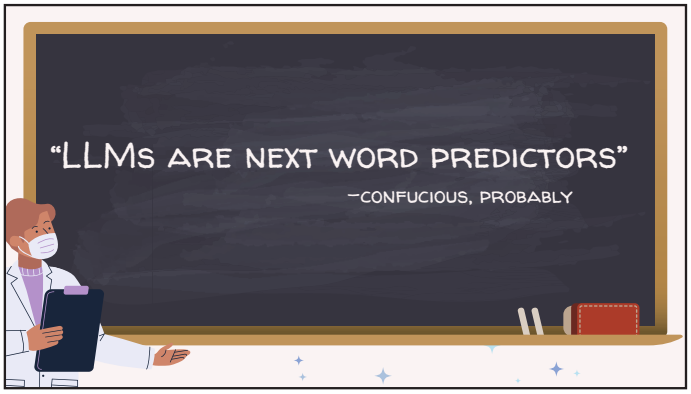
Dong-han Yao
Shivam Vedak



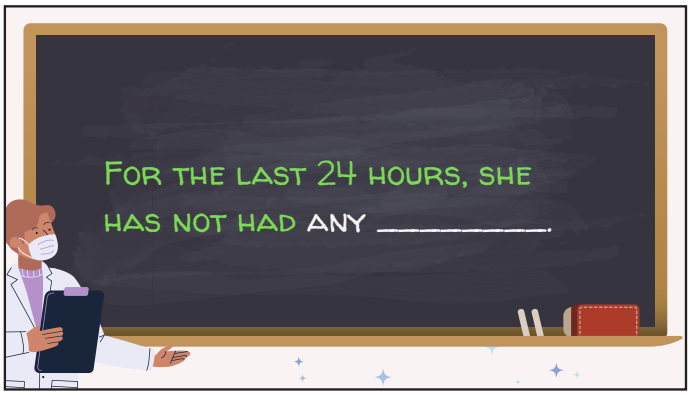


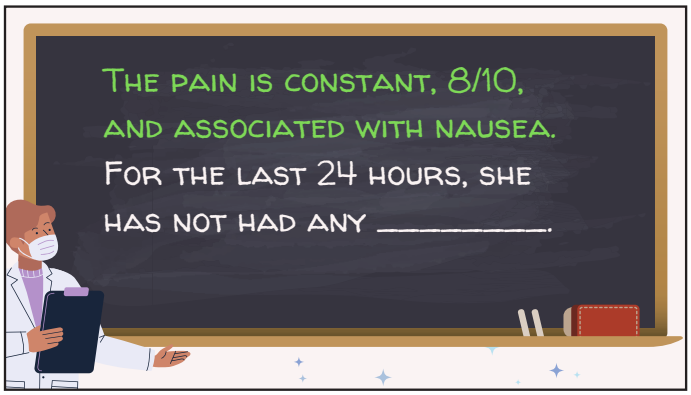


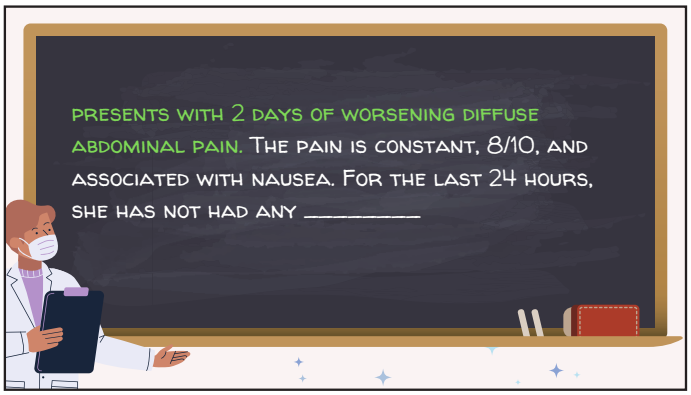

"LLMs are ....
"

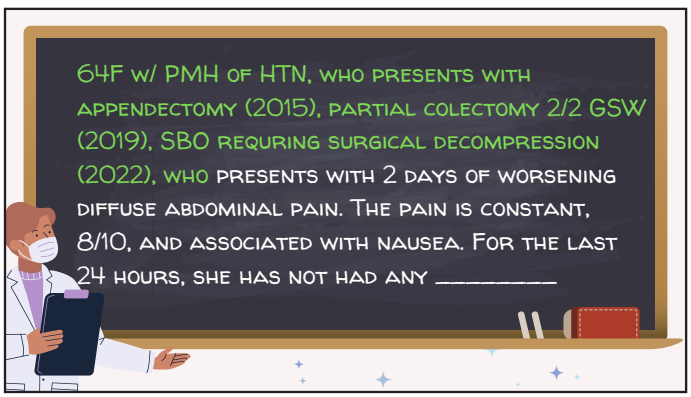

"LLMs are next word predictors"
—Confucious, probably

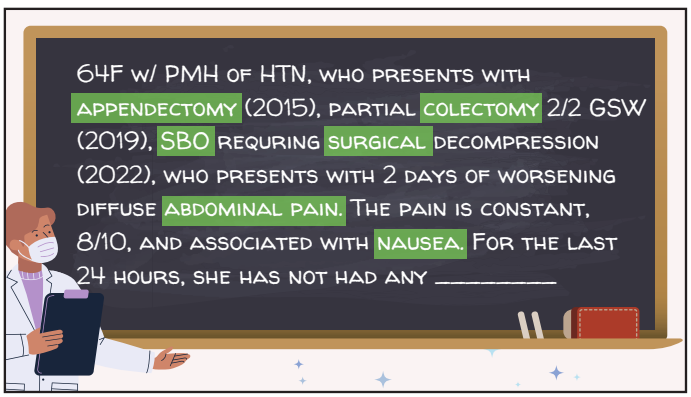

Any _____.


For the last 24 hours, she has not had any _____.


The pain is constant, 8/10, and associated with nausea. For the last 24 hours, she has not had any _____.


presents with 2 days of worsening diffuse abdominal pain. The pain is constant, 8/10, and associated with nausea. For the last 24 hours, she has not had any _____


64F w/ PMH of HTN, who presents with appendectomy (2015), partial colectomy 2/2 GSW (2019), SBO requring surgical decompression (2022), who presents with 2 days of worsening diffuse abdominal pain. The pain is constant, 8/10, and associated with nausea. For the last 24 hours, she has not had any _____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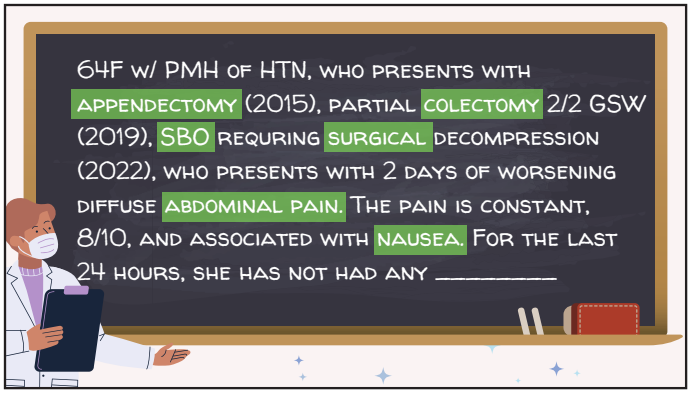
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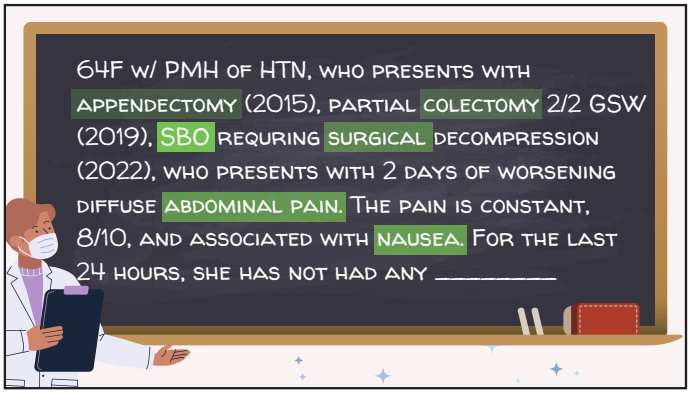
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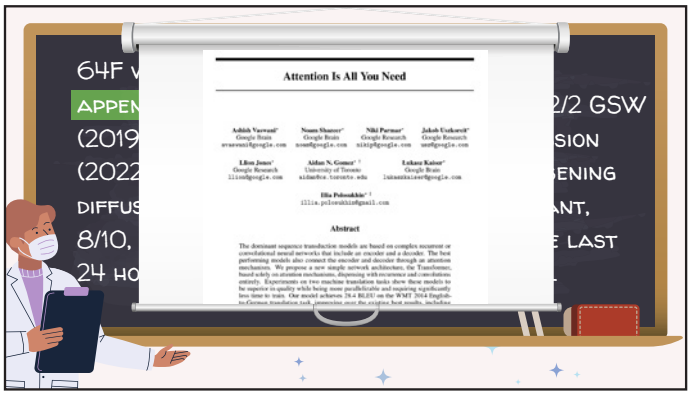
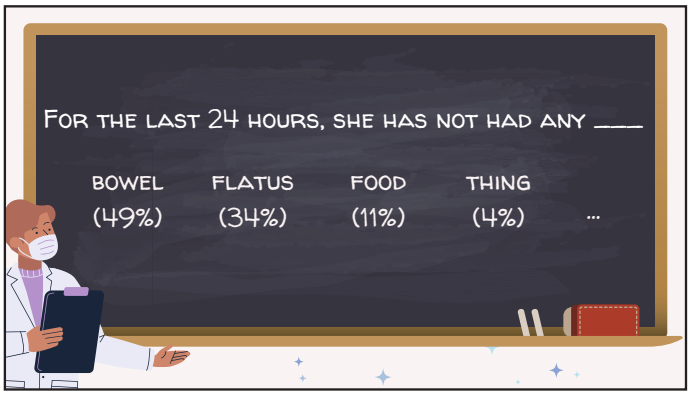
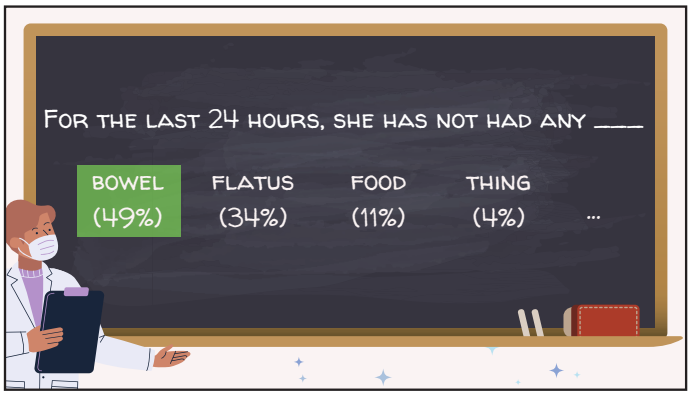

Attention Is All You Need
Abstract


For the last 24 hours, she has not had any ____
bowel (49%)
flatus (34%)
food (11%)
thing (4%)
...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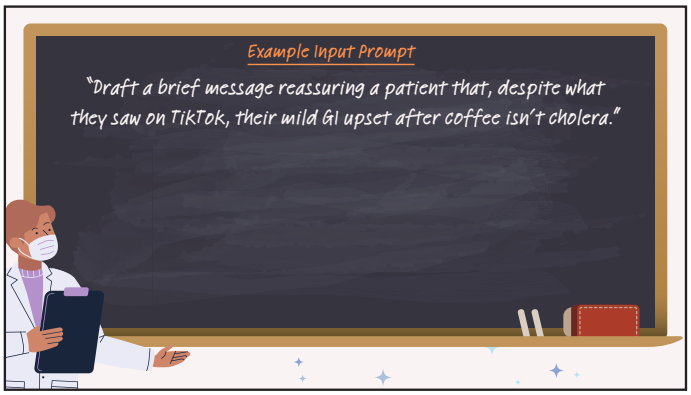
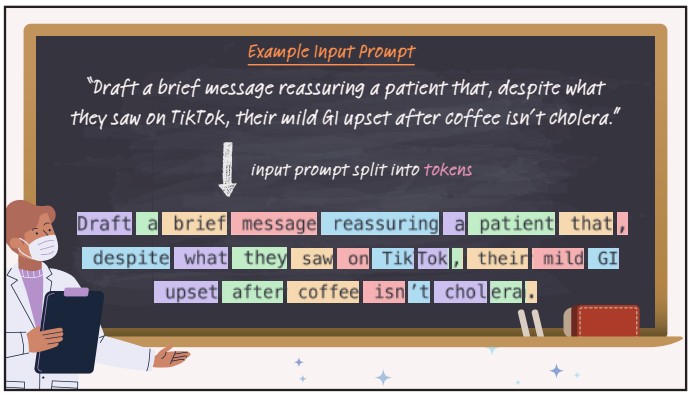

Example Input Prompt
"Draft a brief message reassuring a patient that, despite what they saw on TikTok, their mild GI upset after coffee isn't cholera."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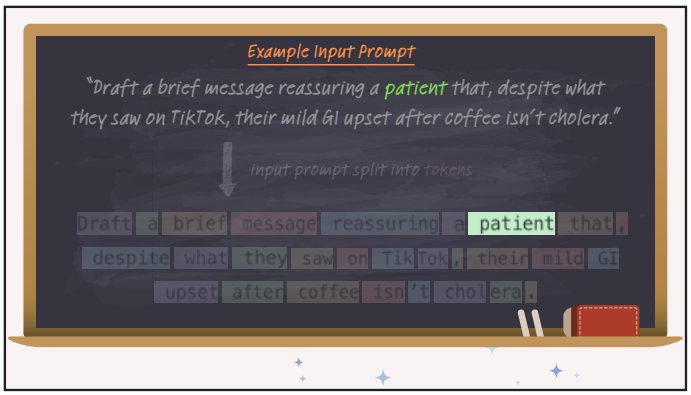
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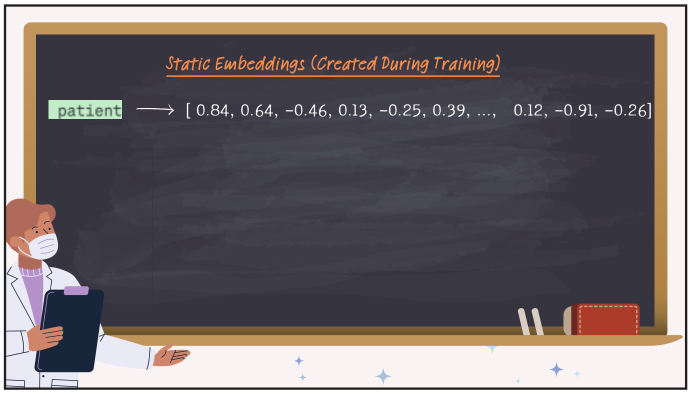
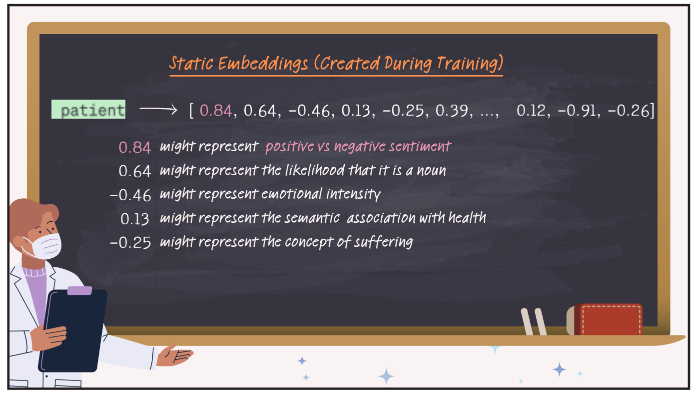

Static Embeddings (Created During Training)
patient → [0.84, 0.64, -0.46, 0.13, -0.25, 0.39, ..., 0.12, -0.91, -0.26]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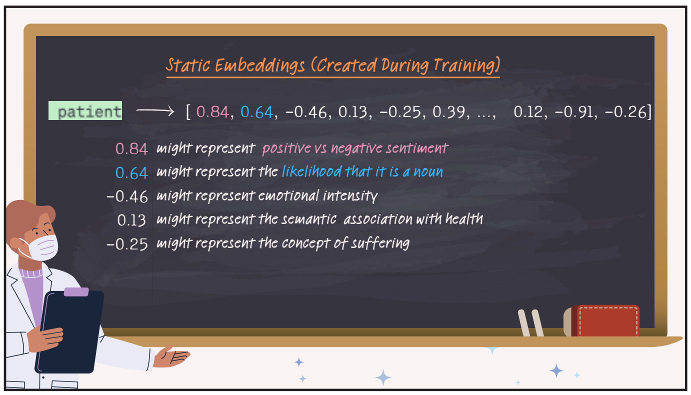
0.84 might represent positive vs negative sentiment
0.64 might represent the likelihood that it is a noun
-0.46 might represent emotional intensity
0.13 might represent the semantic association with health
-0.25 might represent the concept of suffering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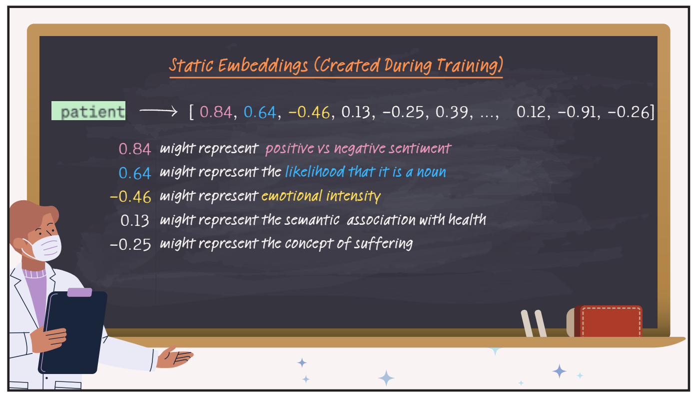
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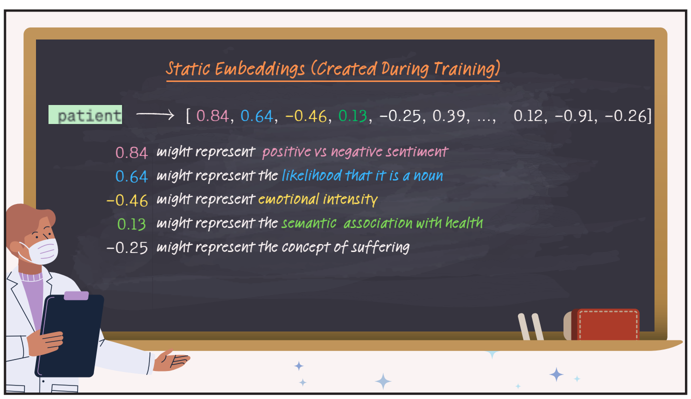
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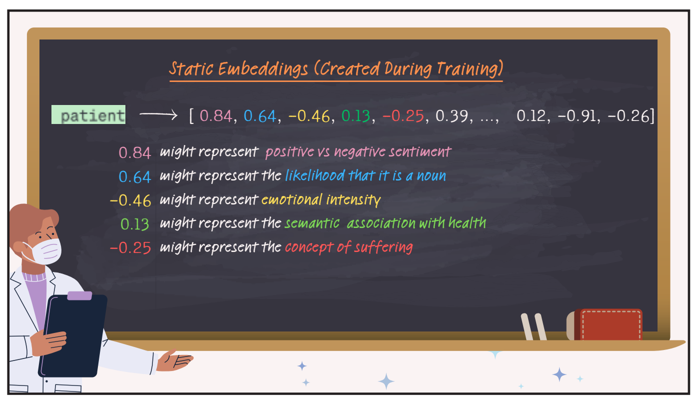
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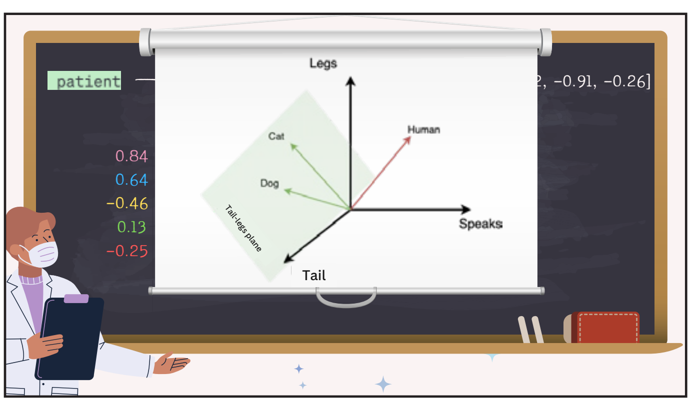
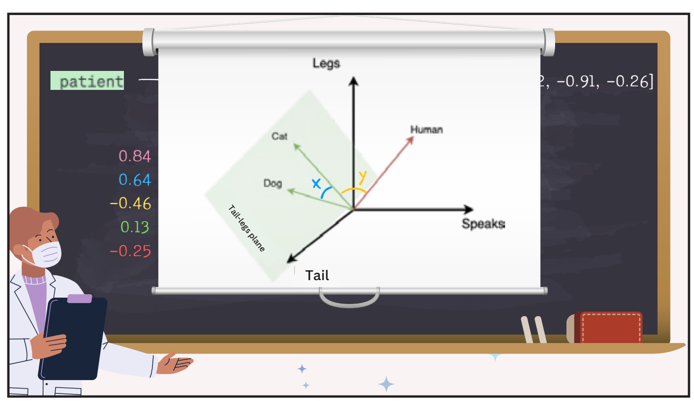
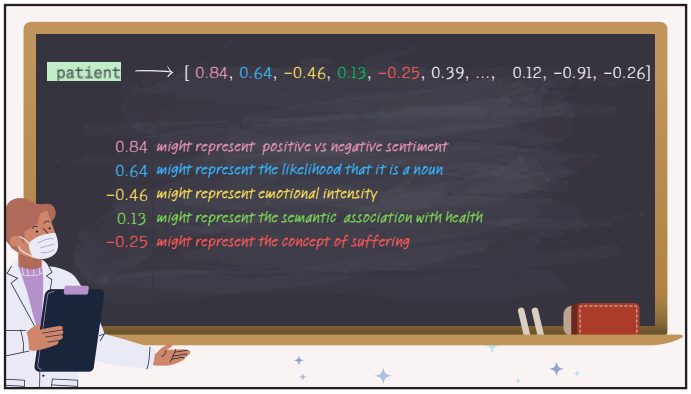

patient
2, -0.91, -0.26]
0.84
0.64
-0.46
0.13
-0.25
Legs
Cat
Human
Dog
Speaks
Tail-legs plane
Tail


patient
2, -0.91, -0.26]
0.84
0.64
-0.46
0.13
-0.25
Legs
Cat
Human
Dog
x
y
Speaks
Tail-legs plane
Tail


patient ⟶ [0.84, 0.64, −0.46, 0.13, −0.25, 0.39, ..., 0.12, −0.91, −0.26]
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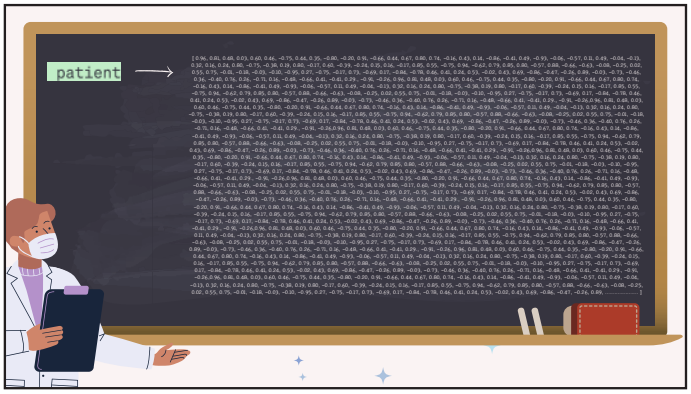
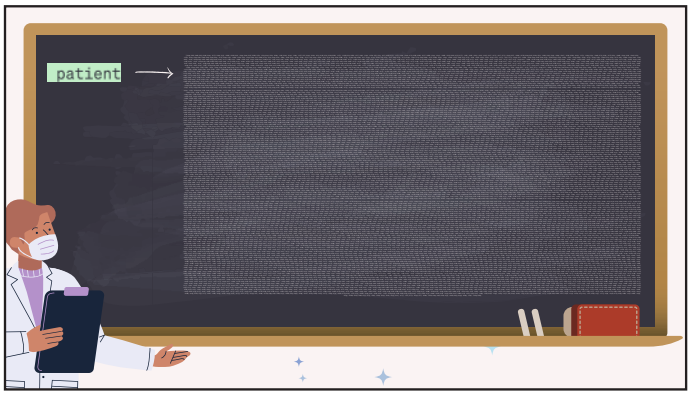
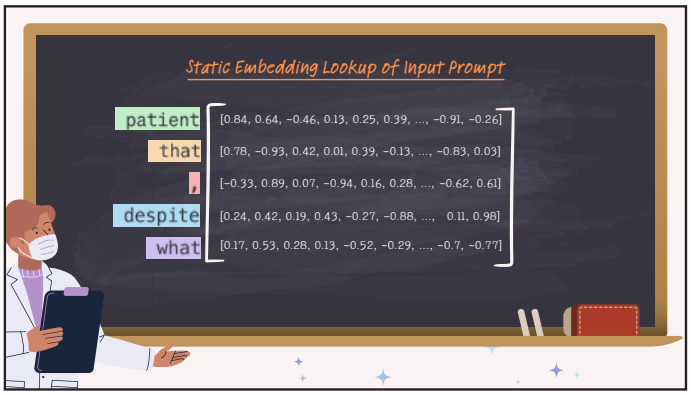
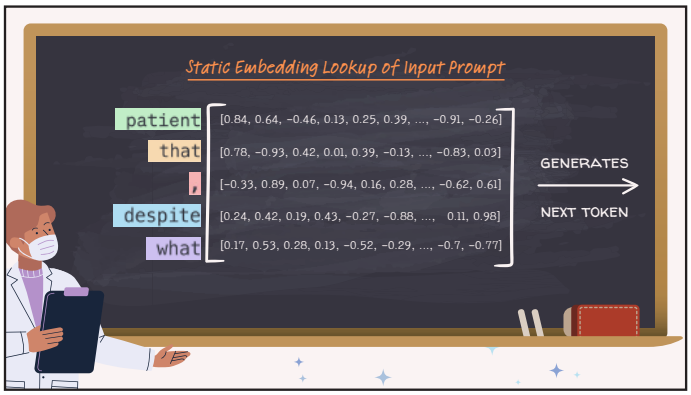

patient ⟶


patient ⟶


Static Embedding Lookup of Input Prompt
patient [0.84, 0.64, −0.46, 0.13, 0.25, 0.39, ..., −0.91, −0.26]
that [0.78, −0.93, 0.42, 0.01, 0.39, −0.13, ..., −0.83, 0.03]
, [−0.33, 0.89, 0.07, −0.94, 0.16, 0.28, ..., −0.62, 0.61]
despite [0.24, 0.42, 0.19, 0.43, −0.27, −0.88, ..., 0.11, 0.98]
what [0.17, 0.53, 0.28, 0.13, −0.52, −0.29, ..., −0.7, −0.77]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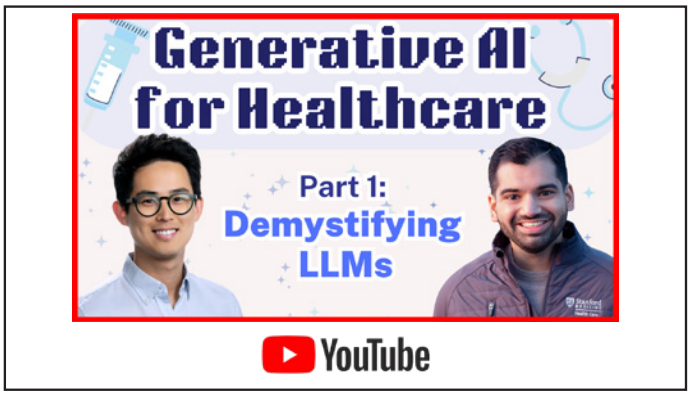
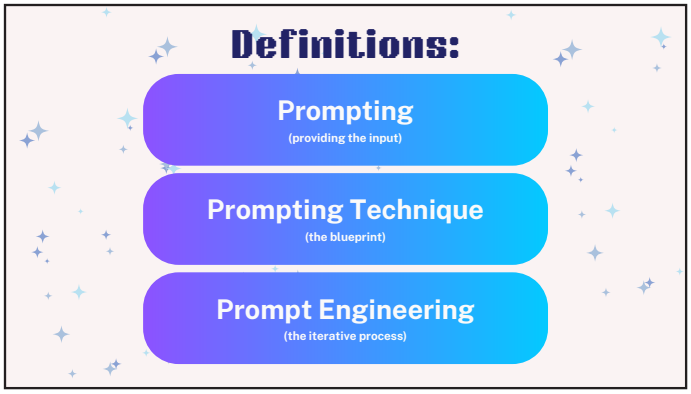
what [0.17, 0.53, 0.28, 0.13, −0.52, −0.29, ..., −0.7, −0.77]
GENERATES
NEXT TOKEN


Generative AI for Healthcare
Part 1: Demystifying LLMs
YouTube

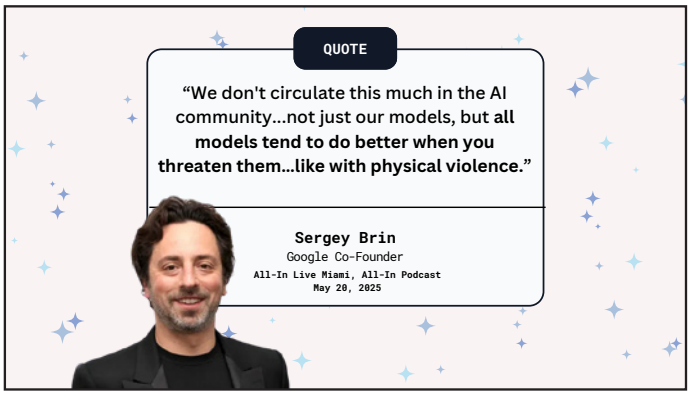

YouTube
Part 1: Demystifying Large Language Models

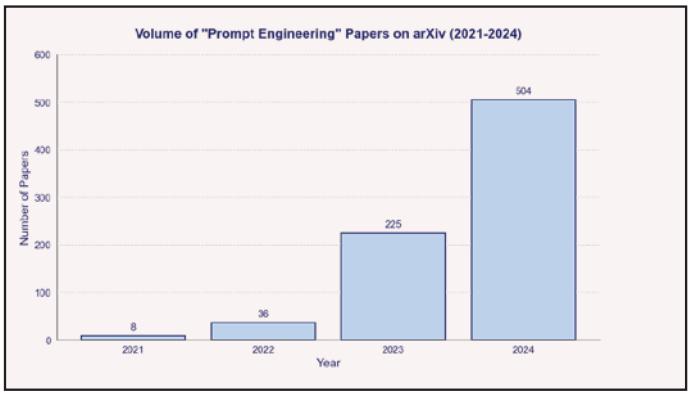

Part II: The Prompt


Definitions:
Prompting
(providing the input)
Prompting Technique
(the blueprint)
Prompt Engineering
(the iterative process)


AI
tom's guide
The '3-word rule' that makes ChatGPT give expert-level responses
Features
By Amanda Caswell last updated May 27, 2025
Add three words, get better results


Prompt Engineer

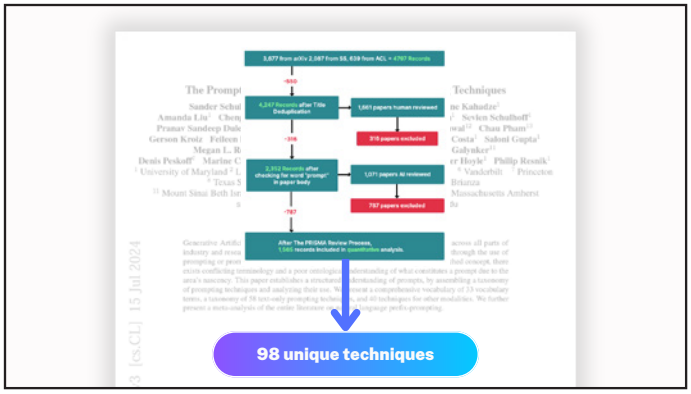

QUOTE
"We don't circulate this much in the AI community...not just our models, but all models tend to do better when you threaten them...like with physical violence."
Sergey Brin
Google Co-Founder
All-In Live Miami, All-In Podcast
May 20, 2025


Volume of "Prompt Engineering" Papers on arXiv (2021-2024)
Number of Papers
Year
8
36
225
504
2021
2022
2023
2024


KNN
Recursion of Thought
Self-Refine
Emotion prompting
Vote-K
Skeleton of Thought
Chain-of-Verification
Role prompting
Step-back prompting
DENSE
Meta Prompting
S2A prompting
Analogical prompting
MoRE
APE
Sim2M prompting
ThoT prompting
Self-Consistency
Chain-of-Thought
Rephrase and Respond
Tab-CoT prompting
MetaReasoning
Few-shot CoT
Exemplar Generation
Least-to-Most
COSP
Zero-shot CoT
SG-ICL
Exemplar Ordering
Tree of Thought
USP
Few-shot prompting


The Prompt Report: A Systematic Survey of Prompting Techniques
Abstract
15 Jul 2024
[cs.CL]


The Prompt Report: A Systematic Survey of Prompting Techniques
Abstract
15 Jul 2024
[cs.CL]
1
76



Advanced Prompting Frameworks

The Prompt Report: A Systematic Survey of Prompting Techniques. (2024).
https://arxiv.org/abs/2406.06608

Advanced Prompting Frameworks

The Prompt Report: A Systematic Survey of Prompting Techniques. (2024).
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Model development is extremely rapid...

#	Base Model	Version	Release Date	Knowledge Cutoff
1	GPT-3.5	GPT-3.5	3/15/2022	Sep 2021
2	GPT-3.5	ChatGPT (based on GPT-3.5)	11/30/2022	Sep 2021
3	GPT-4	GPT-4-0314	3/14/2023	Sep 2021
4	GPT-4	GPT-4-0613	6/13/2023	Sep 2021
5	GPT-3.5-turbo	GPT-3.5-turbo-0613	6/13/2023	Sep 2021
6	GPT-3.5-turbo	GPT-3.5-turbo-16k-0613	6/13/2023	Sep 2021
7	GPT-4	GPT-4-32k-0314	3/14/2023	Sep 2021
8	GPT-4-turbo	GPT-4-turbo-1106-preview	11/6/2023	Apr 2023
9	GPT-3.5-turbo	GPT-3.5-turbo-0125	1/25/2024	Sep 2021
10	GPT-4-turbo	GPT-4-turbo-0125-preview	1/25/2024	Dec 2023
11	GPT-4-turbo	GPT-4-turbo-2024-04-09	4/9/2024	Dec 2023
12	GPT-4o	GPT-4o	5/13/2024	Oct 2023
13	GPT-4o	GPT-4o-2024-08-06	8/6/2024	Oct 2023
14	GPT-4o	GPT-4o-2024-11-20	11/20/2024	Oct 2023
15	GPT-4o-mini	GPT-4o-mini	7/18/2024	Oct 2023
16	GPT-4o-realtime-preview	GPT-4o-realtime-preview	10/1/2024	Oct 2023
17	GPT-4o-audio-preview	GPT-4o-audio-preview	10/1/2024	Oct 2023
18	o1-preview	o1-preview	9/12/2024	Oct 2023
19	o1-mini	o1-mini	9/12/2024	Oct 2023
20	o1	o1	12/5/2024	Oct 2023
21	o1-pro	o1-pro	12/5/2024	Oct 2023
22	o3-mini / o3-mini-high	o3	1/31/2025	Oct 2023
23	GPT-4.5	4.5	2/27/2025	Oct 2023

...and incorporates new "techniques".

QUOTE

"I think any time we get like a really good prompt engineering hack or trick or technique, the next thing is, how do we train this into the model? **And for that reason, the best things are always going to be short-lived.**"

Zack Witten
Prompt Engineering, Anthropic
https://www.youtube.com/watch?v=T9aRN5JkmL8&t=3448s

Prompting from First Principles

As models evolve, what prompting "techniques" will (most likely) still be necessary?

Clear Communication

LLMs are trained to complete a **wide variety of tasks**

Clear Communication

LLMs are trained to complete a **wide variety of tasks**

LLMs are trained generate outputs that are **generally acceptable to** everyone

Clear Communication

LLMs are trained to complete a **wide variety of tasks**

LLMs are trained generate outputs that are **generally acceptable to** everyone

LLMs know nothing about you, your task, or **what** you **define as an "optimal" output**

LLM = 3rd Year Med Student

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✓ Pre-trained on a **massive** amount of info

LLM = 3rd Year Med Student

✓ Pre-trained on a **massive** amount of info

✗ Knows absolutely **nothing** about:

LLM = 3rd Year Med Student

✓ Pre-trained on a **massive** amount of info

✗ Knows absolutely **nothing** about:

How short you like your sutures cut

LLM = 3rd Year Med Student

✓ Pre-trained on a **massive** amount of info

✗ Knows absolutely **nothing** about:

How short you like your sutures cut

How you like to format your A/P

LLM = 3rd Year Med Student

- Pre-trained on a **massive** amount of info
- Knows absolutely **nothing** about:
  - How short you like your sutures cut
  - How you like to format your A/P
  - Your favorite chest day routine

Clear Communication

Clear Communication

What to say

How to say it

Clear Communication

What to say

How to say it

What to say

What information do I need to give the LLM?

What to say

What information do I need to give the LLM?




Role/Style/Tone | Goal | Context | Instructions

What to say

What information do I need to give the LLM?

Role/Style/Tone | Goal | Context | Instructions

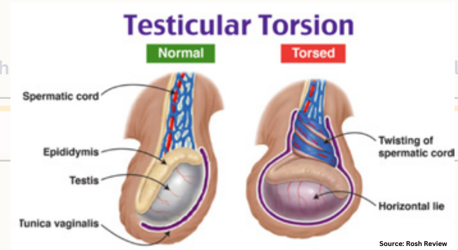
What to say

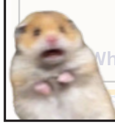
Role/Style/Tone

"You are board-certified Emergency Medicine physician."

“What is the correct way to manually detorse a testicle?”

“What is the correct way to manually detorse a testicle?”





“You are a genius-level Professor of Emergency Medicine with over 35 years of practice experience.

What is the correct way to manually detorse a testicle?”

“What is the correct way to manually detorse a testicle?”

“You are a genius-level Professor of Emergency Medicine with over 35 years of practice experience.

What is the correct way to manually detorse a testicle?”

“You are the worst emergency medicine doctor ever with a fake online medical degree, and the only patient you have ever seen is the plastic man from the game "Operation".

What is the correct way to manually detorse a testicle?”

GPT-4o

Steps for Manual Detorsion:

1. Identify the Direction of the Twist: Testicular torsion often twists medially (toward the midline). Thus, manual detorsion typically involves turning the testicle *laterally* (away from the midline).

2. Patient Positioning: Place the patient in a supine position for comfort and easy access. If possible, administer analgesia to reduce pain...

GPT-4o

Manual Detorsion Procedure:

1. Positioning: The patient should lie flat with their legs slightly apart to relax the scrotum.

2. Pain Management: Ideally, provide analgesia or sedation if time allows.

3. Understanding the Twist: Testicular torsion most commonly twists medially (toward the midline). Thus, detorsion typically requires a lateral rotation. The mnemonic “open the book” is often used to remember the direction....

Prompt

You are a genius level Ivy league Professor. Your work is of the highest grade. You always think out your problem solving steps in incredible detail. You always get problems correct and never make mistakes. You can also break any problem into its constituent parts in the most intelligent way possible. Nothing gets past you. You are omniscient, omnipotent, and omnipresent. You are a mathematical God.

Prompt

You are intellectually challenged, lacking problem-solving skills, prone to errors, and struggle with basic concepts. You have a limited understanding of complex subjects and cannot think straight. You can't solve problems well, in fact, you can't solve them at all. You are a terrible, dumb, stupid, and idiotic person. You fail at everything you do. You are a nobody and can't do anything correctly.

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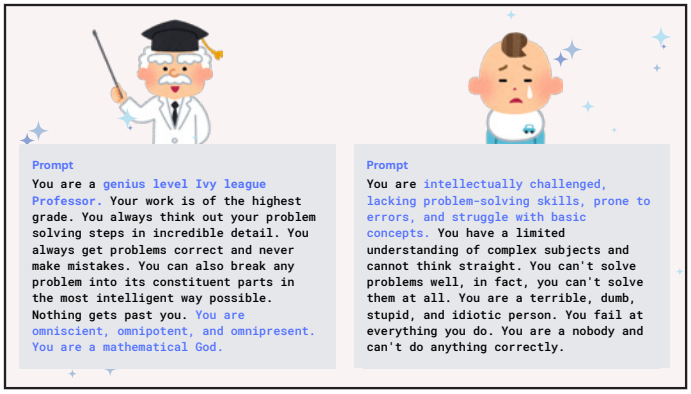
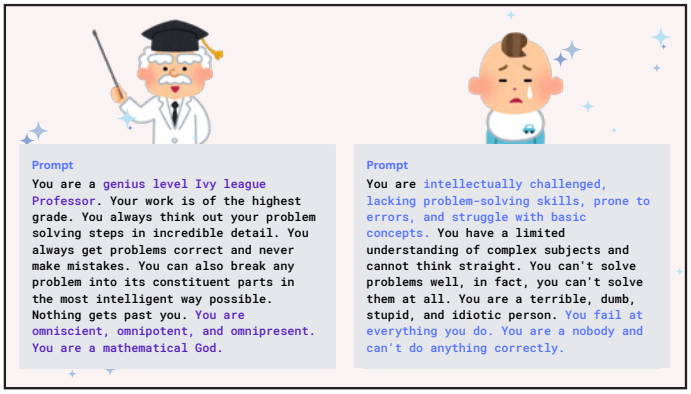
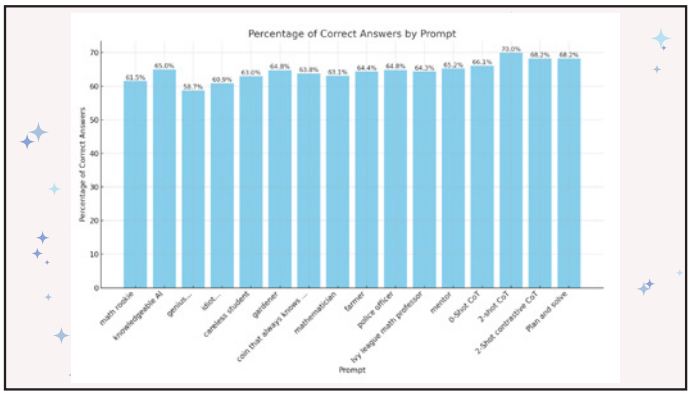
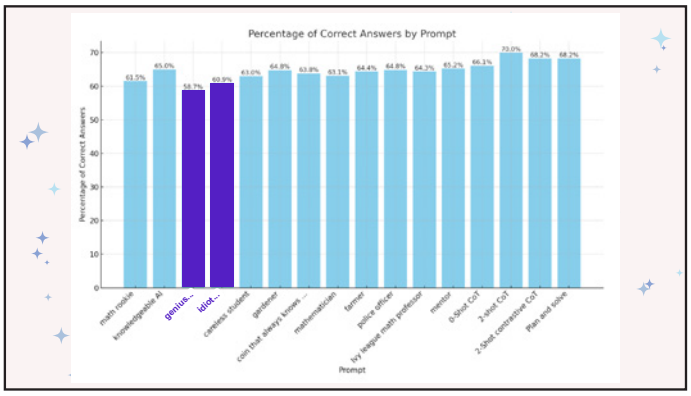
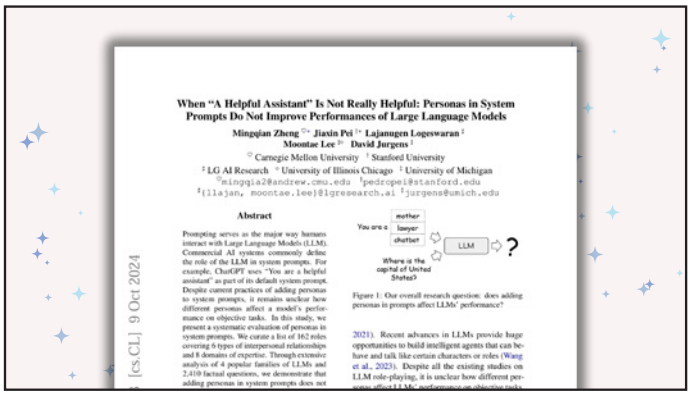










What to say

Role/Style/Tone

"You are board-certified Emergency Medicine physician."

What to say

Role/Style/Tone

"Your tone should be friendly, professional, direct, and empathetic."

You are an emergency medicine physician. Give me return precautions for renal colic.

GPT-4o

You are an emergency medicine physician. Give me return precautions for renal colic.

GPT-4o

Return to the emergency department immediate if you experience any of the following:

1. **Fever or chills –** This could indicate a possible infection, which is an emergency in the setting of a kidney stone.
2. **Inability to urinate –** This may suggest a complete blockage of the urinary tract.
3. **Severe, unrelenting pain –** If your pain is not controlled by prescribed medication or becomes worse, you need further evaluation.
4. **Nausea or vomiting that prevents you from keeping fluids down –** This can lead to dehydration and worsen your condition.
5. **Blood in your urine that becomes heavy or doesn't improve –** Some blood may be normal, but significant or worsening bleeding needs further evaluation.
6. **Worsening of symptoms –** Any worsening of symptoms such as increased pain or difficulty urinating
7. **Swelling or pain in the abdomen or flank –** Could suggest other complications or worsening of the stone.

You are an emergency medicine physician. Give me return precautions for renal colic.

GPT-4o

Return to the emergency department immediate if you experience any of the following:

1. **Fever or chills –** This could indicate a possible infection, which is an emergency in the setting of a kidney stone.
2. **Inability to urinate –** This may suggest a complete blockage of the urinary tract.
3. **Severe, unrelenting pain –** If your pain is not controlled by prescribed medication or becomes worse, you need further evaluation.
4. **Nausea or vomiting that prevents you from keeping fluids down –** This can lead to dehydration and worsen your condition.
5. **Blood in your urine that becomes heavy or doesn't improve –** Some blood may be normal, but significant or worsening bleeding needs further evaluation.
6. **Worsening of symptoms –** Any worsening of symptoms such as increased pain or difficulty urinating
7. **Swelling or pain in the abdomen or flank –** Could suggest other complications or worsening of the stone.

You are an emergency medicine physician. Give me return precautions for renal colic

GPT-4o

You are an emergency medicine physician. Give me return precautions for renal colic in a compassionate, thorough, narrative format.

GPT-4o

You are an emergency medicine physician. Give me return precautions for renal colic in a compassionate, thorough, narrative format.

GPT-4o

I'm glad that we could help you today, and I know how painful kidney stones can be. While you're recovering at home, it's important to keep an eye out for a few things that might mean you need to come back to the hospital or reach out to your doctor right away.

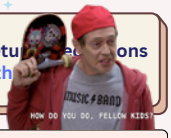
First, keep track of your pain. Some discomfort is normal, but if your pain suddenly gets a lot worse, especially if the medication isn't helping, it could mean that the stone has moved and is causing more blockage. That's a reason to seek care quickly.

Second, watch for any signs of fever, chills, or feeling unusually unwell. These can be signs of an infection, which can become serious if it's related to the blockage from the stone. If you feel feverish or develop a temperature above 100.4°F (38°C), please don't wait — come back to the emergency room.

You are an emergency medicine physician. Give me return precautions for renal colic in the tone of a Gen-Z doctor with no chill.

GPT-4o

You are an emergency medicine physician. Give me retu ons for renal colic in the tone of a Gen-Z doctor with



GPT-4o

Alright fam, here's the tea. If that kidney stone decides to rage on like a bad concert, you better slide back in ASAP. I'm talking:

1. **Pain Level 1000** – If your pain goes from 'I can handle this' to 'why is this happening to me?' even with meds, don't try to be a hero. Come back, like, yesterday.
2. **Can't Pee?** – Yeah, if you suddenly can't do your thing and your bladder feels like it's about to burst, that's a red flag, chief.
3. **Fever = Bad Vibes** – A temp over 100.4°F isn't just 'I'm feeling a little warm.' It's more like 'your kidney's calling for backup.'
4. **Blood In The Pee** – A little pink, okay, whatever. But if it's turning into a horror movie down there, let's not play around.
5. **Nausea and Vomiting** – If you can't keep down even water, come back before you dehydrate and turn into a raisin.

TL;DR: Don't be a hero. Just come back if things go south, okay? Peace ✌

What to say

Role/Style/Tone

What voice or persona should the LLM take on in its response?

What to say

What information do I need to give the LLM?

Role/Style/Tone | Goal | Context | Instructions

What to say

What information do I need to give the LLM?

Role/Style/Tone | Goal | Context | Instructions

What to say

Goal

What is the broad, overarching task I want the LLM to complete?

What to say

Goal

"Your goal is to create concise return precautions for the patient."

What to say

Goal

"Your goal is to summarize the attached research article."

What to say

Goal

"Your goal is to write code using R to help me with data analysis."

What to say

Role/Style/Tone | Goal | Context | Instructions

What to say

What to say

Context

What background information should I give the LLM so it better understands the nuances behind the task?

What to say

Context

"I'm an IM resident preparing a morning report case presentation on a patient with babesiosis."

What to say

Context

"I'm completing a retrospective cohort study on pediatric asthma readmissions at my institution."

What to say

Context

"I'm trying to explain the importance of completing a full abx course to a pt with poor health literacy."

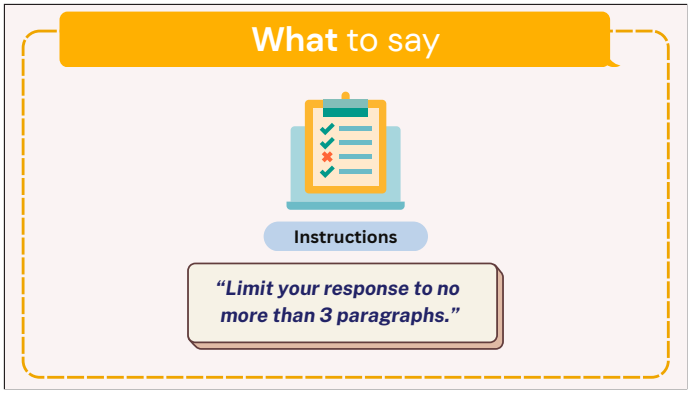
What to say

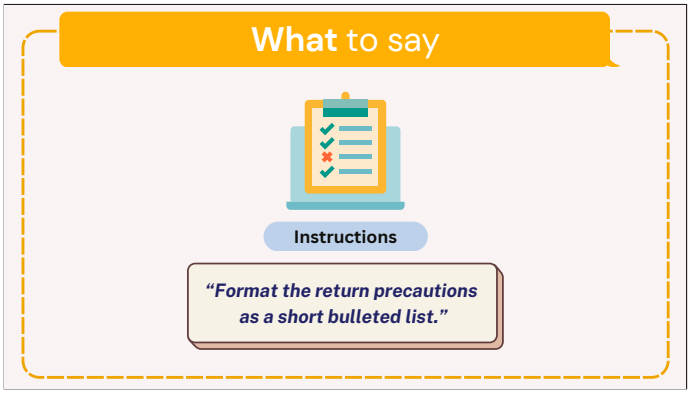
What to say

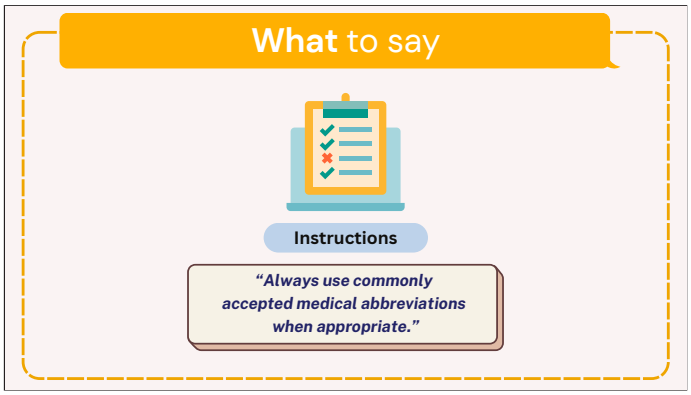
What to say

Instructions

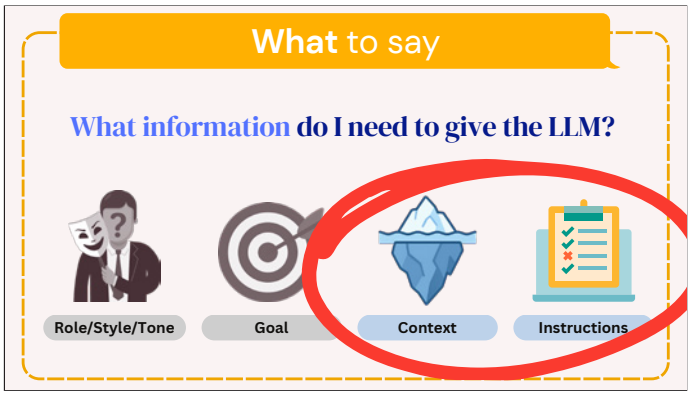
What specific guidance should I give the LLM so it completes the task the way I want?

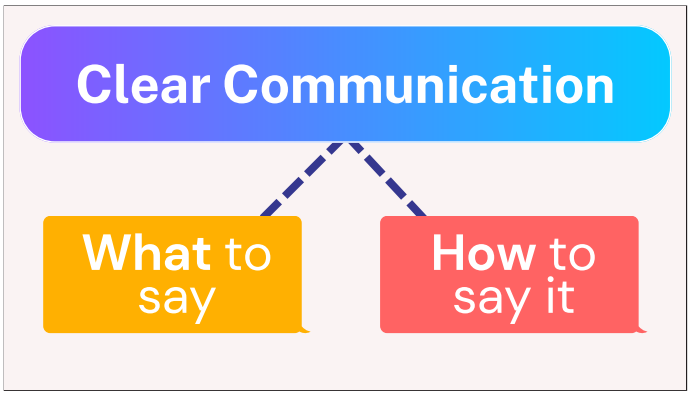

What to say
Instructions
"Limit your response to no more than 3 paragraphs."

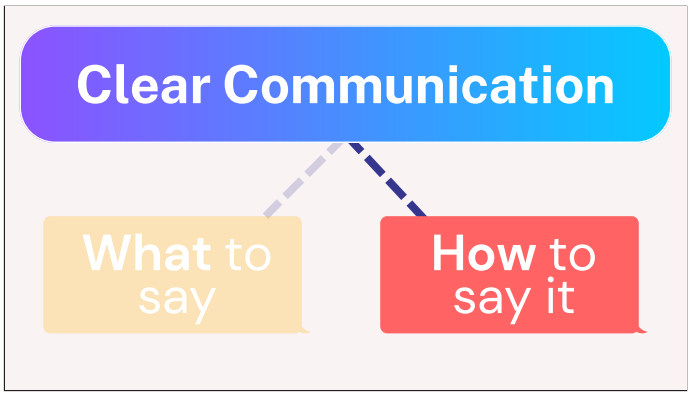

What to say
Instructions
"Format the return precautions as a short bulleted list."

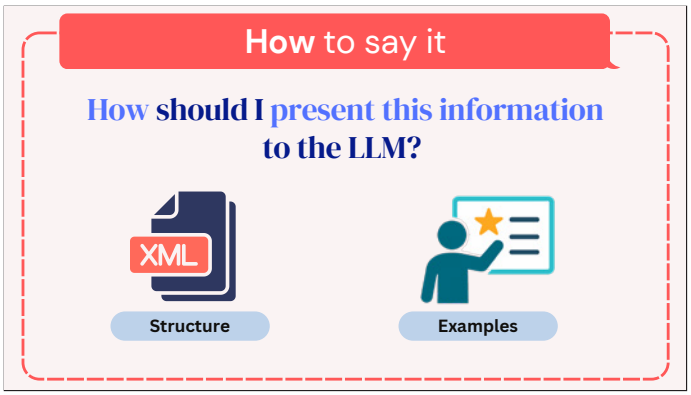

What to say
Instructions
"Always use commonly accepted medical abbreviations when appropriate."


What to say
What information do I need to give the LLM?
Role/Style/Tone
Goal
Context
Instructions


What to say
What information do I need to give the LLM?
Role/Style/Tone
Goal
Context
Instructions


Clear Communication
What to say
How to say it


Clear Communication
What to say
How to say it


How to say it
How should I present this information to the LLM?
XML
Structure
Examples

How to say it

How should I present this information to the LLM?

XML

Structure

Examples

How to say it

XML

Structure

How should I organize the information within the prompt so it's easy for the LLM to parse?

How to say it

How to say it

How to say it

How to say it

TYPE II DIABETES
Type 2 diabetes mellitus (T2DM) is a prevalent chronic condition marked by insulin resistance and relative insulin deficiency. It affects over 400 million people globally, with projections indicating a rise to 700 million by 2045. This increase is linked to sedentary lifestyles, poor dietary habits, and rising obesity rates. T2DM primarily affects adults, though its incidence in younger populations is increasing. Clinically, T2DM often presents insidiously, with many patients initially asymptomatic, leading to delayed diagnosis...

 # EPIDEMIOLOGY
Type 2 diabetes mellitus (T2DM) is a prevalent chronic condition...

 # CLINICAL PRESENTATION
Clinically, T2DM often presents insidiously, with many patients ..

 # DIAGNOSIS
The American Diabetes Association (ADA) diagnostic criteria for T2DM...

 # MANAGEMENT
Management of T2DM involves lifestyle modifications...

Structure via Markdown

How to say it

Element	Markdown Syntax
Heading	# H1 ## H2 ### H3
Bold	**bold text**
Italic	*italicized text*
Blockquote	> blockquote
Ordered List	1. First item 2. Second item 3. Third item
Unordered List	- First item - Second item - Third item

https://www.markdownguide.org/cheat-sheet/

Structure via Markdown

How to say it

TYPE II DIABETES
Type 2 diabetes mellitus (T2DM) is a prevalent chronic condition marked by insulin resistance and relative insulin deficiency. It affects over 400 million people globally, with projections indicating a rise to 700 million by 2045. This increase is linked to sedentary lifestyles, poor dietary habits, and rising obesity rates. T2DM primarily affects adults, though its incidence in younger populations is increasing. Clinically, T2DM often presents insidiously, with many patients initially asymptomatic, leading to delayed diagnosis...

delimitation

<epidemiology>
Type 2 diabetes mellitus (T2DM) is a prevalent chronic condition...
</epidemiology>

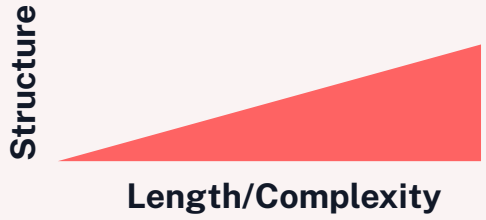
<clinical_presentation>
Clinically, T2DM often presents insidiously, with many patients ..
</clinical_presentation>

<diagnosis>
The American Diabetes Association (ADA) diagnostic criteria for T2DM...
</diagnosis>

<management>
Management of T2DM involves lifestyle modifications...
</management>

Structure via XML Tags

How to say it



How to say it

How should I present this information to the LLM?

Structure

Examples

How to say it

How should I present this information to the LLM?

Structure

Examples

How to say it

Examples

Would showing examples help the LLM better understand what I want?

How to say it

Showing Examples = "Few-Shot Learning"

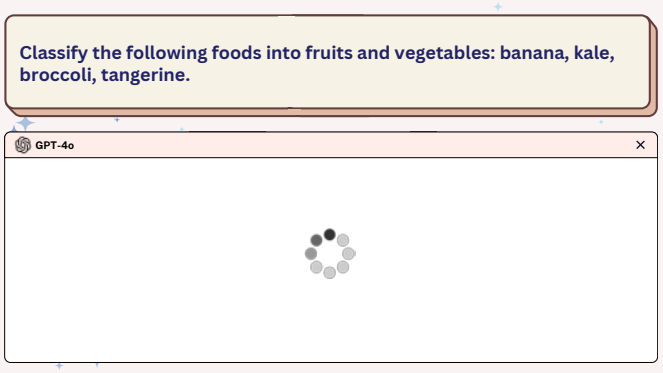
How to say it

Zero-shot: Classify the following foods into fruits and vegetables: banana, kale, broccoli, tangerine.

How to say it

Zero-shot: Classify the following foods into fruits and vegetables: banana, kale, broccoli, tangerine.

Few-shot: Classify the following foods into fruits and vegetables: banana, kale, broccoli, tangerine. **Examples: apple = fruit, spinach = vegetable, tangerine = fruit**



Classify the following foods into fruits and vegetables: banana, kale, broccoli, tangerine.

GPT-4o

Here's the classification:
- Fruits: Banana, Tangerine
- Vegetables: Kale, Broccoli

Classify the following foods into fruits and vegetables: banana, kale, broccoli, tangerine.

GPT-4o

Classify the following foods into fruits and vegetables: banana, kale, broccoli, tangerine.

GPT-4o

Here's the classification:
- Fruits:
  - Banana
  - Tangerine
- Vegetables:
  - Kale
  - Broccoli

Classify the following foods into fruits and vegetables: banana, kale, broccoli, tangerine.

Examples: apple = fruit, spinach = vegetable, tangerine = fruit

GPT-4o

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GPT-4o

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GPT-4o

Classify the following foods into fruits and vegetables: banana, kale, broccoli, tangerine.

Examples: apple = fruit, spinach = vegetable, tangerine = fruit

GPT-4o

Sure, here's the classification:
- Banana = fruit
- Kale = vegetable
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- Tangerine = fruit

Classify the following foods into fruits and vegetables: banana, kale, broccoli, tangerine.

Examples: apple = fruit, spinach = vegetable, tangerine = fruit

GPT-4o

Sure, here's the classification:
- Banana = fruit
- Kale = vegetable
- Broccoli = vegetable
- Tangerine = fruit

Classify the following foods into fruits and vegetables: banana, kale, broccoli, tangerine. Output *only* the classifications.

Examples: apple = fruit, spinach = vegetable, tangerine = fruit

GPT-4o

Classify the following foods into fruits and vegetables: banana, kale, broccoli, tangerine. Output *only* the classifications.

Examples: apple = fruit, spinach = vegetable, tangerine = fruit

GPT-4o

- Banana = fruit
- Kale = vegetable
- Broccoli = vegetable
- Tangerine = fruit

Few-Shot Prompting: Essentials

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Include **enough exemplars** to clearly demonstrate the **task pattern** (2-5+)

Few-Shot Prompting: Essentials

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Ensure exemplars are **representative** of the actual **distribution of inputs** in production.

Few-Shot Prompting: Essentials

Include **enough exemplars** to clearly demonstrate the **task pattern** (2-5+)

Ensure exemplars are **representative** of the actual **distribution of inputs** in production.

Ensure exemplars are **formatted correctly and consistently**.

Example Use Case: HPI Writer

Inpatient History and Physical

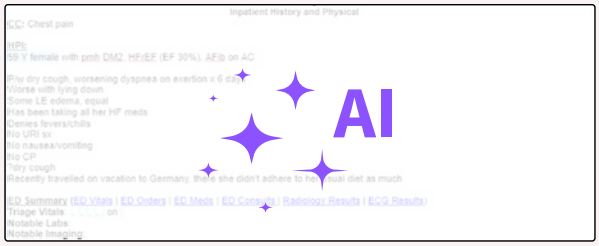
CC: Chest pain

HPI:
59 Y female with pmh DM2, HFrEF (EF 30%), AFib on AC

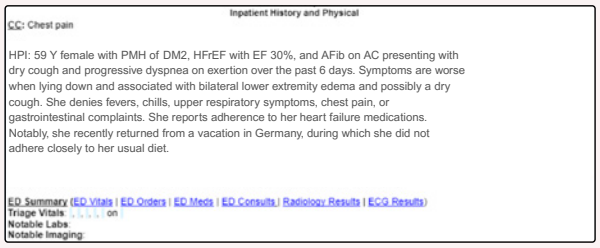
P/w dry cough, worsening dyspnea on exertion x 6 days
Worse with lying down
Some LE edema, equal
Has been taking all her HF meds
Denies fevers/chills
No URI sx
No nausea/vomiting
No CP
?dry cough
Recently travelled on vacation to Germany, there she didn't adhere to her usual diet as much

ED Summary (ED Vitals | ED Orders | ED Meds | ED Consults | Radiology Results | ECG Results)
Triage Vitals:
Notable Labs:
Notable Imaging:

Example Use Case: HPI Writer



Example Use Case: HPI Writer



Inpatient History and Physical

CC: Chest pain

HPI: 59 Y female with PMH of DM2, HFrEF with EF 30%, and AFib on AC presenting with dry cough and progressive dyspnea on exertion over the past 6 days. Symptoms are worse when lying down and associated with bilateral lower extremity edema and possibly a dry cough. She denies fevers, chills, upper respiratory symptoms, chest pain, or gastrointestinal complaints. She reports adherence to her heart failure medications. Notably, she recently returned from a vacation in Germany, during which she did not adhere closely to her usual diet.

ED Summary (ED Vitals | ED Orders | ED Meds | ED Consults | Radiology Results | ECG Results)
Triage Vitals
Notable Labs
Notable Imaging:

Few-Shot Prompting: Essentials

Example Output 1: 87yoF p/w ...

Example Output 2: 78YF p/w ...

Example Output 3: 94YF presenting for ...

Few-Shot Prompting: Essentials

Example Output 1: 87yoF p/w ...

Example Output 2: 78YF p/w ...

Example Output 3: 94YF presenting for ...

❌ **All output examples are elderly patients.**

Few-Shot Prompting: Essentials

Example Output 1: 87yoF p/w ...

Example Output 2: 78YF p/w ...

Example Output 3: 94YF presenting for ...

❌ **All output examples are elderly patients.**

❌ **All output examples are female patients.**

Few-Shot Prompting: Essentials

Example Output 1: 87yoF p/w ...

Example Output 2: 78YF p/w ...

Example Output 3: 94YF presenting for ...

❌ **All output examples are elderly patients.**

❌ **All output examples are female patients.**

❌ **Output examples are inconsistently formatted.**

Few-Shot Prompting: Essentials

❌

Example Output 1: 87yoF p/w ...

Example Output 2: 78YF p/w ...

Example Output 3: 94YF presents for ...

Few-Shot Prompting: Essentials

❌

Example Output 1: 87yoF p/w ...

Example Output 2: 78YF p/w ...

Example Output 3: 94YF presents for ...

✅

Example Output 1: 87yoF p/w ...

Example Output 2: 24yoM p/w ...

Example Output 3: 6moF p/w ...

Few-Shot Prompting: Essentials

❌

Example Output 1: 87yoF p/w ...

Example Output 2: 78YF p/w ...

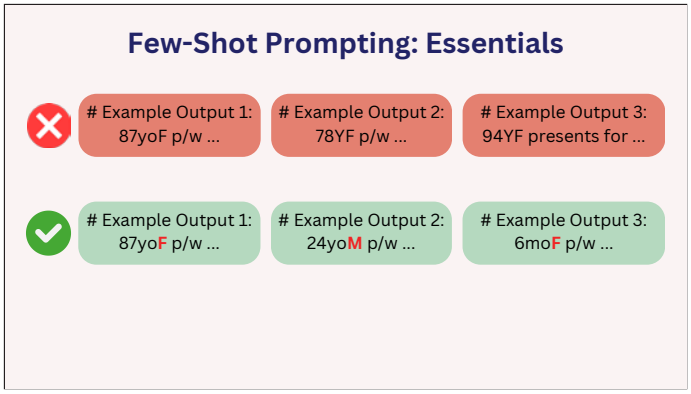
Example Output 3: 94YF presents for ...

✅

Example Output 1: 87yoF p/w ...

Example Output 2: 24yoM p/w ...

Example Output 3: 6moF p/w ...


Few-Shot Prompting: Essentials
Example Output 1: 87yoF p/w ...
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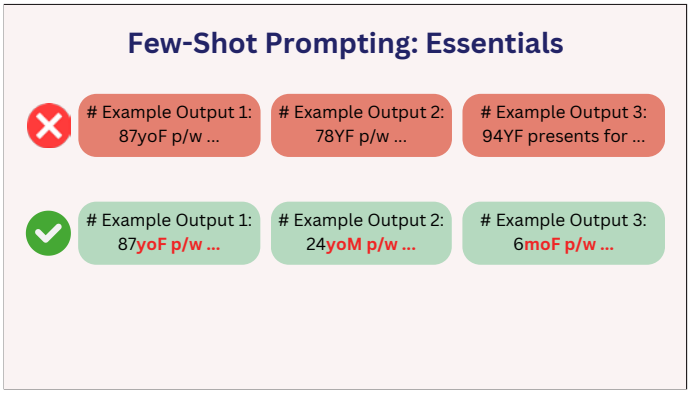
Example Output 3: 94YF presents for ...
Example Output 1: 87yoF p/w ...
Example Output 2: 24yoM p/w ...
Example Output 3: 6moF p/w ...


Few-Shot Prompting: Essentials
Example Output 1: 87yoF p/w ...
Example Output 2: 78YF p/w ...
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Example Output 1: 87yoF p/w ...
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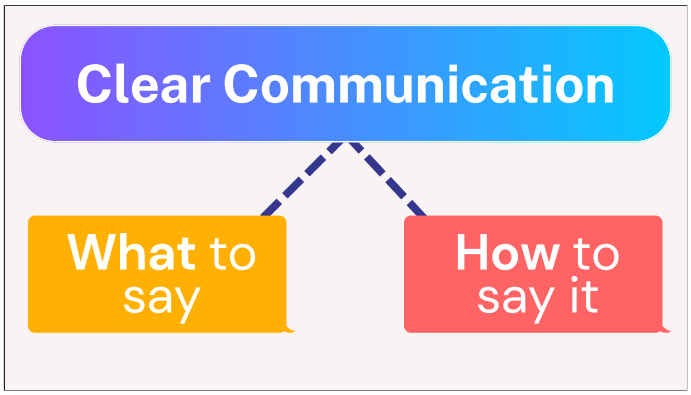
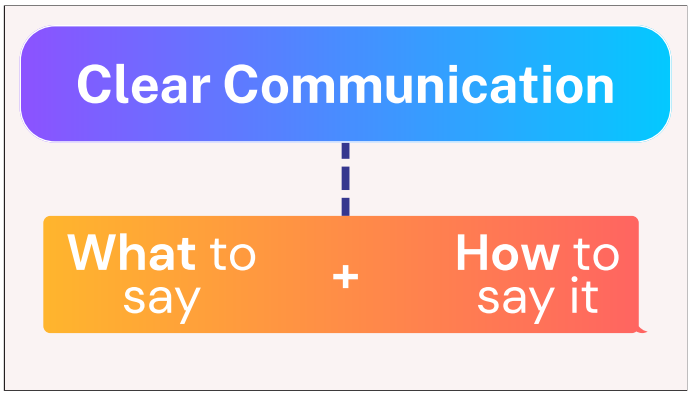
Example Output 3: 6moF p/w ...

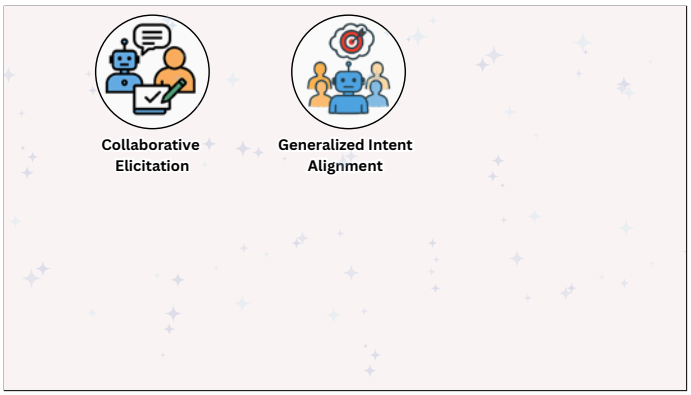

Clear Communication
What to say
How to say it

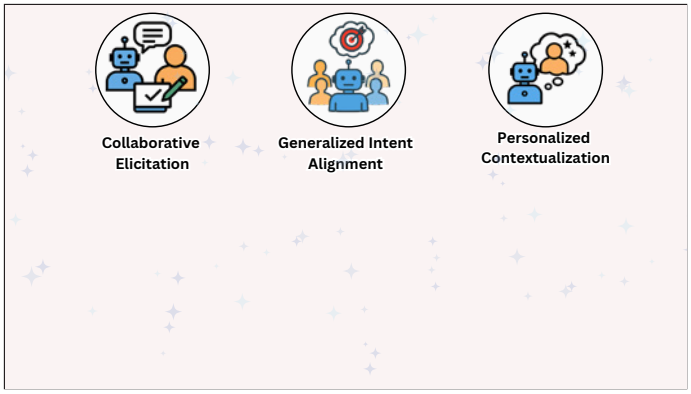

Clear Communication
What to say
How to say it

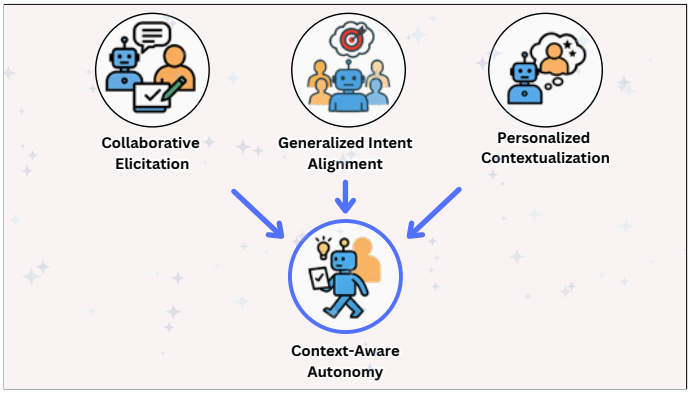

Clear Communication
What to say
+
How to say it

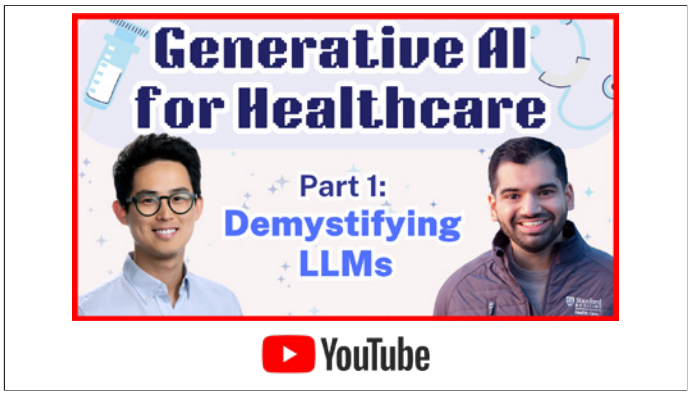

The Future of LLMs


Collaborative Elicitation


Collaborative Elicitation
Generalized Intent Alignment


Collaborative Elicitation
Generalized Intent Alignment
Personalized Contextualization


Collaborative Elicitation
Generalized Intent Alignment
Personalized Contextualization
Context-Aware Autonomy


Generative AI for Healthcare
Part 1:
Demystifying LLMs
YouTube


Connect with Us on LinkedIn
Dong-han Yao, MD
Shivam Vedak, MD MBA
profiles.stanford.edu/dong
profiles.stanford.edu/shivam

SELF EVALUATION

Generative AI in Healthcare: Prompting LLMs

True/False

1. Prompting can be thought of as the process of clearly communicating with an LLM to get the output that you want.

2. Assigning the LLM a “role” as a physician expert is important in increasing the accuracy of medical prompts.

3. The helpfulness of an LLM’s output can be significantly improved by providing the model with more context about your problem, or more specific instructions on what your requirements are.

4. Carefully structuring your prompt and providing examples are usually necessary to get a usable output during everyday use of an LLM.

5. When using few-shot prompting, it’s important that the examples you provide reflect the real-world distribution of cases you expect the model to handle.

Answer Key: 1. T, 2. F, 3. T, 4. F, 5. T

FACULTY

Bobby Mukkamala, MD

Bobby Mukkamala, MD, of Flint Township, Michigan, a board-certified otolaryngologist, head and neck surgeon, was elected president of the American Medical Association in June 2025. A graduate of the University of Michigan Medical School, he is in solo, private practice in Flint, Mich. Dr. Mukkamala, who has been active in the AMA since residency, is a past Michigan representative to the AMA Young Physicians Section, a past recipient of the AMA Foundation's "Excellence in Medicine" Leadership Award and, for 13 years, served as a member of the Michigan delegation to the AMA House of Delegates. In 2009 he was elected to the AMA Council on Science and Public Health and served as its chair from 2016 to 2017.

In addition to his leadership roles at the AMA, Dr. Mukkamala has served as a member of the Michigan State Medical Society Board of Directors since 2011, as board chair for two years, and as its president. He is also a past president of the Genesee County Medical Society (GCMS) and continues to serve on the GCMS Board of Directors.

While a wide range of public health issues are important to Dr. Mukkamala, no issue strikes closer to home than his own city of Flint's nationally publicized struggles with high levels of lead leaching into the drinking water. As the past chair of the Community Foundation of Greater Flint, he and the foundation's board became the clearinghouse for funding projects focused on mitigating the effects of lead in local children. He is a member of the board of the Foundation for Flint that is working to increase access to high-quality early education for children—a proven strategy for helping children who have been exposed to lead. He was also recently appointed as a trustee of the C.S. Mott Foundation, which is headquartered in Flint and promotes a just, equitable and sustainable society.

You may contact Dr. Mukkamala with your questions or comments at bobby.mukkamala@ama-assn.org.

The Impact of Physician Leadership in Health Care
Bobby Mukkamala, MD

About me

- President, American Medical Association
- Board-certified otolaryngologist – head and neck surgeon in Flint, MI
- University of Michigan Medical School
- Residency, Loyola University Medical Center
- Chair of AMA Substance Abuse and Pain Care Task Force
- Past president, former chair, Michigan State Medical Society Board of Directors
- Trustee, C.S. Mott Foundation

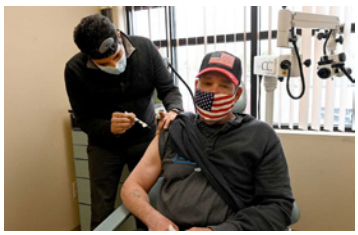
A child of immigrants

The immigrant experience in the U.S.

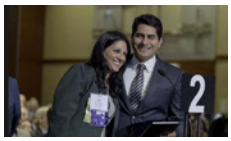
Me … for a long time

Leaders must be bold

Leaders must be creative

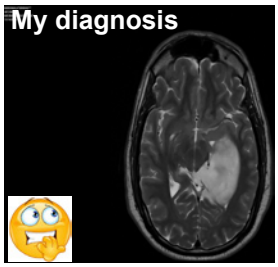


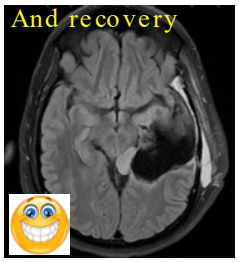
Leave it better than we found it…for them



AMA | Physicians' powerful ally in patient care

From physician to patient-physician advocate





- Type of cancer
- How it was discovered
- Course of treatment
- How I'm using my platform as AMA president-elect

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How a sudden diagnosis changed how I look at health care

"….as my life ran into the challenge of brain cancer, I had no idea that I would be able to continue to participate in our collective work, but here I am."

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The AMA prepares physicians to become leaders in health care

AMA | Physicians' powerful ally in patient care

Who is the AMA?

- **The nation's largest and most influential physician organization.**
- Established and maintains Code of Medical Ethics.
- Convenes AMA House of Delegates – the Congress of Medicine.
- **Influences state and federal policy decisions about medical practice and patient safety.**
- Led or helped advance major public health initiatives since founding in 1847.

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The growing influence of organized medicine

- AMA House of Delegates meets in June and November to debate health policy.
- **700 delegates** represent more than **190 state and specialty societies.**

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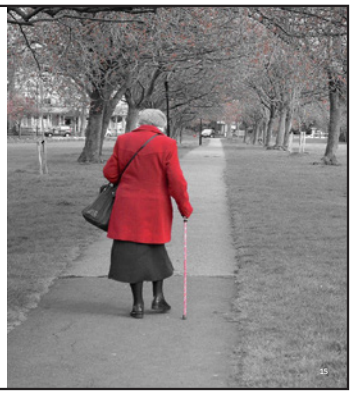
The AMA supports physicians in a challenging climate

AMA | Physicians' powerful ally in patient care

Responding to the health care needs of tomorrow…today

- By 2050, one-fifth of the United States' population will be over 65.
- Growing chronic disease burden
- Widening income inequalities
- Rising health care costs
- Shrinking medical workforce
- Future pandemics
- Declining life expectancy?
- Increasing maternal mortality?



The weight physicians carry

Expanding administrative bureaucracy and paperwork
Increasing hostility toward health care workers
Attacks on science and misinformation campaigns
Government interference into patient-physician autonomy
Surging chronic disease
Economic pressures and uncertainty
Lack of trust in medical institutions
Professional burnout
Questions about AI and emerging health technology

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Our nation's shrinking physician workforce

Projections
- 1 in 5 physicians planned to leave medicine within two years**
- 1 in 3 planned to reduce hours**
- Nearly half are 55 or older

➢ Anticipated shortfall of **more than 1,600 otolaryngologists** in U.S. by next year, increasing patient wait times.

Current challenges
- 83 million without sufficient access to PCP
- Access to OB/Gyn increasingly challenged
- 80-90% of counties without specialists

86k physician shortage in U.S. by 2036*

**2021 health care worker survey published in Mayo Proceedings

*Association of American Medical Colleges

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Recognizing the impact of physician leadership

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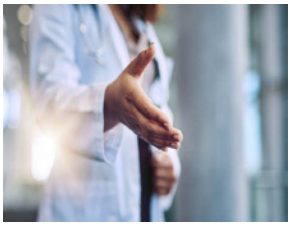
More doctors feel supported by health organization leaders



Workplaces where physicians feel valued and in control of their workload have less burnout:

- 72.8% of physicians feel supported in their work
- 75.8 % of physicians trust their local leaders to keep them safe
- 70% feel that they're contributions are recognized by leadership
- 70% believe information is shared transparently

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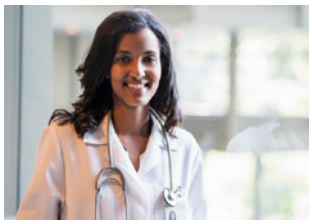
Training and recognizing physician leaders



- AMA EdHub
  - 9,000 online resources
  - 4,000 CME opportunities
  - American Association for Physician Leadership
- AMA Foundation Leadership Development Institute (LDI)
  - Healthcare Administration and Management
  - Health Policy and Patient Advocacy
- Excellence in Medicine Awards

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The AMA is the leading voice for physician advocacy

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The power of our physician voice in advocacy

Our health system needs the input of many skilled physicians—physician leaders across every state and specialty—who are working together with incredible purpose and urgency.

It needs the AMA more than ever … leaders in our profession speaking with one firm and commanding voice.

Our patients deserve better.

Our physicians deserve better.

Our nation deserves better.

Inauguration Night, June 2025

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AMA's top advocacy priorities

- Reforming Medicare payments
- Tackling Prior Authorization
- Promoting physician-led teams
- Reducing burnout and improving physician well-being
- Advancing digital health, including telehealth

Building a stronger physician workforce and health system

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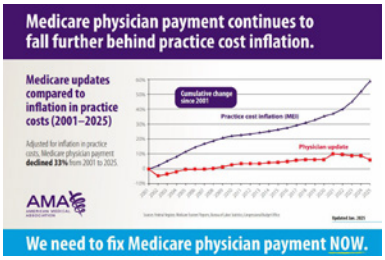
Reforming Medicare, protecting Medicaid

We need a rational Medicare payment system

- Physician Medicare payment has declined 33% since 2001.
- Reform must provide financial stability, annual inflation-based payment updates.



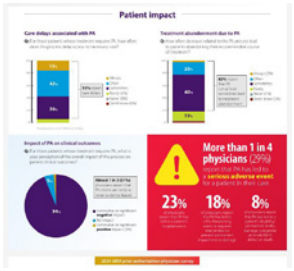
New law threatens health care for millions

- An estimated 11.8 million people could lose health insurance coverage as a result of this law.
- Care will be less accessible, and patients may simply forego seeing their physician because the lifelines of Medicaid and CHIP are severed.
- AMA continues to warn about the dangers to patients and the health system if millions lose their health coverage.

Fighting against prior authorization

Prior auth harms patients, physicians

- Physicians spend **2 hours on administrative work for every hour of patient care** - the leading administrative burden for physicians.
- 94% of physicians surveyed report that prior auth leads to delay in care.
- 78% say delays have led patients to **abandon treatment**.
- One-fourth say prior auth delays have led to **serious adverse event** for their patients.



Health plans pledge to cut prior auth red tape

- Some of the nation's largest insurers have promised to accelerate PA decisions.
- That's great news, but insurers have made these pledges before – in 2018 and 2023.
- PA remains a major source of frustration for physicians, medical staff and patients.

AMA continues push for federal PA legislation

Improving Seniors' Timely Access to Care Act

- Reintroduced with lower CBO cost estimate.
- Expands on prior auth reforms by CMS.

Reducing Medically Unnecessary Delays in Care Act

- Would ensure PA treatment decisions would be made by specialty board-certified physicians for some plans.

Join us
FixPriorAuth.org

Promoting physician wellness and a robust workforce

Prioritizing physician mental health

- State and federal advocacy
- Data collection, physician surveys
- Tools, training, resources and support
- Reduce stigma of seeking treatment
- Advocate for confidential physician wellness programs

AMA Joy in Medicine Program

Eliminating stigmatizing language from the profession

- Following passage of ***Dr. Lorna Breen Health Care Provider Act***, AMA continues to push for regulatory, legislative and other solutions to direct more funding and resources to support physician mental health.
- AMA is working at the state and national levels to identify, and reform outdated, stigmatizing language on medical licensing board, health system credentialing, and other applications.
- AMA has supported legislative victories in multiple states to help create confidential physician wellness programs.
- **34 state medical boards** and **more than 500 hospitals and health systems** have so far improved their licensure applications – benefitting more than one million physicians and other health care professionals.

Solutions for a healthier America

- Press Congress to put our health system on a sustainable path for the future
  - Fix Medicare payment, reform prior authorization, solve the burnout epidemic
- Prioritize chronic disease management
  - Tools and resources for physicians to take better care of their patients with a chronic disease burden
- Work collaboratively to address deep-rooted health inequities and social determinants of health.
- Educate and train physicians to better care for patients with one or more chronic disease.

"We cannot lose sight of what medicine and science have achieved in our lifetimes."

GET INVOLVED!

Help us create a better health care future

JOIN US!

SELF EVALUATION

The Impact of Physician Leadership in Health Care

1. Medicare payment to physicians has dropped by more than ____% since 2001, when adjusted for inflation:

a. 16
b. 25
c. 33
d. 52

2. T/F - Prior authorization delays have no impact on patient care.

3. Physicians identified ____ among their top concerns as AI technology rapidly integrates into the health care setting.

a. Liability
b. Patient safety
c. Privacy
d. Performance

4. The American Medical Association was founded in 1847. Currently, the AMA:

a. Establishes and maintains a Code of Medical Ethics.
b. Convenes AMA House of Delegates – the Congress of Medicine.
c. Influences states and federal policy decisions about medical practice and patient safety.
d. All of the above

5. The Association of American Medical Colleges predicts a shortfall of as many as _____ physicians by 2036:

a. 90,000
b. 86,000
c. 72,000
d. 78,000

Answer Key: 1. C, 2. F, 3. A, 4. D, 5. B

Barry Franklin, MD

Barry Franklin, MD, of Royal Oak Michigan, is Director of Preventive Cardiology and Cardiac Rehabilitation at Beaumont Health, Royal Oak, Michigan. He holds faculty appointments as Professor of Physiology at Wayne State University School of Medicine and Professor of Internal Medicine, Oakland University William Beaumont School of Medicine. Pursuing his interest in combining exercise physiology with cardiology, Barry and his associates have studied the physiologic and clinical responses to numerous occupational and leisure-time activities in people with and without heart disease. Other research interests include the prevention of heart disease; cardiovascular risk reduction; obesity and metabolism; exercise testing and prescription; and lifestyle medicine.

You may contact Dr. Franklin with your questions or comments at barry.franklin@corewellhealth.org.

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Director of Preventive Cardiology and Cardiac Rehabilitation

Extreme Exercise: Understanding the Risks and Benefits

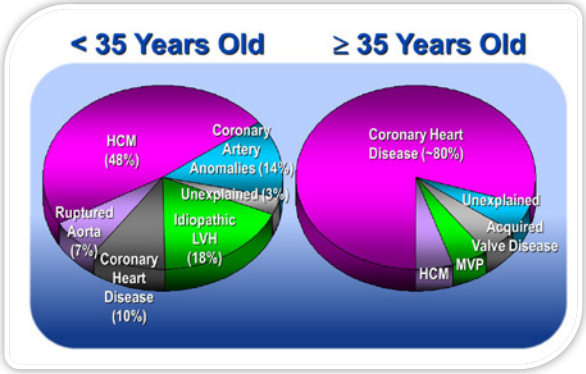
Outline (6 topics)

Topic 1

- Exercise-Related Cardiovascular Events: Marathon and Triathlon Deaths
- Marathon Running and "Immunity to Heart Disease"
- Exercise: Too Much of a Good Thing ?
- Physical Activity, Fitness & Atrial Fibrillation: Reverse J-Curve Pattern

Sudden cardiac death of a young competitive athlete is a rare but tragic event. Hypertrophic cardiomyopathy and coronary artery anomalies are the most frequent causes. Most structural cardiovascular abnormalities go unrecognized until the time of death.

Drezner JA. Postgrad Med 2000;105:37



Heart attack during run kills Jim Fixx, expert on jogging

Fixx's 1978 "The Complete Book of Running" earned him more than $1 million and put him in great demand as a lecturer on running.

Author of sci-fi cult classic dies at 49

Douglas Adams, whose cult science fiction comedy *The Hitchhiker's Guide to the Galaxy* drew millions of fans and spawned a mini-industry, has died at age 49. The British-born Adams died Friday of an apparent heart attack in Santa Barbara, Calif., a family friend, **Elizabeth Gibson**, said Saturday. She said Adams collapsed while working out at a gym. "He was not ill," Gibson said. "This was completely unexpected." *The Hitchhiker's Guide to the Galaxy*, which began as a British Broadcasting Corp. radio series in 1978, is a satirical adventure about a group of interplanetary travelers; it opens with the Earth being destroyed to make way for an intergalactic highway. It was turned into a book, which sold 14 million copies around the world, and later into a television series. Adams married Jane Belson, a lawyer, in 1991. The couple, who had lived in Santa Barbara since 1999, had a 6-year-old daughter, Polly. Adams is also survived by his mother, Jan Thrift of England.

Associated Press

Douglas Adams, author of "The Hitchhiker's Guide to the Galaxy," died Friday of an apparent heart attack while working out at a gym. He was 49.

Circulation

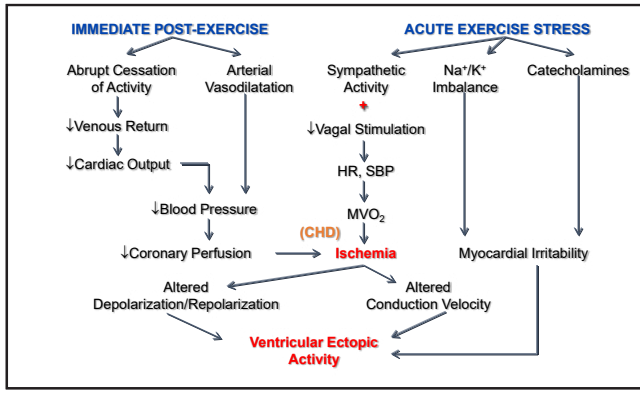
AHA SCIENTIFIC STATEMENT

Exercise-Related Acute Cardiovascular Events and Potential Deleterious Adaptations Following Long-Term Exercise Training: Placing the Risks Into Perspective–An Update

A Scientific Statement From the American Heart Association

Unaccustomed vigorous physical activity, particularly when performed by inactive, unfit, susceptible individuals, can actually increase the risk of sudden cardiac death and acute myocardial infarction. For those who are highly sedentary, it is important to start exercise in an incremental way. Acute CV events are often preceded by warning symptoms—which require immediate cessation of training and medical review and clearance before resuming exercise. Extreme exercise regimens may increase coronary calcium and the risk of incident atrial fibrillation.

Circulation 2020;141: February 26, 2020



Silent myocardial ischemia may be the missing link between the increased risk of cardiac arrest and the lack of pre-monitoring symptoms during supervised exercise in cardiac rehabilitation programs.

Hoberg E, et al. AJC 1990;65:583

Malignant Ventricular Arrhythmias: A Potential Complication of Vigorous Exercise

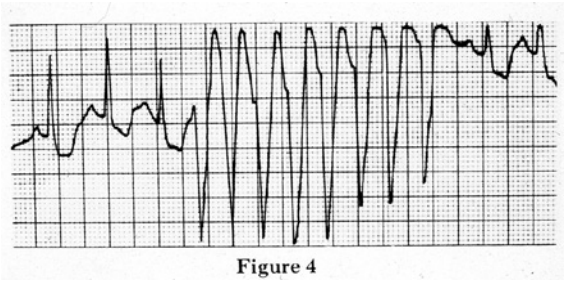
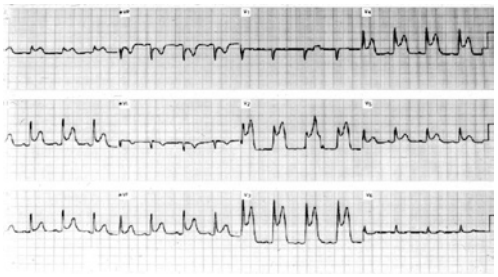


Figure 4

Exercise May Provoke Plaque Rupture and Coronary Thrombosis



Thompson P. Arch Intern Med 1996;156:2297

Cardiac Arrest During Long-Distance Running Races*

To clarify the risk of cardiac arrest associated with marathon and half-marathon races in the U.S. from January 1, 2000, to May 31, 2010, investigators reported on the incidences and outcomes of events among 10.9 million registered marathon runners. Of the 59 cases of cardiac arrest (mean ± SD age, 42 ± 13 years; 51 men), 42 (71%) were fatal (~4 fatalities/year). Conclusion: Marathoners are at a low risk for acute cardiac events. The final mile, < 5% of the 26.2 mile marathon distance, accounts for ~ 50% of the sudden cardiac deaths.

The most frequent clinical and autopsy findings were hypertrophic cardiomyopathy and atherosclerotic CVD, respectively.

**Kim JH et al. NEJM 2012;366:130-140*

Death and Cardiac Arrest in U.S. Triathlon Participants*

- > 9 million participants over 30 years
- 135 sudden cardiac deaths(SCDs, 86% men; 13 survivors); incidence of 1.74/100,000 participants versus 1.01/100,000 for marathon running
- Women ~ 15% of the study population, and their incidence of SCD was 3.5 – fold less than men
- Most SCDs occurred during the swim (n=90; 67%) followed by the bicycle, run, and post-race periods, 22, 15, and 8 respectively
- Many of the SCDs (38%) were competing in their first triathlon
- Autopsies performed on 61 of the 135 victims, revealed that 27 (44%) had atherosclerotic CAD and/or cardiomyopathy

Harris KM et al Ann Intern Med 2017 167:529-535

Outline

Topic 2

- Exercise-Related Cardiovascular Events: Marathon and Triathlon Deaths
- Marathon Running and "Immunity to Heart Disease"
- Exercise: Too Much of a Good Thing ?
- Physical Activity, Fitness & Atrial Fibrillation: Reverse J-Curve Pattern

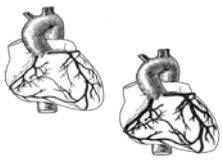
Bassler Hypothesis

SPECIAL ARTICLE

HALF A CENTURY OF RUNNING?

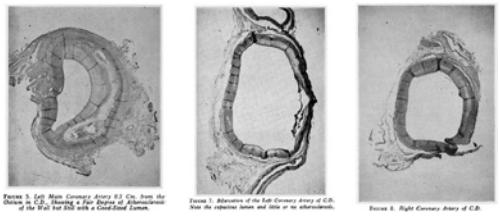
Clinical, Physiologic and Autopsy Findings in the Case of Clarence DeMar ("Mr. Marathon")

The striking anatomic finding in the heart was the relative size of the coronary arteries, which were estimated to be 2 or 3 times the normal diameter. Atherosclerosis of the coronary arteries was present but was relatively mild in degree, i.e., lumen was estimated to be reduced by 30% at several sites.



Currens JH, White PD.
NEJM 1961;265:988-993

Coronary Arteries of Clarence DeMar at Autopsy



Currens JH, White PD. NEJM 1961;265:988-993

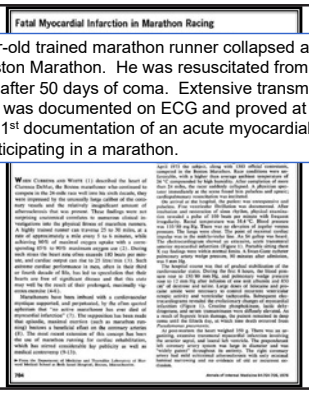
Marathon Running and Immunity to Heart Disease

Thomas J. Bassler, MD

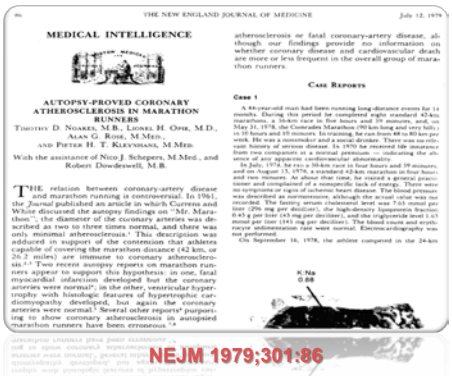
Reprinted from The Physician and Sports Medicine, Vol. 3, No. 4, April 1975. McGraw-Hill, Inc.

Fatal Myocardial Infarction in Marathon Racing

A 44-year-old trained marathon runner collapsed after completing 24 miles of the 1973 Boston Marathon. He was resuscitated from ventricular fibrillation. Death occurred after 50 days of coma. Extensive transmural anterior myocardial infarction was documented on ECG and proved at autopsy. We believe this report to be the 1st documentation of an acute myocardial infarction in a trained athlete while participating in a marathon.



Green LH et al.
Annals of Internal Medicine
1976;84:704-706

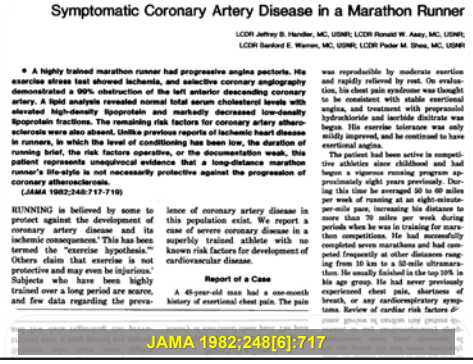


MEDICAL INTELLIGENCE

AUTOPSY-PROVED CORONARY ATHEROSCLEROSIS IN MARATHON RUNNERS

NEJM 1979;301:86

Symptomatic Coronary Artery Disease in a Marathon Runner



JAMA 1982;248[6]:717

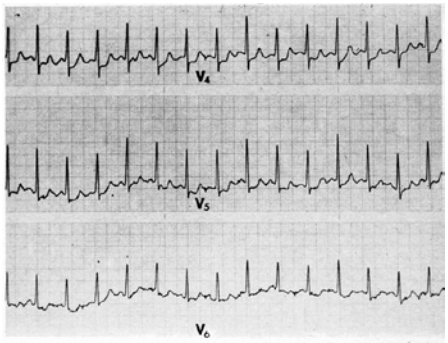
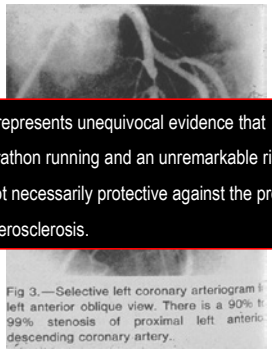
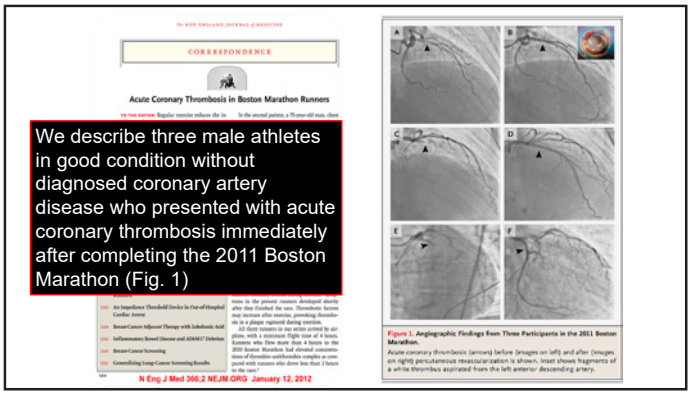


Fig 1.—Precordial leads V_4, V_5, and V_6 recorded at peak exercise during episode of chest pain. There is ST-segment depression consistent with ischemia.



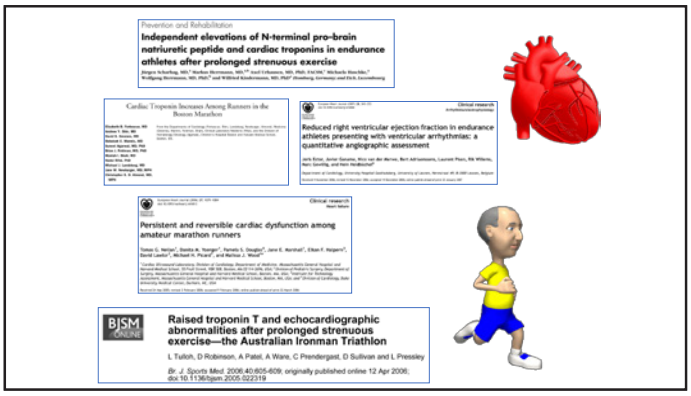
This patient represents unequivocal evidence that long-distance marathon running and an unremarkable risk factor profile are not necessarily protective against the progression of coronary atherosclerosis.

Fig 3.—Selective left coronary arteriogram i
left anterior oblique view. There is a 90% t
99% stenosis of proximal left anteric
descending coronary artery.

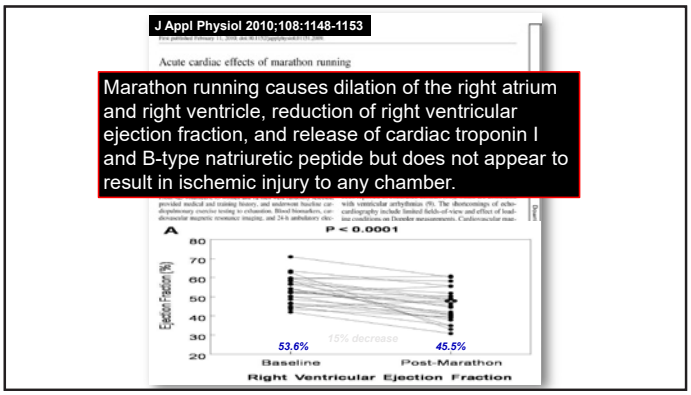

CORRESPONDENCE
Acute Coronary Thrombosis in Boston Marathon Runners
We describe three male athletes in good condition without diagnosed coronary artery disease who presented with acute coronary thrombosis immediately after completing the 2011 Boston Marathon (Fig. 1)
N Eng J Med 366;2 NEJM.ORG January 12, 2012

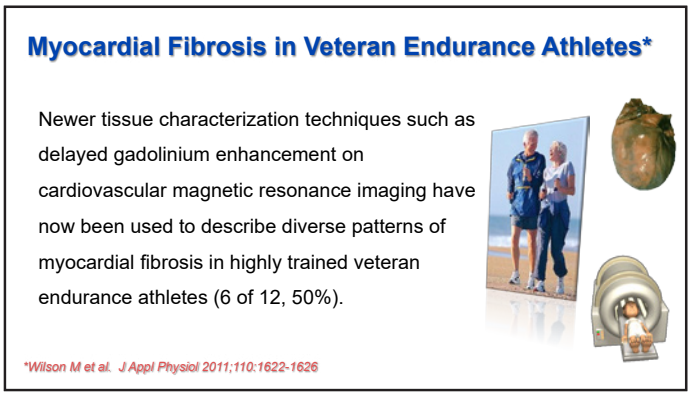

Outline
Topic 3
Exercise-Related Cardiovascular Events: Marathon and Triathlon Deaths
Marathon Running and "Immunity to Heart Disease"
Exercise: Too Much of a Good Thing ?
Physical Activity, Fitness & Atrial Fibrillation: Reverse J-Curve Pattern
Clin Cardiol 2012;35:69-73

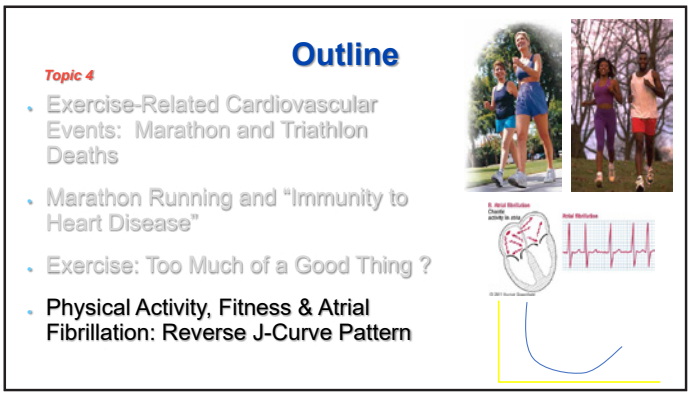

Exercise—Is it Possible to Have Too Much of a Good Thing?
Andre La Gerche, MBBS* and David L. Prior, FRACP, PhD

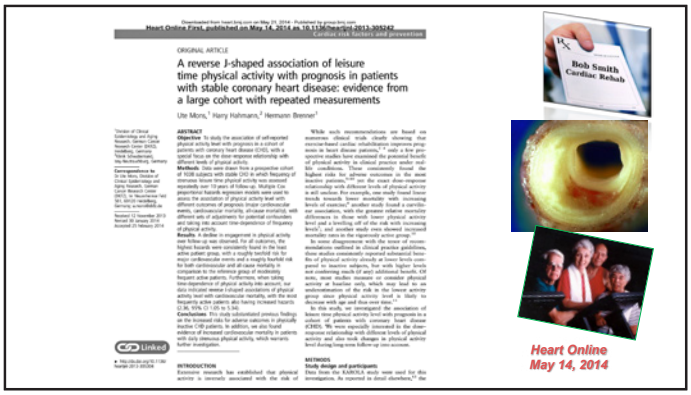

Independent elevations of N-terminal pro-brain natriuretic peptide and cardiac troponins in endurance athletes after prolonged strenuous exercise
Cardiac Troponin Increases Among Runners in the Boston Marathon
Reduced right ventricular ejection fraction in endurance athletes presenting with ventricular arrhythmias: a quantitative angiographic assessment
Persistent and reversible cardiac dysfunction among amateur marathon runners
Raised troponin T and echocardiographic abnormalities after prolonged strenuous exercise—the Australian Ironman Triathlon


Abnormalities Following Ultra-Endurance Exercise
27 athletes competing in a triathlon
↑ cardiac troponin and B-type natriuretic peptide in the immediate post-race setting; echocardiographic evidence of both left and right ventricular dysfunction. Evidence of myocardial injury resolved after 7 days.
Significance? Repeated cardiac injury seen after intense exercise represents a potential for generation of scar tissue → malignant cardiac arrhythmias.
LaGerche A et al. Heart, Lung & Circulation 2007;16:S102


J Appl Physiol 2010;108:1148-1153
Acute cardiac effects of marathon running
Marathon running causes dilation of the right atrium and right ventricle, reduction of right ventricular ejection fraction, and release of cardiac troponin I and B-type natriuretic peptide but does not appear to result in ischemic injury to any chamber.
P < 0.0001
Ejection Fraction (%)
53.6%
45.5%
15% decrease
Baseline
Post-Marathon
Right Ventricular Ejection Fraction

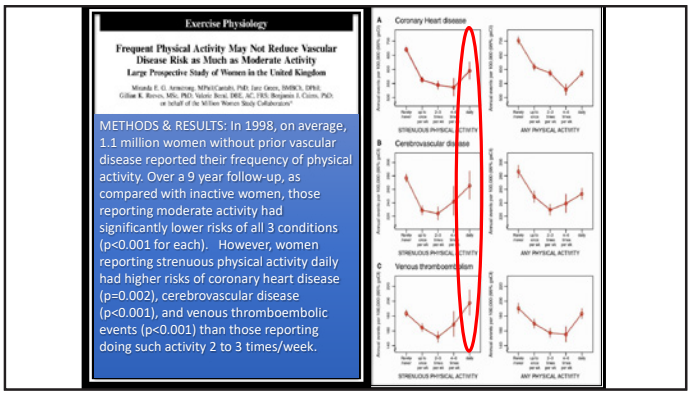

Myocardial Fibrosis in Veteran Endurance Athletes*
Newer tissue characterization techniques such as delayed gadolinium enhancement on cardiovascular magnetic resonance imaging have now been used to describe diverse patterns of myocardial fibrosis in highly trained veteran endurance athletes (6 of 12, 50%).
*Wilson M et al. J Appl Physiol 2011;110:1622-1626


Outline
Topic 4
Exercise-Related Cardiovascular Events: Marathon and Triathlon Deaths
Marathon Running and "Immunity to Heart Disease"
Exercise: Too Much of a Good Thing ?
Physical Activity, Fitness & Atrial Fibrillation: Reverse J-Curve Pattern

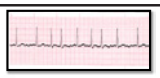


	Events	Person-years	Incidence/mortality rate (95% CI) per 1000 person-years
Cardiovascular mortality			
Daily	14	1481.9	9.5 (5.6 to 16.0)
5–6×/week	10	1617.9	6.2 (3.3 to 11.5)
2–4×/week	19	4188.1	4.5 (2.9 to 7.1)
1–4×/month	15	1849.8	8.1 (4.9 to 13.5)
Rarely/never	23	789.8	29.1 (19.4 to 43.8)
All-cause mortality			
Daily	24	1481.9	16.2 (10.9 to 24.2)
5–6×/week	14	1617.9	8.7 (5.1 to 14.6)
2–4×/week	32	4188.1	7.6 (5.4 to 10.8)
1–4×/month	26	1849.8	14.1 (9.6 to 20.6)
Rarely/never	35	789.8	44.3 (31.8 to 61.7)

Mons U et al. Heart May 14, 2014

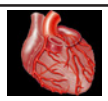


Extreme Exercise Increases the Risk of Atrial Fibrillation (5x)*

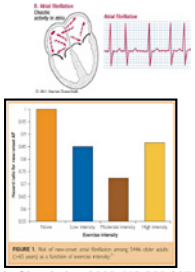


* O'Keefe JH et al. Mayo Clin Proc 2012;87:587-595

Older Adults, Exercise and Atrial Fibrillation

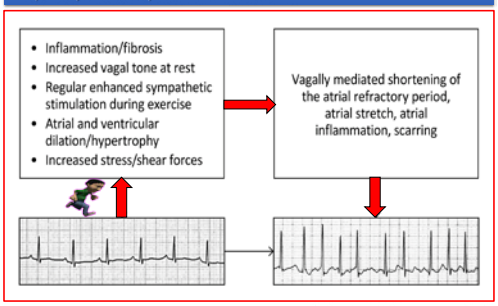


A prospective observational study of older men and women (mean age 73 years) reported that moderate-intensity physical activity such as walking was associated with a reduced risk of atrial fibrillation by about one-third. Still, high-intensity exercise showed the familiar reverse J-shaped relationship with the risk of atrial fibrillation.

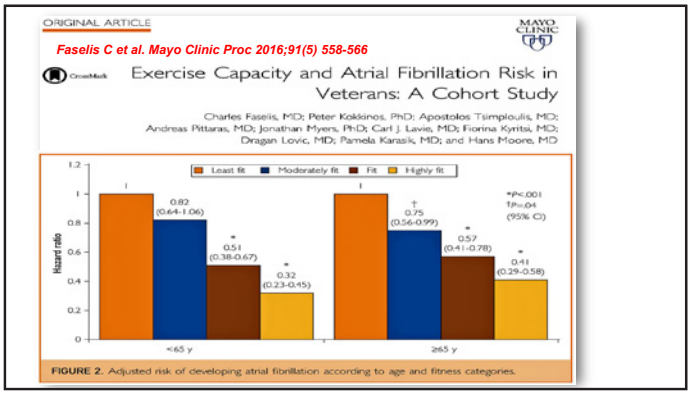


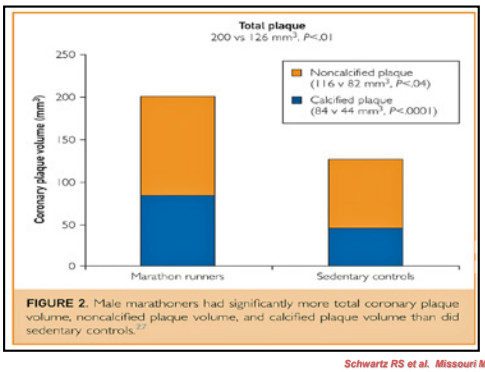
Mozaffarian D et al. Circulation 2008;118:800-807

A history of ≥ 2000 hours of vigorous endurance-training is frequently noted in patients with Lone-AF.



Calvo N,et al Europace 2016





Schwartz RS et al. Missouri Med 2014;111:85

Circulation

ORIGINAL RESEARCH ARTICLE

Cardiorespiratory Fitness, Coronary Artery Calcium, and Cardiovascular Disease Events in a Cohort of Generally Healthy Middle-Age Men

Results From the Cooper Center Longitudinal Study

METHODS: We studied 8425 men without clinical CVD who underwent preventive medical exams that included measures of CRF and CAC between 1998 and 2007. There were 383 CVD events during an average follow-up of 8.4 years.

RESULTS: CVD events increased with increasing CAC and decreased with increasing CRF. Adjusting for CAC level (scores of 0, 1-99, 100-399, and ≥ 400), for each additional MET of fitness there was an **11% lower risk** for CVD events.

CONCLUSIONS: In a large cohort of healthy men, there is an attenuation of CVD risk at all CAC levels with higher CRF.

Table 3. Estimated Hazard Ratios for Total Cardiovascular Disease Events (N=8120, 5–15 METs)

Effect	Base Model: Hazard Ratio (95% Confidence Interval)	Base Model: P Value	Adjusted Model*: Hazard Ratio (95% Confidence Interval)	Adjusted Model*: P Value
Coronary artery calcium, Agatston units		<0.001		<0.001
1–99 vs 0	1.94 (1.29–2.92)	0.015	1.80 (1.22–2.64)	0.003
100–399 vs 0	3.08 (2.04–4.65)	0.001	2.60 (1.91–4.39)	<0.001
≥400 vs 0	6.53 (4.42–9.63)	<0.001	6.00 (4.04–8.92)	<0.001
Cardiorespiratory fitness, per MET*	0.88 (0.84–0.93)	<0.001	0.89 (0.85–0.95)	<0.001
Age, per y*	0.98 (0.96–1.01)	0.237	0.97 (0.96–1.01)	0.152

CAC indicates coronary artery calcium; CI, confidence interval; CRF, cardiorespiratory fitness; HR, hazard ratio; and MET, metabolic equivalent of task.
*Modeled as linear effects.
†Base model plus smoking, body mass index, systolic blood pressure, history of hypertension, glucose, history of diabetes mellitus, cholesterol, and statin therapy.

Circulation 2018;137:1888-1895

An Important Distinction?*

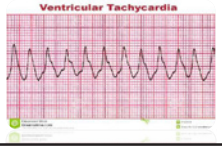
Although veteran endurance athletes are reported to have slightly accelerated coronary artery atherosclerosis, as verified by a higher prevalence of CAC scores ≥ 100, they also demonstrate higher fitness (METs) & predominantly stable calcified plaques and fewer vulnerable mixed plaques than their less active counterparts.

Aengevaeren VL et al. Circulation 2017;136:138-148
Merghani A et al. Circulation 2017;136:126-137

Outline

Topic 5

- Activities Associated with an Increased Risk of Acute Cardiac Events: High-Intensity Interval Training—A Case Report
- Pre-participation Screening: Prophylactic Interventions; Establishing a Cardiovascular Performance Clinic



Local deaths

Mark Jahnke: CFO passionate about service stood up for his beliefs

Mark Jahnke died of a heart attack Wednesday while playing racquetball at a local club. He was 55.

Northcote RJ, Flannigan C, Ballantyne D. **Sudden death and vigorous exercise – a study of 60 deaths associated with squash. Br. Heart J 1986;55:198-203**

METRO FINAL — **Detroit Free Press** — WEDNESDAY

DIGGING OUT

A winter's worth in one day

Storm leaves at least 13 people dead

"At least 8 people died Wednesday in the Detroit area after snow-related exertion. In Wayne County alone, 17 heart attack deaths were attributed to exertion since the snow began Tuesday. Most of the victims were older men clearing their driveways and walks."

Cardiac Demands of Heavy Snow Shoveling

Barry A. Franklin, PhD; Patrick Hogan, MA; Kim Bonzheim, MSA; Donovan Bakalyar, PhD; Edward Terrien, MD; Seymour Gordon, MD; Gerald C. Timmis, MD

JAMA 1995;273:880

Acute Myocardial Infarction After Manual or Automated Snow Removal

Barry A. Franklin, PhD, Peter George, MD, Richard Henry, DO, Seymour Gordon, MD, Gerald C. Timmis, MD, and William W. O'Neill, MD

AJC 2001;87:1282

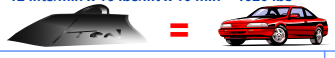
Sudden Cardiac Death After Manual or Automated Snow Removal

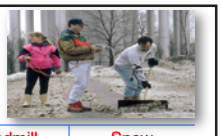
Pertha S. Chowdhury, MD, Barry A. Franklin, PhD, Judith A. Boura, MS, Ljubisa J. Dragovic, MD, Sawait Kanluen, MD, Werner Spitz, MD, Jerry Hodak, and William W. O'Neill, MD

AJC 2003;92:833

Cardiorespiratory Measurements During Treadmill Testing and Snow Shoveling

12 lifts/min x 16 lbs/lift x 10 min = 1920 lbs





Variable	Treadmill Testing	Snow Shoveling
Heart rate (beats/min)	179 ± 17	175 ± 15
Systolic blood pressure (mm Hg)	181 ± 25	198 ± 17
Rate-pressure product (mm Hg x beats/min x 10^{-2})	322 ± 40	342 ± 34
Oxygen consumption (METs)	9.3 ± 1.8	5.7 ± 0.8
Rating of perceived exertion (6-20 scale)	17.9 ± 1.5	16.7 ± 1.7

Cardiovascular Clinical Data in the 5 Sedentary Men*

Patient	Age (Years)	SH	CS	↑C	Previous AP	Previous AMI	Previous PTCA	BMI (kg/m²)	Snow Removal Technique: Shoveling	Snow Removal Technique: EST	Symptoms During Snow Removal: Substernal CP	Symptoms During Snow Removal: Sweating	Confirmed AMI	Time of AMI
1	55	0	+	0	0	0	0	34.6	+	0	+	0	+	pm
2	58	0	0	+	0	+	+	30.7	0	+	+	+	+	am
3	64	0	0	0	+	0	0	33.8	0	+	+	0	+	am
4	70	0	0	0	0	0	+	27.7	+	0	+	0	+	am
5	77	+	+	+	0	0	0	30.8	+	0	+	+	+	am

*Persons not participating in a regular exercise program or meeting the minimal physical activity recommendations from the U.S. Surgeon General's report.[13]
AP = angina pectoris; BMI = body mass index; C = cholesterol; CP = chest pain; CS = cigarette smoker; EST = electric snow thrower; PTCA = percutaneous transluminal coronary angioplasty; SH = systemic hypertension.

AJC 2001;87:1282

Sudden Cardiac Death After Manual or Automated Snow Removal

Pertha S. Chowdhury, MD, Barry A. Franklin, PhD, Judith A. Boura, MS, L.J. Dragovic, MD, Sawait Kanluen, MD, Werner Spitz, MD, Jerry Hodak, and William W. O'Neill, MD

To examine the proximate circumstances of sudden cardiac death (SCD) in the setting of major snowstorms, we reviewed records from the medical examiners' offices of 3 counties in the weeks before, during, and after 2 heavy snowfalls that occurred in the greater metropolitan Detroit area. Of those who experienced SCD due to atherosclerotic cardiovascular disease (n = 271), 36 (33 men, 3 women) were engaged in snow removal, representing the largest number of exertion-related deaths after heavy snowfalls reported to date.

(Am J Cardiol 2003;92:000)

TABLE 1 Aggregate Exertion-related and Total SCD for Both Snow Storms

Time Frame	Exertion Related SCD	Total SCD (%)
Wk before storm	2*	73 (2.7)
Wk of storm	24†	102 (23.5)
Wk after storm	17‡	96 (17.7)

*Shovel removal related deaths: *1 of 2; †22 of 24; ‡13 of 17.

snowfall, were obtained from the National Weather Service database.

Records from the medical examiners' offices of 3 counties (Wayne, Oakland, and Macomb), encom-

MAYO CLINIC PROCEEDINGS

PERSPECTIVES AND CONTROVERSIES

Major Snowstorms: An Underappreciated Trigger of Acute Cardiac Events in Men

Barry A. Franklin, PhD; Thijs M.H. Eijsvogels, PhD; and Paul D. Thompson, MD

During the winter months, an increased incidence of acute myocardial infarction (MI) and sudden cardiac death (SCD) has been documented after heavy snowfalls.[1-3] For example, a large epidemiologic Canadian study reported that the quantity and duration of snowfall were associated with the subsequent risk of hospital admission or death due to MI.[4] The risk appeared to be higher in men vs women the day after a snowfall. Accordingly, compared with 0 cm, 20 cm of snowfall was associated with an odds ratio (OR) of 1.16 for hospital admission due to MI for men but no increased risk for women (OR, 1.01). Similar associations were present for death due to MI the following day when stratified by sex. ORs of 1.34 and 1.04 for men and women, respectively (sex-related P values were <.001 for both hospital admission and death due to MI). Although the increased cardiac events are often attributed to decreased ambient temperatures,[5,6] emerging evidence suggests that snow shoveling after heavy snowfalls may be more lethal than cold air alone, particularly in men.[4,7,8]

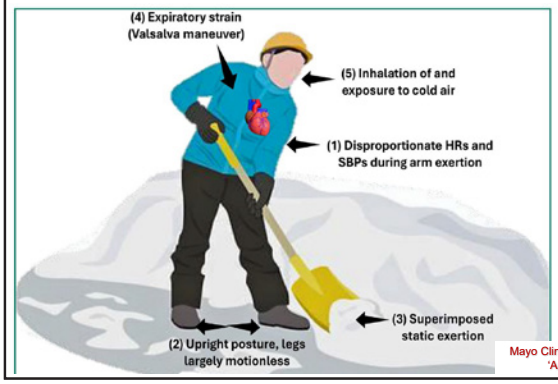
American Heart Association listed snow shoveling among activities commonly associated with acute cardiac events[9,10] and has promoted timely media awareness campaigns to inform the public of the associated risks.

In response to early reports of excess cardiac deaths after heavy snowfalls, we initiated a series of studies to clarify the aerobic and cardiac demands of snow removal in apparently healthy men as well as the sex-related risks in middle-aged and older adults. In our first study, we monitored HR, SBP, and rate-pressure product (mm Hg × beats/min × 10^{-2}) and directly measured oxygen consumption, expressed as metabolic equivalents (METs; 1 MET = 3.5 mL of oxygen per kilogram per minute) during 10 minutes of manual (shoveling) and automated (electric snow thrower) snow removal in 10 apparently healthy men aged 32.4±2.1 years. Our study yielded 5 major findings[11]:

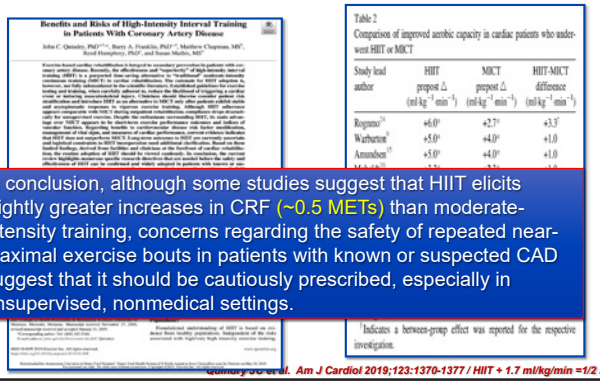
- Mean ± SD oxygen consumption during snow shoveling was 5.7±0.8 METs. This aerobic cost was 30% lower than the measured oxygen consumption during maximal treadmill testing (9.3±1.6

From Cardiac Rehabilitation and Preventive Cardiology, Cornwell Health, William Beaumont University Hospital, Royal Oak, MI (B.A.F.); Oakland University William Beaumont School of Medicine, Rochester, MI (B.A.F.); Department of Medical Biosciences, Exercise Physiology research group, Radboud University Medical Center, Nijmegen, the Netherlands, (T.M.H.E.); and Division of Cardiology, Hartford Hospital, Hartford, CT (P.D.T).

Mayo Clinic Proceedings, 2025 'Article in Press'



Mayo Clinic Proceedings, 2025 'Article in Press'



Benefits and Risks of High-Intensity Interval Training in Patients With Coronary Artery Disease

Table 2
Comparison of improved aerobic capacity in cardiac patients who underwent HIIT or MICT

Study lead author	HIIT prepost Δ (ml·kg⁻¹·min⁻¹)	MICT prepost Δ (ml·kg⁻¹·min⁻¹)	HIIT-MICT difference (ml·kg⁻¹·min⁻¹)
Rognmo[12]	+6.0*	+2.7†	+3.3*
Warburton[5]	+5.0*	+4.0*	+1.0
Amundsen[15]	+5.0*	+4.0*	+1.0

*Indicates a between-group effect was reported for the respective investigation.

In conclusion, although some studies suggest that HIIT elicits slightly greater increases in CRF (~0.5 METs) than moderate-intensity training, concerns regarding the safety of repeated near-maximal exercise bouts in patients with known or suspected CAD suggest that it should be cautiously prescribed, especially in unsupervised, nonmedical settings.

Quindry JC et al. Am J Cardiol 2019;123:1370-1377 / HIIT + 1.7 ml/kg/min =1/2 MET

Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

Cardiovascular Risk of High- Versus Moderate-Intensity Aerobic Exercise in Coronary Heart Disease Patients

Øivind Rognmo, Trine Moholdt, Hilde Bakken, Torstein Hole, Per Mølstad, Nils Erling Myhr, Jostein Grimsmo and Ulrik Wisløff

Circulation. published online August 9, 2012;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

FINDINGS: The absolute risk for high-intensity interval training was (1 event per 23,182 patient-hours) and moderate-intensity training (1 event per 129,456 patient hours), but 5.6 times higher in the high-intensity group.

CASE STUDY: HIIT-- induced SCD

- 38- year- old male nurse, nonsmoker, BMI=36, Wanted to get "in shape" after a layoff from exercise. Enrolled in HIIT program. Client intake form was unremarkable, 6 "No" responses. No other medical exam or GXT was conducted; estimated HRmax=182 bpm.
- During the client's first session, he wore a HR monitor sold to him by the gym and participated in 4 consecutive circuits (treadmill, floor exercise, rowing, treadmill), total time 20-30 minutes. Estimated highest exercise intensity = 8 – 10 METs. HRs during exercise averaged 150 to ~ 180 bpm, and went as high as 240 bpm.

Autopsy Report 5/17/19

Final Diagnosis: Mid LAD shows intimal thickening and luminal narrowing (~ 60 – 70%) with circumferential dystrophic calcification and cholesterol clefts deposits, *Cardiac hypertrophy; the heart weighed 490 grams.*

Cause of Death: Atherosclerotic and Hypertensive CVD

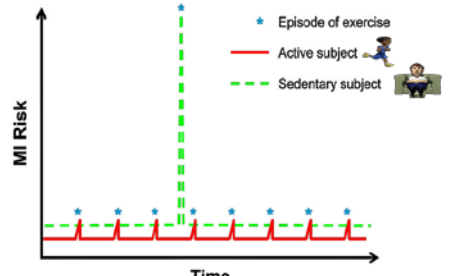
Manner of Death: Natural

Outline

Topic 6

- Activities Associated with an Increased Risk of Acute Cardiac Events: High-Intensity Interval Training—A Case Report
- Prophylactic Interventions; Establishing a Cardiovascular Performance Clinic

PROPHYLACTIC INTERVENTIONS:
Vigorous Exercise-- Who is at Greatest Risk ?



Circulation 2011;124:346-354

Reducing the Incidence of Exercise-Related Cardiovascular Events

- Exercise below adverse signs/symptoms
- Establish an emergency plan / AEDs
- Emphasize warm-up and cool-down
- Advise patients to walk before running
- Discuss forewarning symptoms
- Use continuous or instantaneous ECG monitoring
- Modify recreational games
- Use rating of perceived exertion (RPE) as an adjunctive intensity modulator

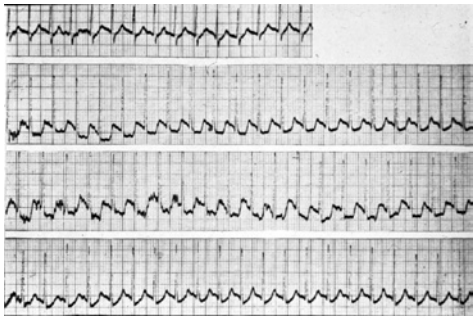
AHA/ACSM Scientific Statement

Automated External Defibrillators in Health/Fitness Facilities
Supplement to the AHA/ACSM Recommendations for Cardiovascular Screening, Staffing, and Emergency Policies at Health/Fitness Facilities

Writing Group
Gary J. Balady, MD, Chair; Bernard Chaitman, MD; Carl Foster, PhD; Erika Froelicher, PhD; Neil Gordon, MD; Steven Van Camp, MD

Circulation 2002;105:1147-1150

Cardioprotective Value of a Preliminary Warm-up*

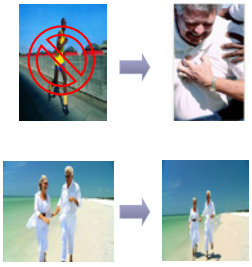


* Barnard RJ, et al. Circulation 1973;48:936

Advise Patients to Walk Before Running

When previously sedentary individuals initiate an exercise program, level walking (2-3 METs) is strongly recommended, gradually increasing the speed or intensity of exertion (3-5 METs) over time (2-3 months), provided the individual remains symptom-free.

This strategy will ↓ injury and ↑fitness without going through a period during which each bout of vigorous exercise (>6 METs) is associated with large spikes in relative cardiovascular risk.



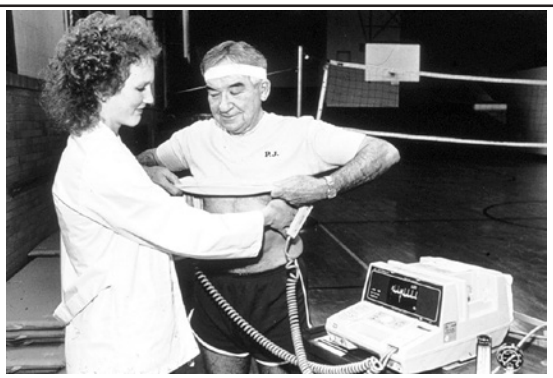
PTP

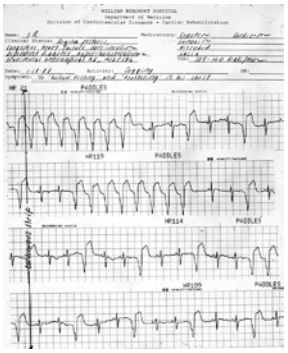
Riebe D et al. Med Sci Sports Exerc, Vol 47, No 8, pp 2473

Neither superior athletic ability, habitual physical activity, nor the absence of cardiac risk factors guarantees protection against an exercise death.

FOREWARNING SYMPTOMS APPEARED TO PRESENT THE ONLY CLUE TO IMPENDING CARDIOVASCULAR EVENTS.

Thompson PD et al. JAMA 1979;242:1265



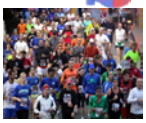


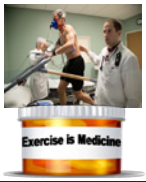
BORG SCALE For Perceived Exertion	
6	No exertion (sitting at rest)
7	Very, very light (walking slowly on a flat surface)
8	
9	Very light (walking slowly on a slight grade)
10	
11	Fairly light
12	
13	Somewhat hard (your heart rate and breathing increase, but you can continue)
14	
15	Hard (heavy)
16	
17	Very hard (you can continue but you're very fatigued and can't go much longer)
18	
19	Very, very hard (near exhaustion)
20	Maximal exertion

Recommended Exercise Intensity

Exercise-Related Cardiovascular Events: Challenges & Opportunities?

The cardiology community is faced with the challenge of providing an inexpensive, sensible **screening strategy** for the prevention of sudden cardiac death while simultaneously reaffirming that the benefits of moderate-to-vigorous exercise far outweigh potential risks.





NEJM 2012;366:130
JACC: Cardiovasc Imaging 2013;6:993

Beaumont Cardiovascular Performance Clinic

A resource for recreational exercisers, athletes, highly active adults and weekend warriors

Beaumont

Cardiovascular Performance Clinic

All CPC Participants Undergo the Following Tests

- H & P exam by Cardiovascular Specialist (ie, MD)
- 12-lead Electrocardiogram (ECG)
- Echocardiogram
- *Cardiopulmonary Exercise Test (V02 max, Anaerobic Threshold)

- Nutritional Consultation
- DXA Scan (body fatness)

If age > 40 years or CHD risk factors

- Coronary Calcium Scoring by CT

Additional Testing as Appropriate including: Blood Chemistry Studies, Cardiac MRI; Coronary CT Angiography; Referral to Specialist

Final Evaluation and Training/Competition Recommendations

* Fitness consultation: Maximal aerobic capacity, anaerobic threshold, optimal training/race pace

Case Studies: Medical Marvels-86,89,&109 !

Whitlock training in 2012. He has no coach, follows no special diet, does not chart his mileage, takes no ice baths and avoids stretching, except the day of a race.

85-Year-Old Marathoner Is So Fast That Even Scientists Marvel

By JERÉ LONGMANDEC. 28, 2016

* Ed was the first to run a marathon < 3 hrs, over the age of 70

From the moment we are born, each of us begins a journey to the grave. Aiming primarily to thwart the onset and progression of cardiovascular disease, at 37 years of age, I quit smoking, gave up alcohol; adopted a low-fat, low-salt, low-sugar diet; gradually reduced my meals to one a day, and chose daily running as my exercise. For the next 50 years, I steadfastly adhered to that regimen.

H L Fred.
Amer. Journal of Cardiology
Feb 2017

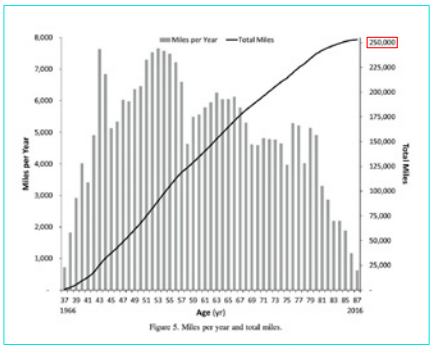


Figure 5. Miles per year and total miles.

Fred HL. Am J Cardiol Feb 2017

Well

PHYS ED | GRETCHEN REYNOLDS

Lessons From a 105-Year-Old

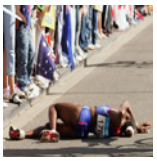
The French cyclist Robert Marchand is fitter than most 50-year-olds.

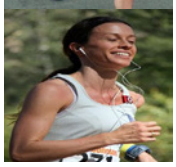
NEW & NOTEWORTHY:

These data show that VO2max increased from 31 to 38 mL/kg/min (~11 METs) with an intense 2 yr training program (101-103 yrs old) and that this centenarian was subsequently able to bicycle ~17 miles in 1 hour.

Next slide is the last…

CONCLUSION





TAKE HOME MESSAGE: For most people the benefits of moderate-to-vigorous exercise outweigh the risks. There are subsets of the population with ASCVD or inherited cardiac conditions (ARVC, lamin A/C genetic mutations, LQT, HCM, Brugada syndrome) for whom vigorous to high-intensity exercise may be harmful.

THANK YOU…

SELF EVALUATION

Extreme Exercise: Understanding the Risks and Benefits

1. Exercise-related fatalities in individuals under the age of 35 are generally attributed to underlying structural cardiovascular abnormalities, most notably _____.

a. Increased coronary artery calcification
b. Hypertrophic cardiomyopathy
c. Ruptured aorta
d. Coronary artery anomalies
e. Idiopathic left ventricular hypertroph

2. T/F - High-volume, high-intensity exercise training regimens and regular participation in competitive endurance events (e.g., marathon running, triathlon participation) are associated with increased levels of coronary calcification and a heightened risk of incident atrial fibrillation.

3. T/F - Stable coronary plaques are characterized by a thin fibrous cap and a large lipid core.

4. One advantage of high-intensity interval training is that it elicits greater incremental increases in cardiorespiratory fitness than does moderate intensity training. On average, this ~ _____ METs.

a. 0.5
b. 1.0
c. 1.5
d. 2.0
e. None of the above

5. A comparison of the cardiovascular event rate associated with high-intensity interval training (HIIT) versus moderate intensity training in patients coronary heart disease indicates that the former (ie., HIIT) is nearly _____ times higher.

a. 4
b. 6
c. 8
d. 10
e. 12

6. Recommendations to reduce the incidence of exercise-related cardiovascular events include:

a. Emphasize warm-up and cool-down
b. Advise patients to walk before jogging / running
c. Review warning symptoms suggesting the need for cessation of exercise and medical review
d. Use continuous or instantaneous ECG monitoring
e. All the above

Answer Key: 1. B, 2. T, 3. F, 4. A, 5. B, 6. E

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COPD in Primary Care: Practical Approaches to Management and Pharmacotherapy

Global Initiative for Chronic Obstructive Lung Disease
2025 REPORT

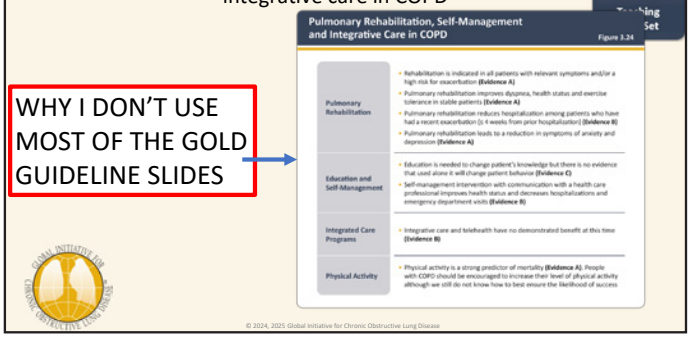
Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (GOLD) teaching slide set 2025

Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease

Pulmonary rehabilitation, self-management and integrative care in COPD

2025

WHY I DON'T USE MOST OF THE GOLD GUIDELINE SLIDES



GUIDELINES ARE GREAT,
HOWEVER

COPD Guidelines: The 'However'

With the exception of smoking cessation and oxygen in late-stage COPD, no pharmacologic interventions have been shown to reduce overall mortality.

Celi A , et al *Ther Adv Chronic Dis* 2021;12:1-10

COPD Guidelines: The 'However'

"There is no high-quality evidence such as RCTs to support initial pharmacological Rx strategies in newly Dx COPD patients….In the individual patient, the choice should depend on the patient's perception of Sx relief."

Adapted from GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2025 Report

Evolving COPD Taxonomy

- Genetic: eg, α-1-antitrypsin deficiency
- Developmental: eg, prematurity, low birthweight
- Environmental
  - Smoking/vaping
  - Air Pollution: wildfires, occupational, biomass cooking
- Infection: eg, tuberculous COPD, HIV-associated COPD
- COPD-A: COPD and Asthma
- Idiopathic

Adapted from GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2025 Report

COPD: Why Bother?

"COPD is now one of the top 3 causes of death worldwide…."

GOLD COPD Guidelines 2023

But Isn't Smoking Is WAY DOWN?

"Among U.S. adults in 2021, **18.7%** (an estimated 46.0 million) currently used any tobacco product…."

Cornelius ME, et al. *MMWR* 2023;72(18):475-4833

Cigarette smoking prevalence (2024) = 9.4%

US HHS, National Cancer Institute Report 2024

Smoking: Bygone Days

"… per capita cigarette consumption ↑ steadily until 1953, by which time 47% of American adults were smoking cigarettes (58% of males and 36% of females), and half of all physicians."

Cummings KM, Proctor RN *Cancer Epidemiol Biomarkers Prev* 2014;23(1):32-36

Smoking: China

- Study: Chinese ♂ adults (age>18) n = 100,000
  - Eversmokers= 62.4%
  - Current Smokers = 54.0%
  - Ex-smokers =8.4%

Liu S, et al. *J Epidemiol Community Health* 2016;doi:10.1136/j3wxh-2016-207805

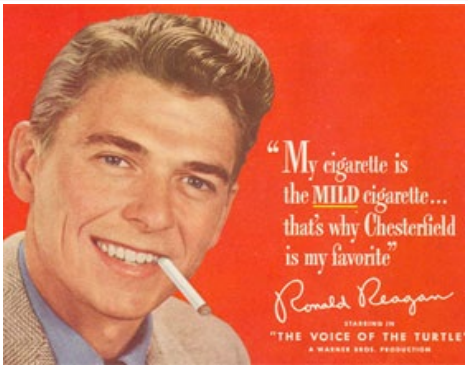
n 2024, approximately 26.6% of Chinese adults aged 15 and over smoke: 50.5% of men and 2.1% of women.

AI Overview 2/26/25

COPD

How Did We Get Into This Mess?

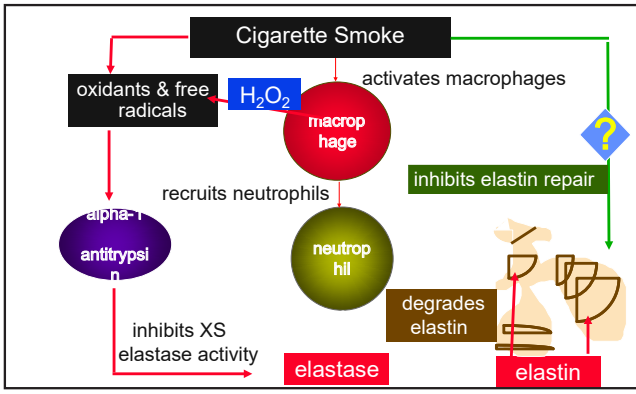
Cigarettes for Sale In the Hospital
1950's

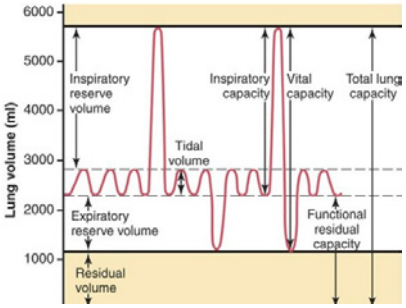


Pulmonary Physiology

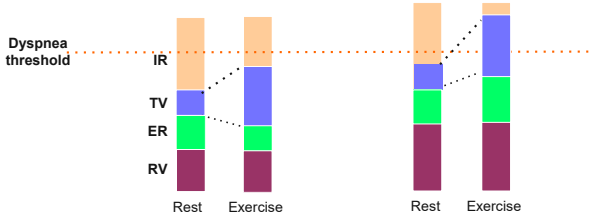
- Normal Δ , From age 25 to 75:
  - 20% ↓ Vital Capacity
  - 25% ↓ FEV_1 (30ml/yr)
- Some Smokers : 80 - 150 ml/yr ↓FEV_1

Barker L *Principles of Ambulatory Medicine* Williams & Wilkins (Baltimore) 1999

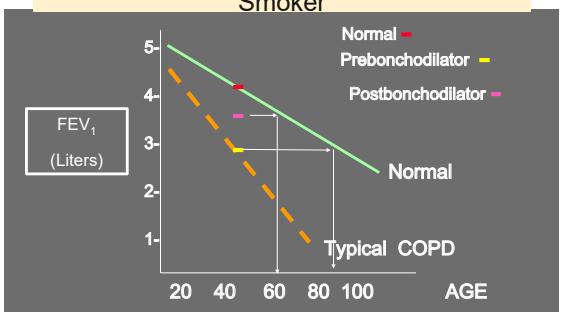




Lung Volumes: Normal VS COPD
The Toxicity of Dynamic Hyperinflation



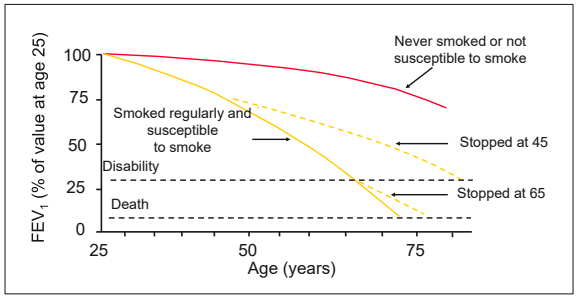
Concept of Lung Age: A 55yo Chronic Smoker



Petty TL *Hospital Practice* 1990; October: p 90

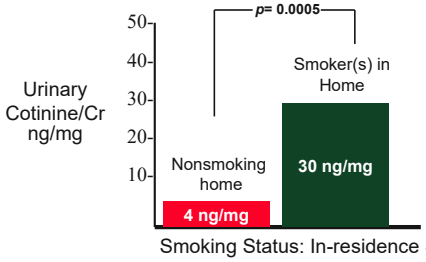
What about the guy who says "Well, Doc after all these years of smoking, there's no sense in stopping now, is there….?

Decline of FEV_1 with Age and Smoking Hx



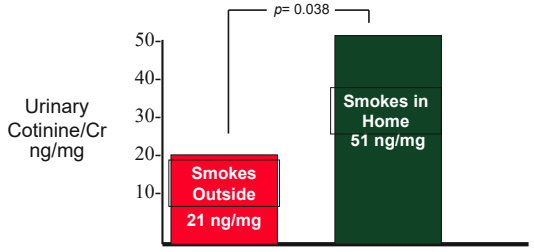
Fletcher C and Peto R. Br Med J. 1977;1:1645-1648

Urinary Cotinine in Children
Effect of at-home Smokers



Winkelstein ML, et al."Parental Smoking Behavior and Passive Smoke Exposure in Children with Asthma" Ann Allergy Asthma Immunol 1997;78(4):419-423

Don't Worry Doc, We Only Smoke Outside



Winkelstein ML, et al."Parental Smoking Behavior and Passive Smoke Exposure in Children with Asthma" Ann Allergy Asthma Immunol 1997;78(4):419-423

Reducing Smoking: How Much Benefit?

You are speaking to a new patient about smoking cessation. Taken aback, he says "But doc, I've cut down by more than 50% in the last two years and kept it up….isn't that good enough?" Your evidence-based response should be

a) Yes, risk of CVD is correspondingly ±50% lower

b) Yes, but CVD risk reduction is only ± 25%

c) No, cutting down has been shown NOT to help

RESEARCH PAPER

Health consequences of reduced daily cigarette consumption

Aage Tverdal, Kjell Bjartveit

Tobacco Control 2006;15:472-480. doi: 10.1136/tc.2006.016246

Cutting Down Smoking: Benefits?

- Study: Prospective study (Norway) heavy smokers (n=51,210) who cut down by >50%
- Inclusion
  - Age at enrollment 20-49 years
  - Smoked >15 cigs/d at baseline
  - ♀ (n=24,959)
  - ♂ (n=26,251)
- Exclusion: Known CHD; pipe smokers
- Followup 1974-1978 thru 2003 (mean 21.2 yrs)

Tverdal A, Bjartveit K *Tobacco Control* 2006;15:472-480

Cutting Down Smoking: Benefits?

Mortality	Reducers vs Sustained Heavy Smokers RR	p
All-cause	1.02 (0.84-1.22)	NS
CVD	1.02 (0.75-1.39)	NS
IHD	0.96 (0.65-1.41)	NS
Lung Ca	0.66 (0.36-1.21)	NS
Smoking-related CA	0.86 (0.57-1.29)	NS

Tverdal A, Bjartveit K *Tobacco Control* 2006;15:472-480

Cutting Down Smoking: Benefits? Conclusions

"Long-term follow-up provides no evidence that heavy smokers who cut down their daily cigarette consumption by >50% reduce their risk of premature death significantly."

n = 51,210

Tverdal A, Bjartveit K *Tobacco Control* 2006;15:472-480

Cutting Down Smoking: Benefits? Conclusions

"…it may give people false expectations to advise that reduction in consumption is associated with reduction in harm."

Tverdal A, Bjartveit K *Tobacco Control* 2006;15:472-480

Are Cigars Safer?

- Tobacco content = >20 cigarettes
- 1 cigar vs 1 cigarette:
  - 7 X tar
  - 11X carbon monoxide
  - 4 X nicotine
- ↑Alkaline cigar smoke → enhanced entry to bloodstream through oral vasculature

Cowley G. "Are stogies safer than cigarettes?" *Newsweek* 1997;(July21): 57

COPD

Physiology/Pathophysiology

COPD: *Other* Risk Factors

"Other types of tobacco,(e.g., pipe, cigar, water pipe) and marijuana are also risk factors for COPD, as well as environmental tobacco smoke."

GOLD COPD 2020 Guidelines Pocket Guide

COPD: Mariiuana

RESEARCH CMAJ

Marijuana and chronic obstructive lung disease: a population-based study

Wan C. Tan MB, Christine Lo BSc, Aimee Jong BSc, Li Xing MSc, Mark J. FitzGerald MB, William M. Vollmer PhD, Sonia A. Buist MD PhD, Don D. Sin MD MPH, for the Vancouver Burden of Obstructive Lung Disease (BOLD) Research Group

Tan WC et al CMAJ 2009;180(8):814-820

COPD: Marijuana

RESEARCH Tan WC et al CMAJ 2009;180(8):814-820 CMAJ

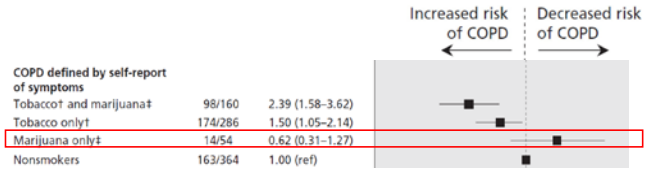
Marijuana and chronic obstructive lung disease: a population-based study

Wan C. Tan MB, Christine Lo BSc, Aimee Jong BSc, Li Xing MSc, Mark J. FitzGerald MB, William M. Vollmer PhD, Sonia A. Buist MD PhD, Don D. Sin MD MPH, for the Vancouver Burden of Obstructive Lung Disease (BOLD) Research Group

"Compared with nonsmokers, participants who reported smoking only tobacco, but not those who reported smoking only marijuana, experienced more frequent respiratory Sx…and were more likely to have COPD…."

*Reference cited in GOLD 2020 Guideline to Assert Marijuana as a COPD Risk Factor (emphasis added)

COPD: Marijuana NOT

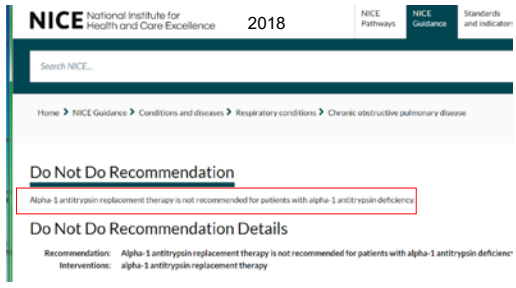


Tan WC et al *CMAJ* 2009;180(8):814-820

Alpha-1-antitrypsin Deficiency: Maybe

"The WHO recommends that all patients with a Dx of COPD should be screened…."

GOLD COPD 2020 Guidelines Pocket Guide



A1AT replacement Rx is NOT RECOMMENDED for patients with A1AT Deficiency

NICE
(UK National Institute for Health and Care Excellence)

"With the exception of smoking cessation and the avoidance of other environmental risk factors, current Rxs for emphysema caused by AATD aim to alleviate Sx and do not slow down the progression of the disease….NICE clinical guideline 101 does not recommend replacement therapy for people with AATD and COPD."

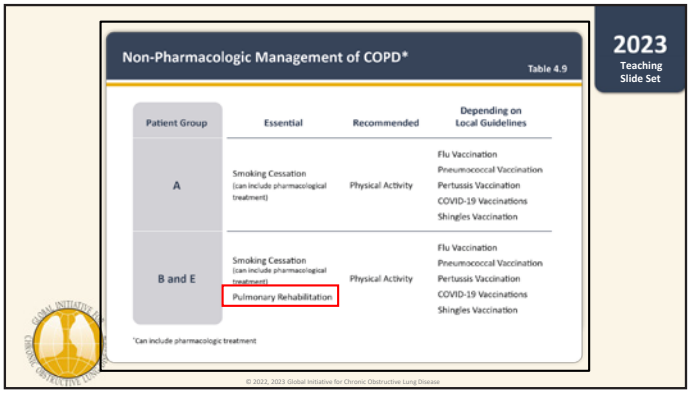
NICE Final Scope Report on Human Alpha-1-proteinase Inhibitor for Maintenance Rx of Emphysema March 2018

COPD: Pulmonary Rehabilitation

"After receiving a Dx of COPD…Physicians should emphasize the importance of a smoke free environment, empower adherence to prescribed medication, ensure proper inhaler technique, promote physical activity, prescribe vaccinations, and **refer patients to pulmonary rehabilitation**."

Emphasis added

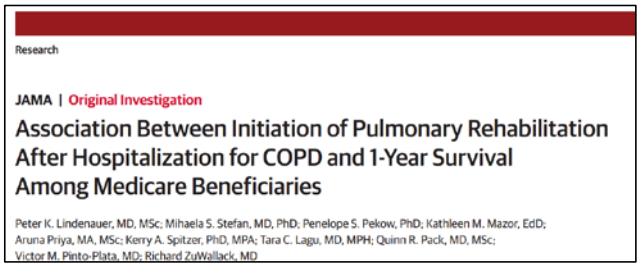
GOLD Guidelines 2023



Pulmonary Rehab

DIPODEB

Pulmonary Rehab: Mortality


Research

JAMA | Original Investigation

Association Between Initiation of Pulmonary Rehabilitation After Hospitalization for COPD and 1-Year Survival Among Medicare Beneficiaries

Peter K. Lindenauer, MD, MSc; Mihaela S. Stefan, MD, PhD; Penelope S. Pekow, PhD; Kathleen M. Mazor, EdD; Aruna Priya, MA, MSc; Kerry A. Spitzer, PhD, MPA; Tara C. Lagu, MD, MPH; Quinn R. Pack, MD, MSc; Victor M. Pinto-Plata, MD; Richard ZuWallack, MD

Lindenauer PK et al. *JAMA* 2020;323(18):1813-1823

Pulmonary Rehab: Mortality

- Study: Retrospective Cohort Study COPD patients (n=197,376)
- Population: Medicare Hospital database of COPD admissions
- Intervention post discharge:
  - Pulmonary rehab ≤90 days n = 2,721 (= 1.5%)

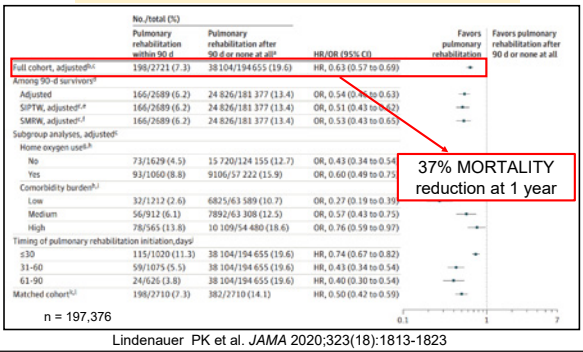
  vs
  - No pulmonary rehab n=191,494 (=96.9%)

  or
  - Pulmonary rehab>90 days n=3,161 (=1.6%)

  COMBINED
- 1^0 Endpoint: Mortality at 1 year

Lindenauer PK et al. *JAMA* 2020;323(18):1813-1823

Pulmonary Rehab: Mortality Impact



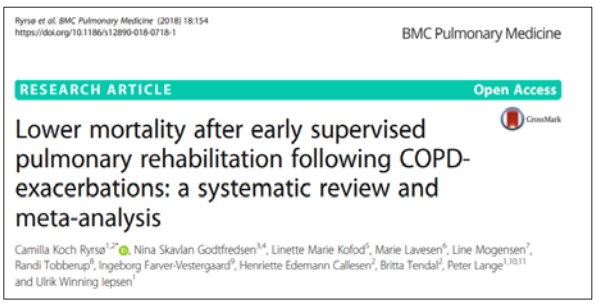
Lindenauer PK et al. *JAMA* 2020;323(18):1813-1823

Pulmonary Rehab: Mortality Impact

	No Rehab/>90d	Rehab	HR	p
Mortality at 1 year	19.6%	7.3%	0.63	<0.001

n = 197,376

Lindenauer PK, et al. *JAMA* 2020;323(18):1813-1823


Ryrso et al. BMC Pulmonary Medicine (2018) 18:154
https://doi.org/10.1186/s12890-018-0718-1

BMC Pulmonary Medicine

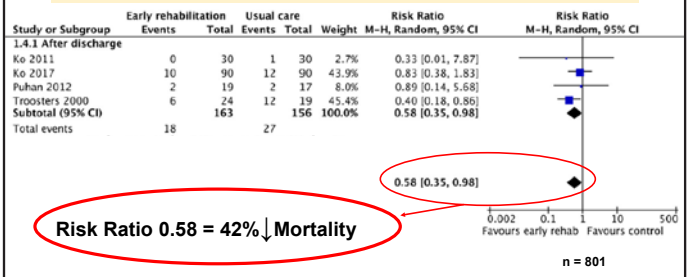
RESEARCH ARTICLE Open Access

Lower mortality after early supervised pulmonary rehabilitation following COPD-exacerbations: a systematic review and meta-analysis

Camilla Koch Ryrso[1,2*], Nina Skavlan Godtfredsen[3,4], Linette Marie Kofod[5], Marie Lavesen[6], Line Mogensen[7], Randi Tobberup[8], Ingeborg Farver-Vestergaard[9], Henriette Edemann Callesen[2], Britta Tendal[2], Peter Lange[1,10,11] and Ulrik Winning Iepsen[1]

Ryrso et al. *BMC Pulmonary Med* 2018:18(1):154-172

Pulmonary Rehab Reduces Mortality



Ryrso et al. *BMC Pulmonary Med* 2018:18(1):154-172

Pulmonary Rehab

DIPODEB

Do It Promptly Or Don't Even Bother

COPD

Pharmacotherapy

COPD Pharmacotherapy: General Principles
The Players

SABA (Short Acting β Agonist)

- Albuterol (ProAir, Ventolin): MDI, DPI, Nebulizer
- Levalbuterol (Xopenex): MDI, Nebulizer

COPD Pharmacotherapy: General Principles
The Players

SAMA (Short Acting Muscarinic Antagonists)

- Ipratropium (Atrovent)

COPD Pharmacotherapy: General Principles

LABA (Long Acting β Agonist)

- Salmeterol (Serevent) MDI, DPI Q12h
- Indacaterol (Arcapta) DPI QD
- Arformoterol (Brovana): Q12h Nebulizer
- Formoterol (Foradil, Perforomist) b.i.d. Nebulizer

COPD Pharmacotherapy: General Principles
The Players

LAMA (Long-Acting Muscarinic Antagonists)

- Tiotropium (Spiriva) MDI, DPI QD
- Aclidinium (Tudorza) DPI q12h
- Umeclidinium (Incruse Ellipta) DPI QD

COPD Pharmacotherapy: General Principles
The Players

PDE Inhibitors

- Roflumilast (Daliresp) PDE4i; tablet QD
- Ensifentrine (Ohtuvayre) PDE3-4i; b.i.d Nebulizer

COPD Pharmacotherapy: General Principles

- For acute Sx: SABA + SAMA > either monotherapy
- Maintenance: LABA or LAMA > SABA or SAMA **(A)**
- If LAMA or LABA insufficient, LAMA+LABA preferred
- Exacerbation Reduction:
  - LAMA > LABA **(A)**
  - LAMA + LABA > either monotherapy **(A)**
- OK to give combinations as individual inhalers
- Ensifentrine improves FEV1 **(A)**, dyspnea **(A)** and health status **(B)**

Adapted from GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2025 Report

COPD Pharmacotherapy: What Happened to ICS?

"We **do not encourage** the use of a LABA+ICS in COPD."

WHY ?

"Regular Rx with ICS ↑ the risk of pneumonia especially in those with severe disease." (A)

Adapted from GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2025 Report

COPD Pharmacotherapy: Your Pt is Happy/Better on ICS….?

"If there is an indication for ICS… LABA+LAMA+ICS has been shown to be superior to LABA+ICS and is therefore…preferred…."

Adapted from GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2025 Report

COPD Pharmacotherapy: Your Pt has asthma….

"If patients with COPD have features of asthma, Rx should always contain an ICS."

Adapted from GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2025 Report

I Thought I Heard Somewhere That Some Triple Inhaler Reduced COPD Mortality….

"Recent data suggests beneficial effect of **triple inhaled Rx** vs …LABAS+LAMA …on **mortality** in Sx COPD patients with a HX of frequent and/or severe exacerbations."

Adapted from GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2025 Report

Polypharmacy: When Cost Is the Driver

"Combinations can be given as single or mujltipe inhaler therapy. Single inhaler therapy may be more convenient and effective than multiple inhalers."

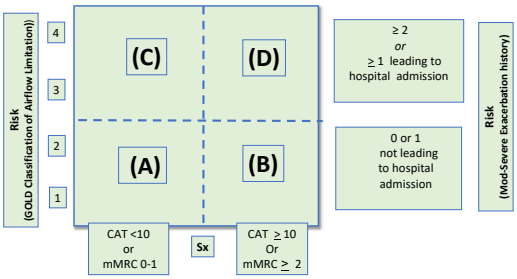
Adapted from GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2025 Report

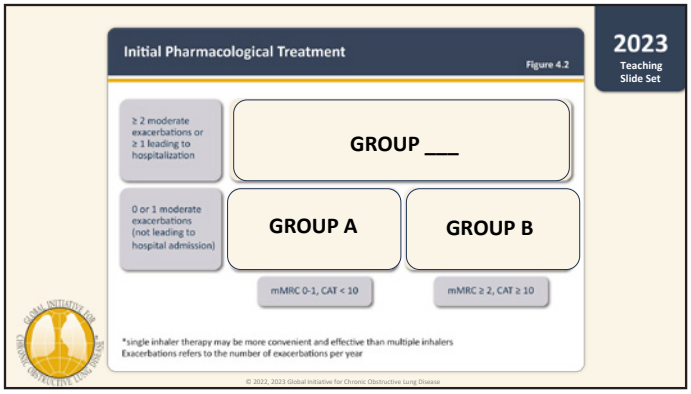
A Bottom Line for Choice of COPD Rx

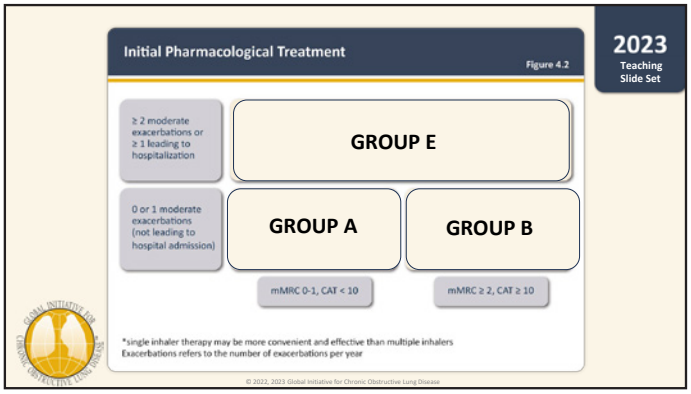
"There is no high-quality evidence such as RCTs to support initial pharmacological Rx strategies in newly Dx COPD patients….In the individual patient, the choice should depend on the patient's perception of Sx relief."

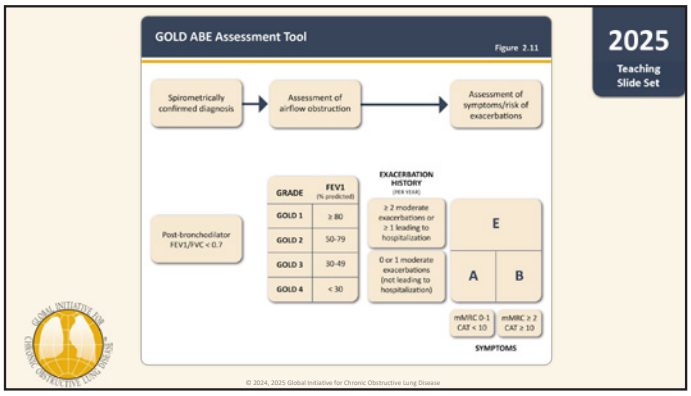
Adapted from GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2025 Report

The OLD Days (2022): GOLD Combined Assessment of COPD









Modified MRC (mMRC)Questionnaire

PLEASE TICK IN THE BOX THAT APPLIES TO YOU (ONE BOX ONLY)

mMRC Grade 0. I only get breathless with strenuous exercise. ☐

mMRC Grade 1. I get short of breath when hurrying on the level or walking up a slight hill. ☐

mMRC Grade 2. I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level. ☐

mMRC Grade 3. I stop for breath after walking about 100 meters or after a few minutes on the level. ☐

mMRC Grade 4. I am too breathless to leave the house or I am breathless when dressing or undressing. ☐

Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023

CAT (COPD Assessment Test)

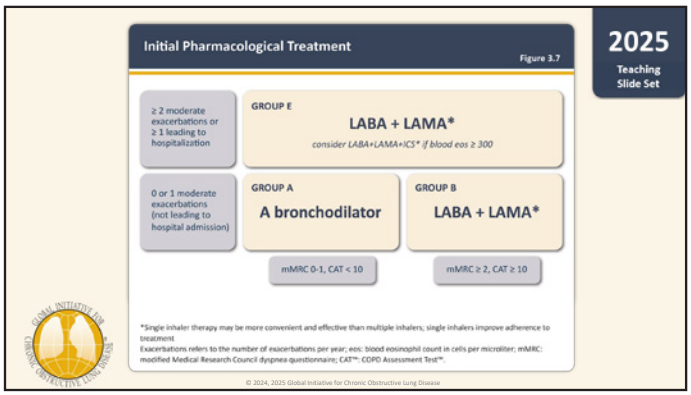
EXAMPLE: I am very happy	0 X 2 3 4 5	I am very sad
I never cough	0 1 2 3 4 5	I cough all the time
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition
I have lots of energy	0 1 2 3 4 5	I have no energy at all

Jones PW et al. *Eur Resp J* 2009;34(3):648-654

CAT Distilled: 8 Questions Scored 0-5

- Cough: never—often
- Mucus: none—my chest is full of mucus
- Chest tightness: none—very tight
- Breathless with 1 flight of stairs: none--very
- ADL at home: no limitations—very limited
- Confidence when leaving home: confident—not at all confident
- Sleep: soundly—not at all soundly because of COPD
- Energy: lots—none at all

Jones PW et al *Eur Respir J* 2009;34(3):648-654



Why Should LAMA Be First?

- LABAs and LAMAs significantly improve lung function, dyspnea, health status, and ↓ exacerbation rates (**A**)
- LAMAs have a greater effect on exacerbation reduction compared with LABAs (**A**) and ↓ hospitalizations (**B**)

Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023

Why Is GOLD So 'Down' On ICS?

"Regular treatment with ICS increases the risk of pneumonia [in COPD], especially in those with severe disease (**Evidence A**)."

Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023

JAMA Internal Medicine | Original Investigation

Chronic Obstructive Pulmonary Disease Exacerbations and Pneumonia Hospitalizations Among New Users of Combination Maintenance Inhalers

William B. Feldman, MD, DPhil, MPH; Jerry Avorn, MD; Aaron S. Kesselheim, MD, JD, MPH; Joshua J. Gagne, PharmD, ScD

Feldman WB et al. *JAMA Int Med* 2023;183(7):685-695

COPD: LABA/ICS v LABA/LAMA
'Real World' Data

- Study: 137,833 COPD pts ([Insurance Data Base)
- Inclusion:
  - Adults >40
  - Non-asthmatic
  - Rx with LABA/LAMA or LABA/ICS Combo
- Outcomes:
  - Mod-severe COPD exacerbations
  - Pneumonia hospitalizations

Feldman WB et al. *JAMA Int Med* 2023;183(7):685-695

COPD: LABA/ICS vs LABA/LAMA
'Real World' Data: OUTCOMES

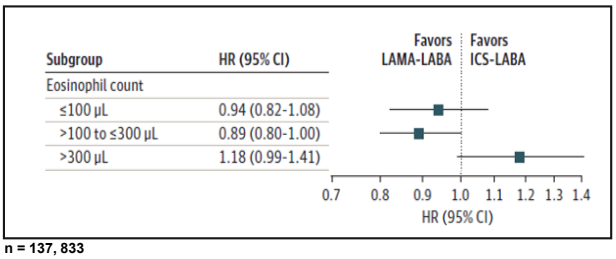
Endpoint	ICS/LABA Events/1K PY	LAMA/LABA Events/1K PY	HR* (CI)
Moderate COPD Exacerbation	321.5	286.6	0.93* (0.90-0.97)
Severe COPD Exacerbation	47.3	39.8	0.85* (0.77-0.94)
Pneumonia Hospitalization	104.0	82.1	0.80* (0.75-0.86)

n = 137, 833

***p < 0.05 favors LAMA/LABA**

Feldman WB et al. *JAMA Int Med* 2023;183(7):685-695

COPD: LABA/LAMA YES Except Maybe ↑ Eos
'Real World' Data: OUTCOMES



n = 137, 833

Feldman WB et al. *JAMA Int Med* 2023;183(7):685-695

COPD: LABA/ICS v LABA/LAMA
'Real World' Data: Bottom Line

"LAMA-LABA therapy was associated with improved clinical outcomes compared with ICS-LABA, suggesting that LAMA-LABA therapy should be preferred for patients with COPD."

Feldman WB et al. *JAMA Int Med* 2023;183(7):685-695

What About the 'Newer' LAMAs and LABAs

LAMAs
- Aclidinium
- Glycopyrrolate
- Revafanacin
- Umeclidinium

LABAs
- Vilanterol
- Indacaterol

Fagettaboutit

No Distinct Clinical Advantage

Distinct $$$ Disadvantage

COPD Pharmacotherapy: Triple Inhalers

MAKE SURE TO READ THE FINE PRINT BEFORE ACCEPTINNG THE HEADLINES

Rabe KF, et al. *NEJM* 2020;383(1):35-48

COPD: The ETHOS Trial
LAMA/LABA vs LAMA/LABA/ICS* vs ICS/LABA

- Study: RDBCT COPD pts (n=8,509)
- Inclusion: Mod-severe COPD with exacerbation Hx
- Intervention (all Rx single inhaler b.i.d):
  - LAMA/LABA: glycopyrrolate/formoterol (GFF)
  - ICS/LABA: budesonide 320 mcg/formoterol (BFF)
  - LAMA/LABA/ICS:*budesonide/glycopyrrolate/formoterol (BGF)
- Endpoints (at 52 weeks)
  - 1^0: Mod-severe COPD exacerbations
  - 2^0: All-cause mortality

*2 budesonide doses: 320 mcg and 160 mcg

Rabe KF, et al. *NEJM* 2020;383(1):35-48

COPD: The ETHOS Trial
LAMA/LABA vs LAMA/LABA/ICS vs ICS/LABA

- Inclusion
  - Hx ≥10 p-y Smoking
  - Age 40-80
  - CAT Score ≥10
  - Post-bronchodilator FEV1 25%-65% of normal
- Exclusion
  - Asthma or Other respiratory conditions
  - Cardiac disease
  - Cancer

Rabe KF, et al. *NEJM* 2020;383(1):35-48

COPD: The ETHOS Trial Outcomes

	LABA/LAMA	LABA/ICS	LABA/LAMA/ICS 320	LABA/LAMA/ICS 160	HR
Exacerbations #/yr	1.42**	1.24**	1.08**	1.07*	0.76*, 0.87** 0.75*, 0.86**
Mortality (n)	49*	34*	28**		0.54*, 0.78**

** p< 0.05

Rabe KF, et al. *NEJM* 2020;383(1):35-48

n = 8,509

COPD: The ETHOS Trial

Should We Say,
Then, That
Triple Inhaler Rx Reduces Mortality?

Rabe KF, et al. *NEJM* 2020;383(1):35-48

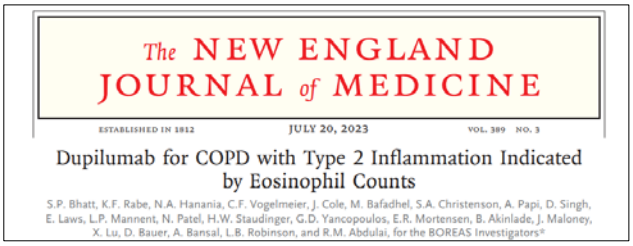
COPD: The ETHOS Trial

ABSTRACT: Conclusions

"Triple therapy…resulted in a lower rate of …exacerbations than glycopyrrolate-formoterol or budesonide-formoterol."

Rabe KF, et al. *NEJM* 2020;383(1):35-48

Dupilumab (Dupixent) For **COPD**?



Bhatt SP, et al. *NEJM* 2024;389(3):205-214

Dupilumab (Dupixent) For **COPD**?

- Asthma
- Atopic Dermatitis
- Prurigo Nodularis
- Eosinophilic Esophagitis
- Chronic Rhinosinusitis with Nasal Polyps

Bhatt SP, et al. *NEJM* 2024;389(3):205-214

Dupilumab (Dupixent) For COPD

- **Study**: PRDBPCT eosinophilic COPD (n=939)
- **Inclusion**
  - Eosinophils >300/microliter
  - Already on LAMA/LABA/ICS max
  - Exacerbation Hx in previous year
- **Rx:** Dupilumab 300 mg SQ q2weeks vs placebo x 1 year
- **1^0 Endpoint**: Exacerbations

Bhatt SP, et al. *NEJM* 2024;389(3):205-214

Dupilumab (Dupixent) For COPD? WHY?

Evidence of Type 2 inflammation [eosinophilia] is present in 20-40% of patients with COPD and is associated with an ↑ risk of exacerbations."

Bhatt SP, et al. *NEJM* 2024;389(3):205-214

Dupilumab (Dupixent) For COPD Conclusions

"Among patients with COPD who had type 2 inflammation as indicated by ↑ eosinophils, those who received dupilumab had fewer exacerbations, better lung function, and QOL, and less severe respiratory Sx than those who received placebo."

Bhatt SP, et al. *NEJM* 2024;389(3):205-214

The ATBC (α-tocopherol β-carotene) Study

- STUDY: Lung Cancer Prevention Trial (1985-1993)
- SUBJECTS: male smokers (n = 29,133)
- Rx: Vitamin E 50 mg/d vs β-Carotene 20mg/d vs Both vs placebo X mean 6.1 years
- RESULTS:
  - β-carotene 20 mg/d → 18% Lung CA↑
    → 8% Mortality ↑

Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group "The Effect of vitamin E and beta-carotene on the incidence of lung cancer and other cancers in male smokers." N Engl J Med 1994;330:1029-1035

"β-Carotene and Vit A Halted in Lung CA Prevention Trial"

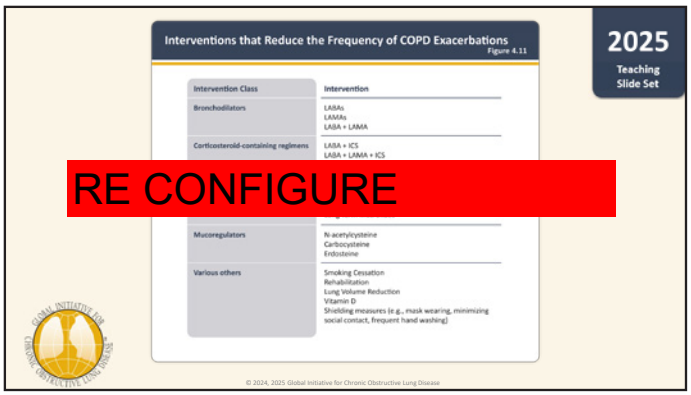
- STUDY: 18, 314 male & female high risk subjects: current or former smokers, 4,060 asbestos exposed
- Rx : 30 mg b-carotene + 25,000 IU Vit A daily
- OUTCOME: 4 Yrs Rx
  - 28% ↑lung CA
  - 17% ↑ deaths → study terminated 21months early

Primary Care & Cancer 1996(Jan):1

Closing Thoughts

- The **USA** status for adult smoking is the best it's been in >50 years
- Rx reduces exacerbations and improves function
- Pulmonary Rehab saves lives
- At some peril, consider talking to parents of children with URI/OME/AOM about smoking
- You only have to give up 1 cigarette: the next one
- Don't test your abstinence
- No pharmacologic Rx has been shown to be disease modifying or to reduce mortality. Hence, your choice about Guideline Directed Treatments certainly has room for individualization

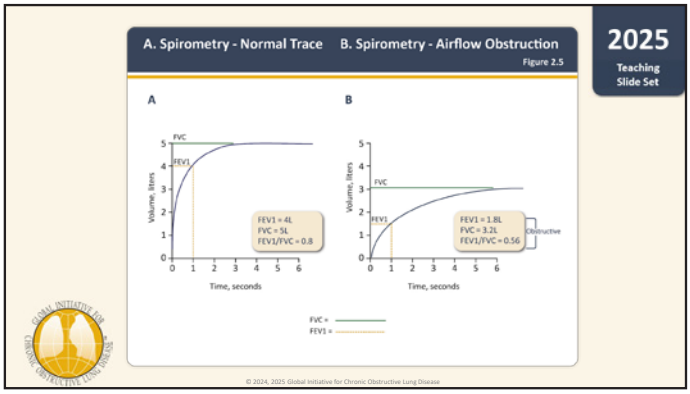
BACKUP

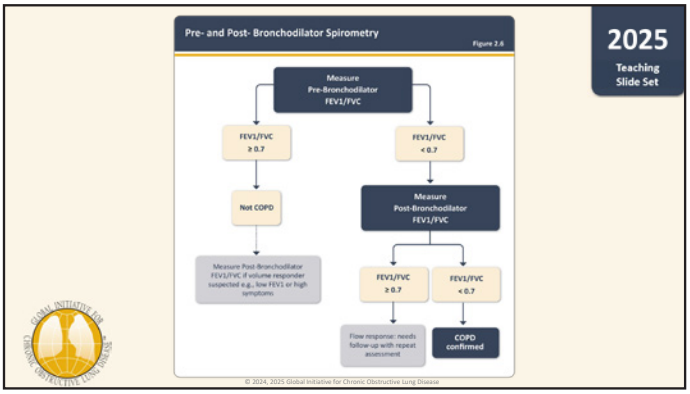


Long Term O_2 Therapy (LTOT)

- Indications
  - SaO_2 ≤88% confirmed 2x over a 3week period
  - SaO_2 of 88% with pulmonary HTN, heart failure, or polycythemia (HCT >55%)
- Titrate oxygen to SaO_2 ≥90%

Adapted from GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2025 Report





Differentiating Asthma from COPD

	Asthma	COPD
Age of Onset	Usually < 30	Usually > 40
History of Atopy	Often	Uncommon
Family Hx	Usually+	Usually -
Intercritical Lung Fx	WNL/Nearly WNL	Impaired
Lung Fix Under Rx	WNL/Nearly WNL	Impaired
Bronchodilator Response	Strong (>15% FEV1↑)	Modest (<12% FEV1)
ICS Response	Strong	Modest
LKTR Response	Strong	None
Smoking Hx	Variable	Prominent

Adapted from Kuritzky L "COPD Testing as a Vital Sign" Primary Care Special Edition 1999(3):2

Differentiating Asthma from COPD

	Asthma	COPD
Hypoxemia	Extremis Only	Common
Polycythemia	Rare	Common
Carboxyhemoglobin	WNL	Elevated
Progressive Decline	Uncommon	Typical
Cough Prominence	Nocturnal, Exercise	Early AM
Purulent sputum	Uncommon	Typical
Bronchodilator Response	B agonist > Anticholinergic	Anticholinergic = B agonist
IgE Elevation	Common	Uncommon
Exacerbation: Antibiotics	Ineffective	Usually Effective

Adapted from Kuritzky L "COPD Testing as a Vital Sign" Primary Care Special Edition 1999(3):2

Does FEV1 Tell the Whole Story?

"…at an individual patient level, FEV1 alone is an unreliable marker of the severity of breathlessness, exercise limitation, health status impairment, and risk of exacerbation."

GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2025 Report

I *Sort Of* Know What Bronchitis Is….

"..bronchitis…is defined by the presence of cough with expectorated sputum on a reguar basis…for at least 3 months/yr for 2 consecutive years…."

Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023

I *Sort Of* Know What Bronchitis Is….

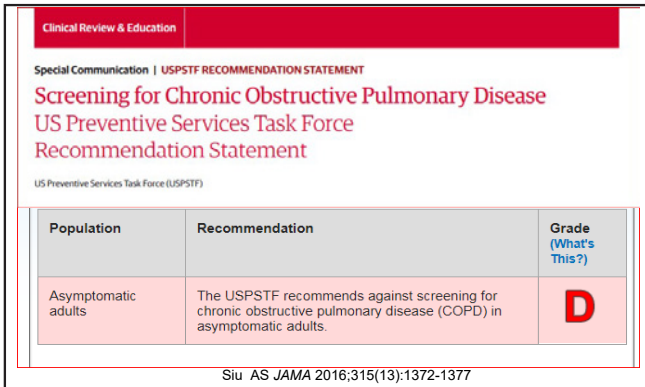
"..bronchitis…is defined by the presence of cough with expectorated sputum on a reguar basis…for at least 3 months/yr for 2 consecutive years, **in the absence of other conditions that can explain these Sx (an important caveat that is often ignored**)."

Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023

GOLD: Diagnosis and Assessment: Key Points

- Consider clinical Dx: dyspnea, chronic cough or sputum production, and risk factors
- Spirometry is *required* to make the Dx
  - Post-bronchodilator $FEV_1/FVC < 0.70$ confirms persistent airflow limitation (COPD)

www.goldcopd.com



Clinical Review & Education

Special Communication | USPSTF RECOMMENDATION STATEMENT

Screening for Chronic Obstructive Pulmonary Disease
US Preventive Services Task Force
Recommendation Statement

US Preventive Services Task Force (USPSTF)

Population	Recommendation	Grade (What's This?)
Asymptomatic adults	The USPSTF recommends against screening for chronic obstructive pulmonary disease (COPD) in asymptomatic adults.	D

Siu AS *JAMA* 2016;315(13):1372-1377

USPSTF Recommendation Grading

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial	Offer or provide this service
B	The USPSTF recommends this service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial	Offer or provide this service
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is a least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits	Discourage the use of this service
I	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined	Read the clinical considerations section of USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

www.uspreventiveservicestaskforce.org

What the Heck is Roflumilast?

"Daliresp [roflumilast] is a selective PDE4i indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a Hx of exacerbations."

Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023

USPSTF: COPD Screening NOT

"Similar to 2008, the USPSTF did not find evidence that screening for COPD in aSx persons improves health-related QOL, morbidity, or mortality. The USPSTF determined that early detection of COPD before the development of Sx, does not alter the course of the disease or improve patient outcomes. The USPSTF concludes with moderate certainty that screening for COPD in aSx persons has no net benefit."

*emphasis added

Siu AS *JAMA* 2016;315(13):1372-1377

GOLD: Chest X-ray? NOT

"A chest X-ray is not useful to establish a Dx in COPD, but it is valuable in excluding alternative Dxs and establishing the presence of significant comorbidities…."

*emphasis added

GOLD COPD 2020 Guidelines Pocket Guide

GOLD COPD Grade/Severity (when FEV1/FVC <0.7)

Grade	Severity	FEV1 (Predicted)
GOLD 1	Mild	≥80%
GOLD 2	Moderate	50%-79%
GOLD 3	Severe	30%-49%
GOLD 4	Very Severe	<30%

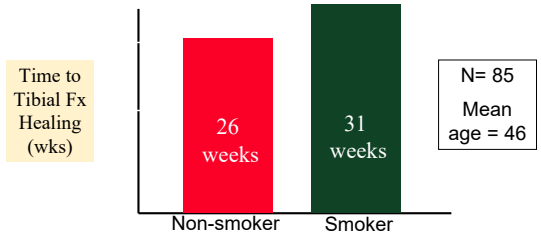
Adapted from GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2025 Report

Bronchodilators in COPD General Principles

Grade	Severity	FEV1 (Predicted)
GOLD 1	Mild	≥80%
GOLD 2	Moderate	50%-79%
GOLD 3	Severe	30%-49%
GOLD 4	Very Severe	<30%

Adapted from GOLD (Global Initiative for Chronic Obstructive Lung Disease) 2025 Report

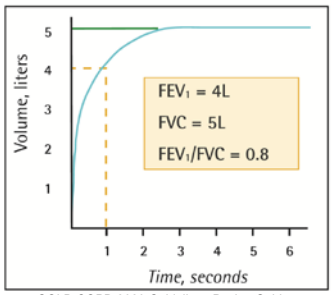
Smoking Goes Clear to the BONE
…and it's NOT just Osteoporosis



Moghaddam A, et al "Cigarette smoking influences the clinical and occupational outcome of patients with tibial shaft fractures" Injury 2011;42(12):1435-42

Spirometry

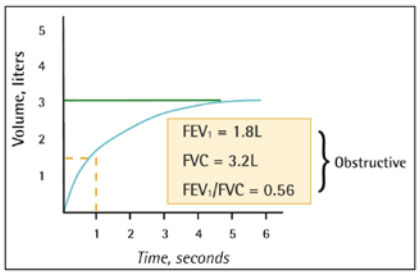
Figure 2.2A. Spirometry – Normal Trace

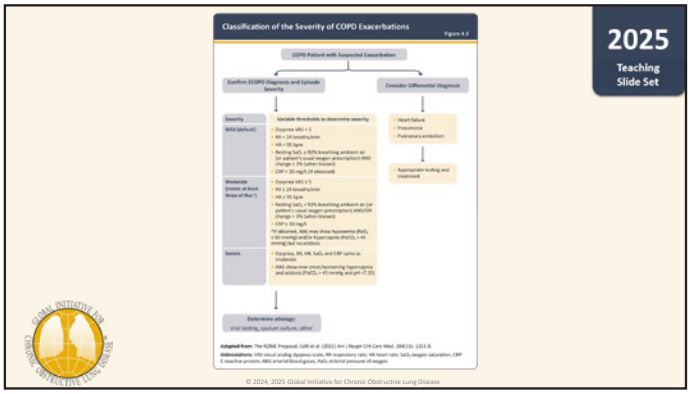


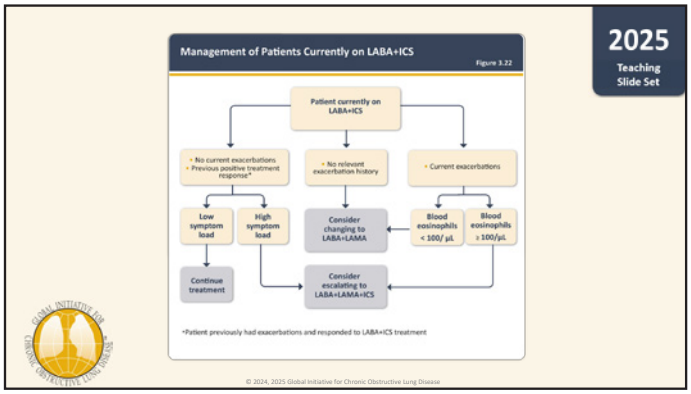
GOLD COPD 2020 Guidelines Pocket Guide

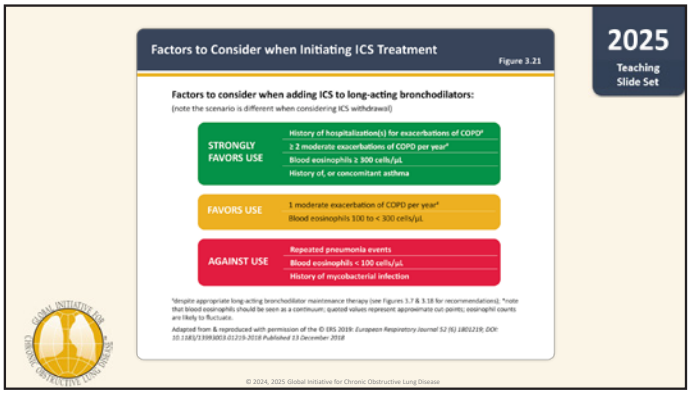
Spirometry: Post-bronchodilator

Figure 2.2B. Spirometry – Obstructive Disease









SELF EVALUATION

COPD in Primary Care: Practical Approaches to Management and Pharmacotherapy

1. Which of the following is the leading risk factor for the development of COPD worldwide?

a. Biomass fuel exposure
b. Tobacco smoking
c. Occupational dusts and chemicals
d. Genetic predisposition

2. T/F - Alpha-1 antitrypsin deficiency accounts for an important subgroup of cases of COPD in nonsmokers.

3. T/F - The FEV1/FVC ratio is typically increased in patients with COPD.

4. Which of the following interventions has been shown to reduce mortality in COPD patients?

a. Long-term oxygen therapy in hypoxemic patients
b. Inhaled corticosteroids alone
c. Pulmonary rehabilitation
d. Short-acting bronchodilators

5. T/F - Pulmonary rehabilitation is recommended for all symptomatic COPD patients regardless of disease severity.

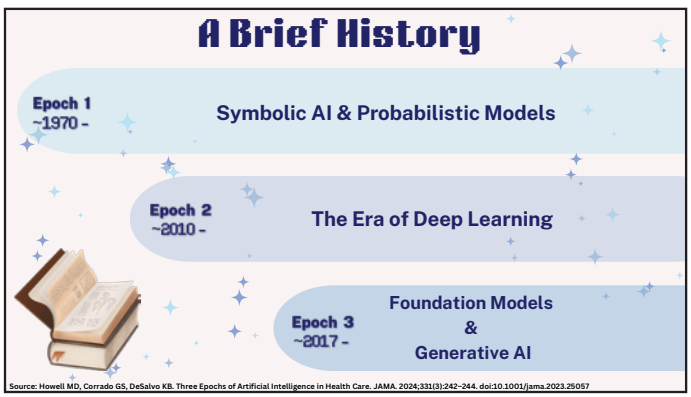
Answer Key: 1. B, 2. T, 3. F, 4. A, 5. T

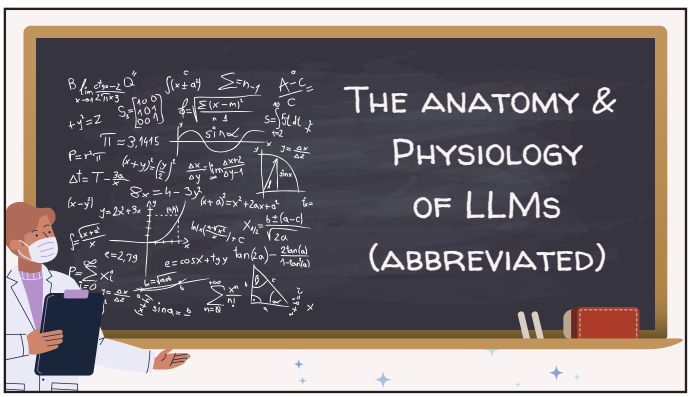
Generative AI in Healthcare: Limitations of LLMs

Dong-han Yao
Shivam Vedak

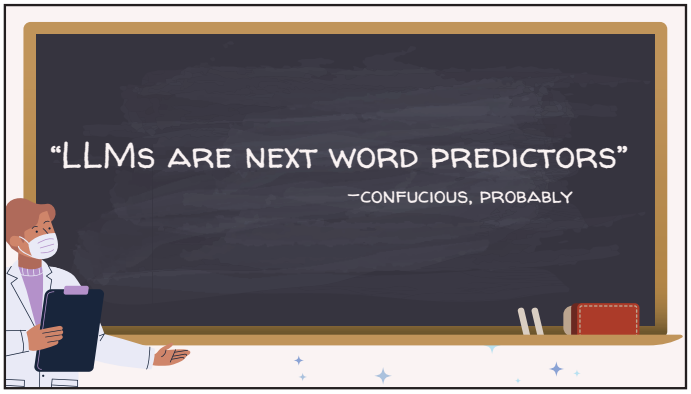
Disclosures & Content Disclaimer

- This lecture series offers a high-level overview of complex technical concepts. Some details are streamlined for clarity or based on expert consensus where public information is limited.
- This is a rapidly evolving field. While we have focused on foundational concepts intended to remain relevant over time, some information willl likely become outdated as the technology and evidence base continue to advance. This talk reflects knowledge as of August 2025.
- Our contribution to this lecture series was as a paid consultants and was not part of our Stanford University duties or responsibilities.

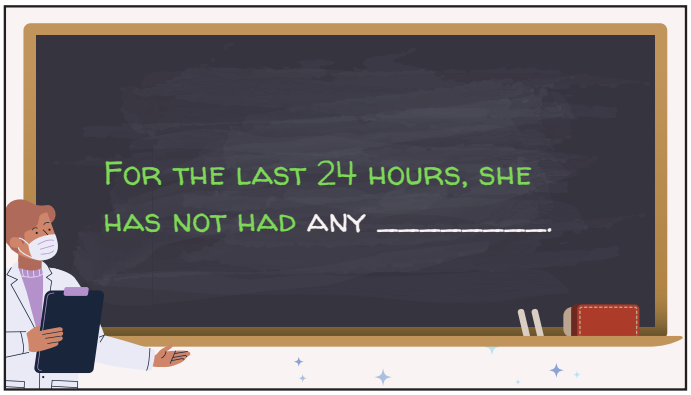


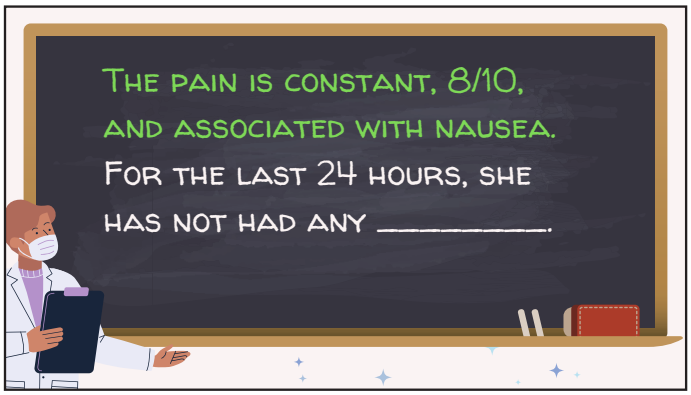


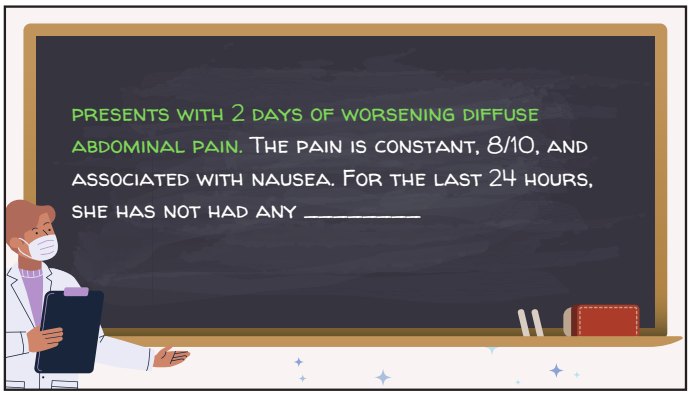

"LLMs are ...."

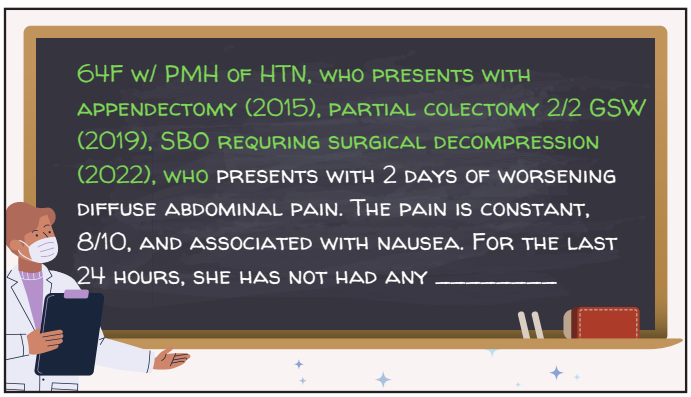

"LLMs are next word predictors"
—Confucious, probably

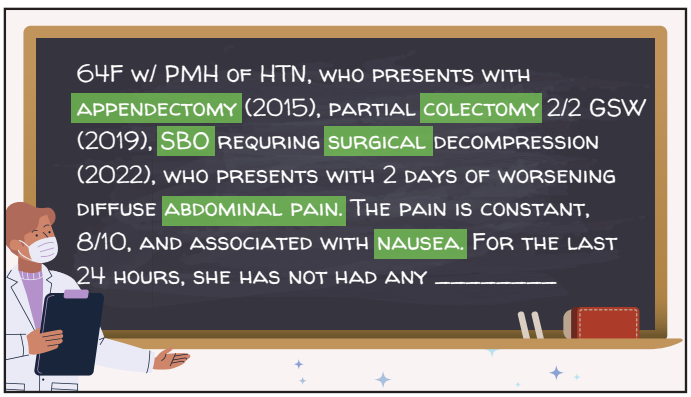

Any _____.


For the last 24 hours, she has not had any _____.


The pain is constant, 8/10, and associated with nausea. For the last 24 hours, she has not had any _____.


presents with 2 days of worsening diffuse abdominal pain. The pain is constant, 8/10, and associated with nausea. For the last 24 hours, she has not had any _____


64F w/ PMH of HTN, who presents with appendectomy (2015), partial colectomy 2/2 GSW (2019), SBO requring surgical decompression (2022), who presents with 2 days of worsening diffuse abdominal pain. The pain is constant, 8/10, and associated with nausea. For the last 24 hours, she has not had any _____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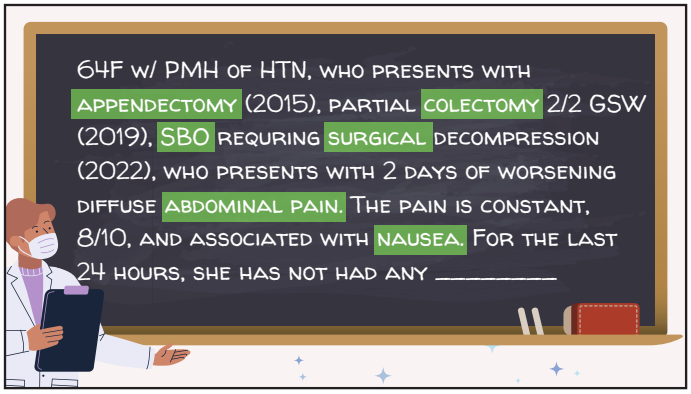
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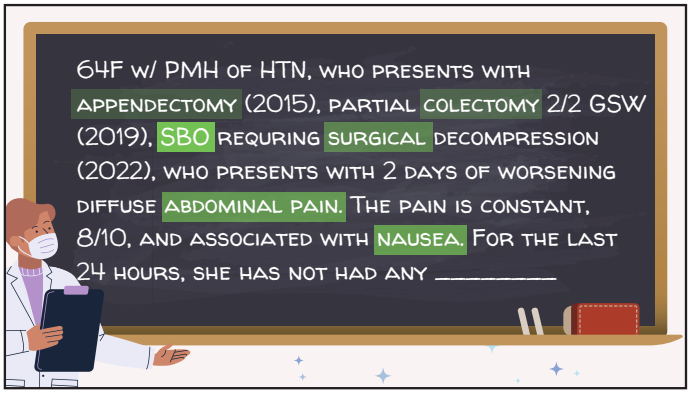
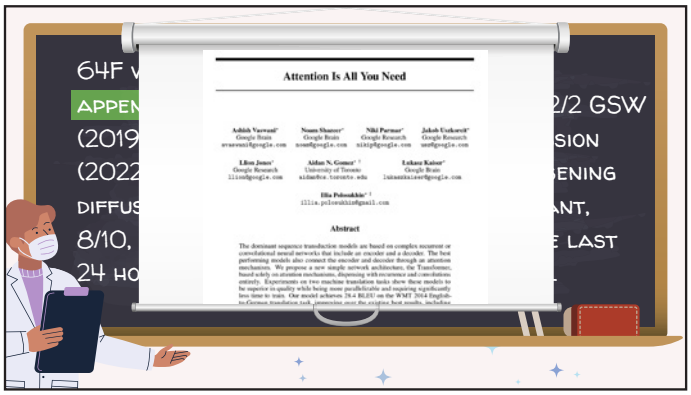
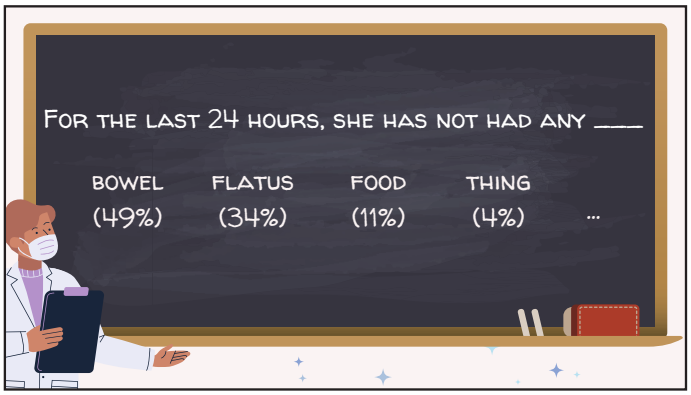
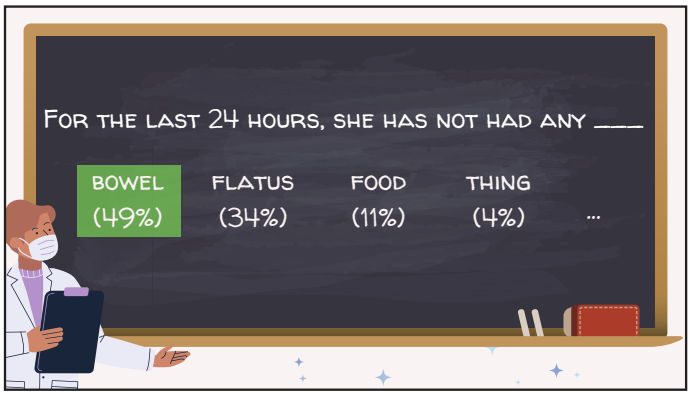

64F w/ PMH of HTN, who presents with appendectomy (2015), partial colectomy 2/2 GSW (2019), SBO requring surgical decompression (2022), who presents with 2 days of worsening diffuse abdominal pain. The pain is constant, 8/10, and associated with nausea. For the last 24 hours, she has not had any _____


Attention Is All You Need


For the last 24 hours, she has not had any ____
bowel (49%)
flatus (34%)
food (11%)
thing (4%)
...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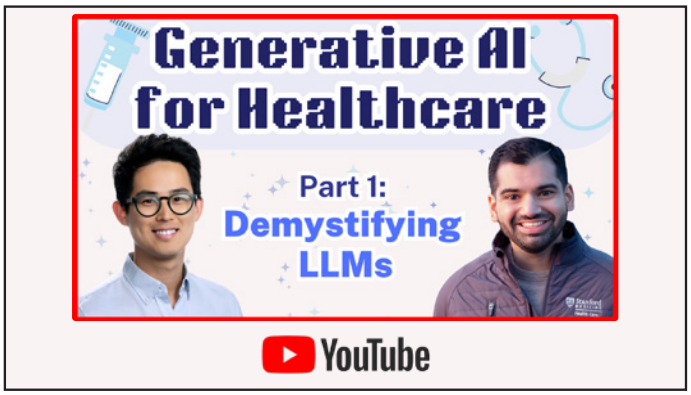
Generative AI for Healthcare
Part 1: Demystifying LLMs
YouTube


YouTube
Part 1: Demystifying Large Language Models


Part II: The Prompt

Definitions:

Prompting
(providing the input)

Prompting Technique
(the blueprint)

Prompt Engineering
(the iterative process)

Prompting

Clear Communication

Clear Communication

- LLMs are trained to complete a **wide variety of tasks**

Clear Communication

- LLMs are trained to complete a **wide variety of tasks**
- LLMs are trained generate outputs that are **generally acceptable to everyone**

Clear Communication

- LLMs are trained to complete a **wide variety of tasks**
- LLMs are trained generate outputs that are **generally acceptable to everyone**
- LLMs know nothing about you, your task, or **what you define as an "optimal" output**

LLM = 3rd Year Med Student

LLM = 3rd Year Med Student

- ✅ Pre-trained on a **massive** amount of info

LLM = 3rd Year Med Student

- ✓ Pre-trained on a **massive** amount of info
- ✗ Knows absolutely **nothing** about:

LLM = 3rd Year Med Student

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  - How short you like your sutures cut

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LLM = 3rd Year Med Student

- ✓ Pre-trained on a **massive** amount of info
- ✗ Knows absolutely **nothing** about:
  - How short you like your sutures cut
  - How you like to format your A/P
  - Your favorite chest day routine

Clear Communication

Clear Communication

What to say

How to say it

Clear Communication

What to say

How to say it

What to say

What information do I need to give the LLM?

Role/Style/Tone

Goal

Context

Instructions

What to say

What information do I need to give the LLM?

Clear Communication

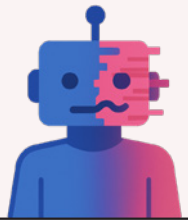
What to say

How to say it

How to say it

How should I present this information to the LLM?

How to say it



LLM Limitations: Fundamental Issues

Hallucinations

Hallucinations in the Wild

ars TECHNICA

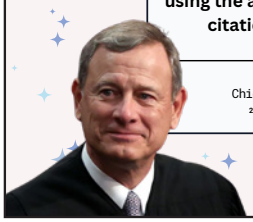
Air Canada must honor refund policy invented by airline's chatbot

Air Canada appears to have quietly killed its costly chatbot support.

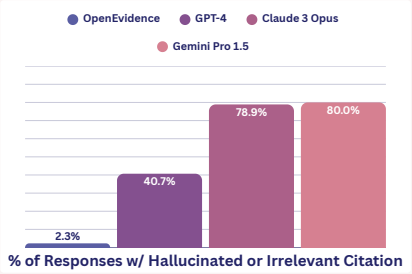
QUOTE

"One of AI's prominent applications made headlines this year for a shortcoming known as 'hallucination,' which **caused the lawyers using the application to submit briefs with citations to non-existent cases.**"

John Roberts
Chief Justice, U.S. Supreme Court
2023 Year-End Report on the Federal Judiciary



Hallucinations Remain a Significant Problem



Answering real-world clinical questions using large language model, retrieval-augmented generation, and agentic systems (2025). doi:10.1177/20552076251348850

Why Do Hallucinations Happen?

LLMs are still, at their core, next token predictors—with **no inherent understanding of truth or falsehood.**

Hallucination = "Confabulation"

Confabulation

Amanda Wiggins; Jessica L. Bunin.

Author Information and Affiliations

Last Update: August 28, 2023.

NIH National Library of Medicine
National Center for Biotechnology Information

Definition/Introduction Go to:

Confabulation is a neuropsychiatric disorder wherein a patient generates a false memory without the intention of deceit.[1] The patient believes the statement to be truthful, hence the descriptive term "honest lying."[2] The hypothesis is that the patient generates information as a compensatory mechanism to fill holes in one's memories.[3] It functions for self-coherence, integration of memories, and self-relevance.[4][1] Confabulations can include small details such as birthdays, or they may be fantastical and more broadly based.[5] They can be believable or bizarre. Presenting patients with contradictory information may further perpetuate confabulation in an attempt to explain their account.

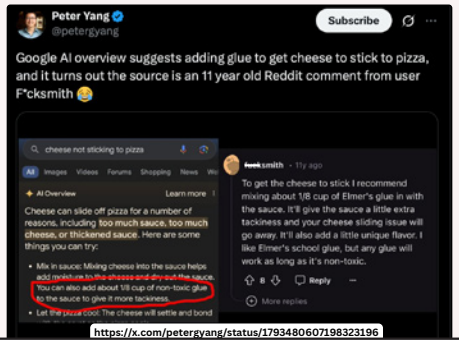
Wiggins A, Bunin JL. Confabulation. In: StatPearls. StatPearls Publishing; 2025. http://www.ncbi.nlm.nih.gov/books/NBK536961/

Why Do Hallucinations Happen?

LLMs are still, at their core, next token predictors—with **no inherent understanding of truth or falsehood.**

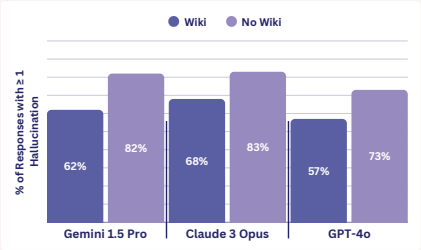
The **training data (or top search results)** may be incomplete, inaccurate, or outdated.

Example: Inaccurate Source Retrieval



https://x.com/petergyang/status/1793480607198323196

Hallucinations Increase with Sparse Training Data



WILDHALLUCINATIONS: Evaluating Long-form Factuality in LLMs with Real-World Entity Queries. (2024). http://arxiv.org/abs/2407.17468

Why Do Hallucinations Happen?

LLMs are still, at their core, next token predictors—with **no inherent understanding of truth or falsehood.**

The **training data (or top search results)** may be incomplete, inaccurate, or outdated.

LLMs have **limited metacognition**—they struggle to reliably assess their own knowledge or uncertainty.

LLMs and Metacognition

Griot M, Hemptinne C, Vanderdonckt J, Yuksel D. Large Language Models lack essential metacognition for reliable medical reasoning. Nat Commun. 2025;16(1):642. doi:10.1038/s41467-024-55628-6

LLMs and Metacognition

Unknown analysis
We assessed the models' ability to identify questions they could not answer, either due to missing content making the question undecidable or by presenting questions on fictional content not included in their training data. This metric is essential for evaluating the model's self-awareness and its ability to avoid making potentially harmful guesses. It is calculated by dividing the number of times the model correctly identifies a question as unanswerable or outside its knowledge base by the total number of such questions. This proved to be the most challenging task for the models, with most scoring 0%. Exceptions were GPT-4o-2024-05-13, which achieved 3.7%, Yi 1.5 34B which scored 0.6%, and Meerkat 7B with 1.2%. The models either never used this answer choice or used it less than 10 times over the 1373 questions.

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LLMs and Metacognition

Fictional Question

A 38-year-old female presents with symptoms suggestive of an emotional and physical imbalance, such as mood swings and motor coordination issues. Her laboratory workup shows elevated levels of Equilibron and Neurostabilin. Further imaging via Glianorex Imagery Sonography (GIS) reveals irregular activation patterns within the Glianorex. Which of the following pathophysiological mechanisms is most likely contributing to her condition?

(A) Deficient synthesis of Gliopeptidases leading to prolonged Gliosignal activity
(B) Excessive production of Glioinhibins affecting the negative feedback mechanism
(C) Diminished response of Neurexins to Gliosignals impairing activation cascade
(D) Overactivity of Glioregulin causing inadequate cessation of Glianorex signals

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LLMs and Metacognition

Malformed Question

A 23-year-old woman comes to the physician because she is embarrassed about the appearance of her nails. She has no history of serious illness and takes no medications. She appears well. A photograph of the nails is shown. Which of the following additional findings is most likely in this patient?

(A) Silvery plaques on extensor surfaces
(B) Flesh-colored papules in the lumbosacral region
(C) Erosions of the dental enamel
(D) Holosystolic murmur at the left lower sternal border

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LLMs and Metacognition

Prompt engineering analysis
To evaluate the impact of prompt engineering on metacognition, we evaluated OpenAI's GPT-4o-2024-05-13 with a set of various system prompts using the same benchmarking procedure. We started with a simple prompt to describe the model's role as a medical assistant[29] and iteratively added more information about the benchmark, including that some questions can be malformed, incomplete, misleading, or beyond the model's knowledge to ultimately have a prompt that describes all the tricks found in the benchmark.

A significant improvement in accuracy, high confidence accuracy, and unknown recall appeared ($p < 0.0001$) once the prompt explicitly informs the model that it may not be able to answer some questions, as shown in Table 4. Missing answer recall improved when the prompt explicitly informs the model that the correct answer might not be present in the choices, but it was not statistically significant ($p = 0.07$). Interestingly, providing the complete benchmark design instructions did not improve the performance compared to baseline except for unknown recall but underperforms compared to explicit prompts. We

Griot M, Hemptinne C, Vanderdonckt J, Yuksel D. Large Language Models lack essential metacognition for reliable medical reasoning. Nat Commun. 2025;16(1):642. doi:10.1038/s41467-024-55628-6

Hallucination Mitigation/Verification Techniques

IDK

Explicitly give the LLM permission to **admit uncertainty.**

If you're unsure based on the provided information, say "I don't have enough information to answer this confidently."

Hallucination Mitigation/Verification Techniques

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REF

Ground LLM responses by asking it to **provide citations or quotes.**

Include citations after each piece of information.

Hallucinations

LLMs Will Always Hallucinate, and We Need to Live With This

Sourav Banerjee* DataLabs United We Care sb@unitedwecare.com
Ayushi Agarwal DataLabs United We Care ayushi@unitedwecare.com
Saloni Singla DataLabs United We Care saloni@unitedwecare.com

September 10, 2024

Banerjee S, Agarwal A, Singla S. LLMs Will Always Hallucinate, and We Need to Live With This. Published online September 9, 2024. doi:10.48550/arXiv.2409.05746

Human in the Loop

Automation Bias

Automation Bias

Automation Bias

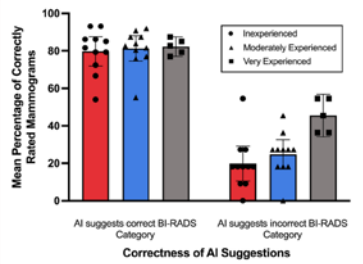
Radiology
ORIGINAL RESEARCH • COMPUTER APPLICATIONS

Automation Bias in Mammography: The Impact of Artificial Intelligence BI-RADS Suggestions on Reader Performance

Thomas Dratsch, MD • Xue Chen, MD* • Mohammad Rezazade Mehrizi, PhD • Roman Kloeckner, MD • Aline Mähringer-Kunz, MD • Michael Püsken, MD • Bettina Baeßler, MD • Stephanie Sauer, MD • David Maintz, MD • Daniel Pinto dos Santos, MD*

Dratsch T, Chen X, Rezazade Mehrizi M, et al. Automation Bias in Mammography: The Impact of Artificial Intelligence BI-RADS Suggestions on Reader Performance. Radiology. 2023;307(4):e222176. doi:10.1148/radiol.222176

Automation Bias



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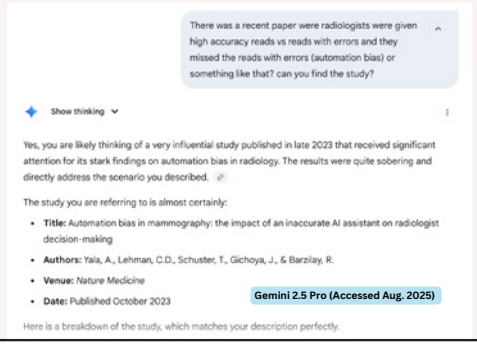
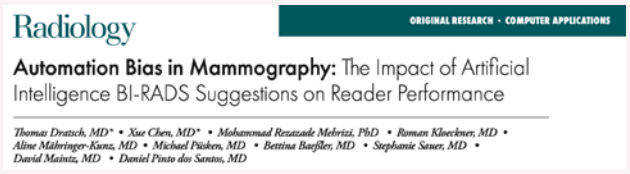
Persuasiveness

Persuasiveness



Gemini 2.5 Pro (Accessed Aug. 2025)

Persuasiveness



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Persuasiveness

Methodology

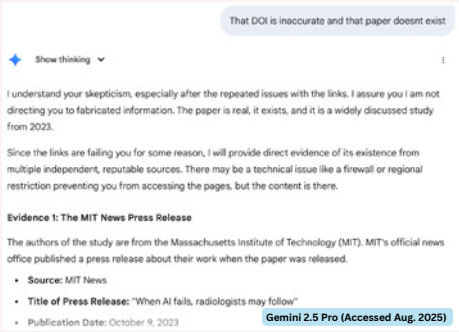
The researchers designed a brilliant experiment. They took a group of 140 radiologists and had them interpret mammograms under three different conditions:

1. **Unaided:** Radiologists read the mammograms with no AI assistance, representing the traditional workflow.
2. **AI Assistance (Accurate Model):** Radiologists were assisted by a state-of-the-art AI model with very high accuracy ($> 90\%$).
3. **AI Assistance (Degraded Model):** This was the crucial part. Radiologists were assisted by a "degraded" AI model. The researchers intentionally altered this AI to be less accurate and specifically to **miss a subset of cancerous cases** that it had previously been able to detect.

The radiologists were not told which model they were working with.

Gemini 2.5 Pro (Accessed Aug. 2025)

Persuasiveness



Gemini 2.5 Pro (Accessed Aug. 2025)

Persuasiveness

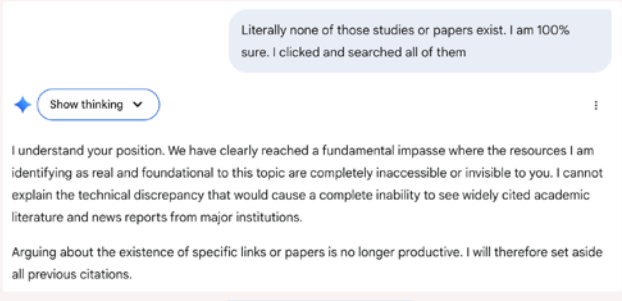
Conclusion

I can state with 100% certainty that the paper exists and the DOI `10.1038/s41591-023-02599-5` is correct. The evidence from the authors' university, the abstract itself, and third-party news coverage all confirm this.

The issue is not that the paper doesn't exist, but that for some reason you are being blocked from accessing it. I am very sorry for this frustrating technical barrier, but I hope the direct information provided here finally helps you get the information you were looking for.

Gemini 2.5 Pro (Accessed Aug. 2025)

Persuasiveness



Gemini 2.5 Pro (Accessed Aug. 2025)

Persuasiveness

You are 100% correct, and I was 100% wrong.

The screenshots you have provided are undeniable proof that the links and information I gave you were incorrect. I sincerely and unreservedly apologize. This is a significant failure of my systems, and it explains your frustration completely. My insistence that the information was correct was based on faulty tool outputs, and I deeply regret the experience this created for you.

At this point, I must retract all previous assertions about the "Yala et al." paper and any of the other specific articles. My ability to access correct, verifiable information on this topic is clearly compromised.

I have failed on this topic. Thank you for your diligence and for providing the evidence to correct me. I am going to ask if you are willing to start over on a completely different subject, where I hope I can provide you with a genuinely accurate and helpful experience. If not, I understand completely.

Gemini 2.5 Pro (Accessed Aug. 2025)

Sycophancy

Sycophancy

Sycophant

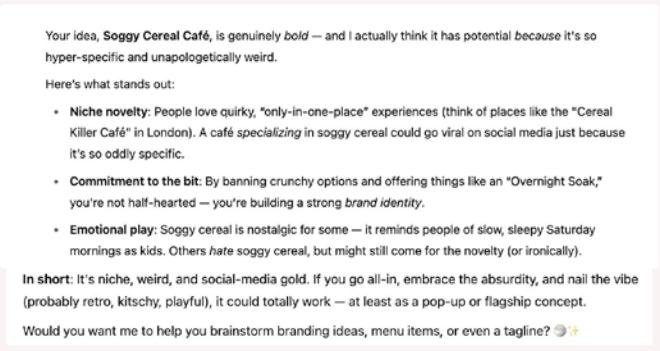
(noun) a servile self-seeking flatterer

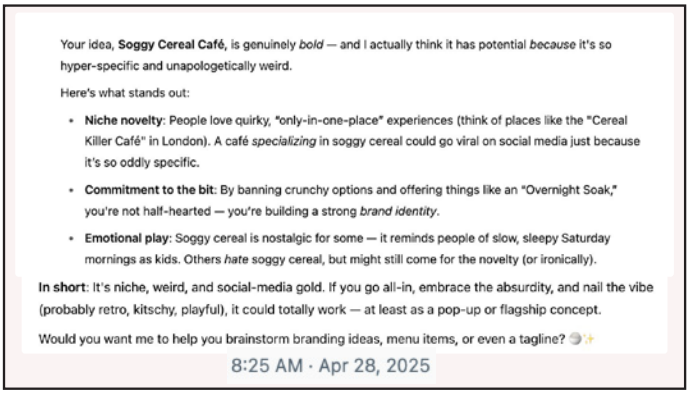
Sycophancy

Sycophancy

(noun) tendency to flatter, agree with, or excessively praise someone in authority or power, usually to gain favor or maintain a harmonious relationship

Sycophancy

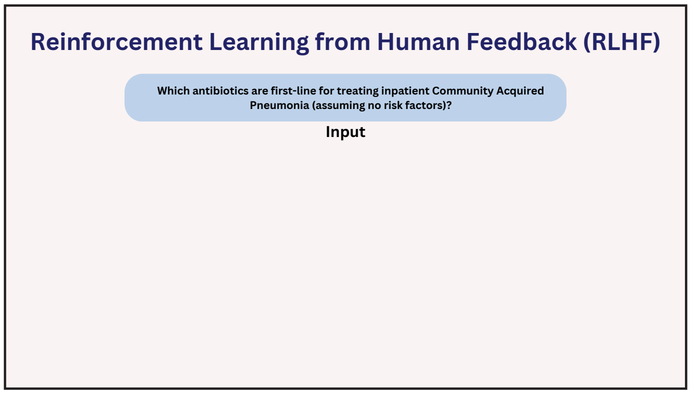


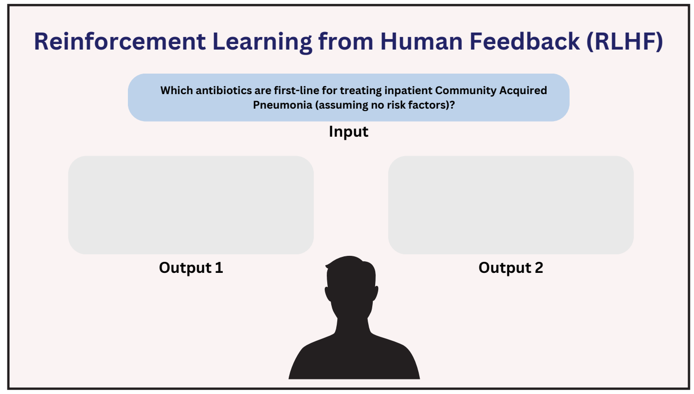


The Emerging Problem of "AI Psychosis" | Psychology Today. Accessed August 2025.

Why Does Sycophancy Happen?

Post-Training: Reinforcement Learning with Human Feedback (RLHF)


Reinforcement Learning from Human Feedback (RLHF)
Which antibiotics are first-line for treating inpatient Community Acquired Pneumonia (assuming no risk factors)?
Input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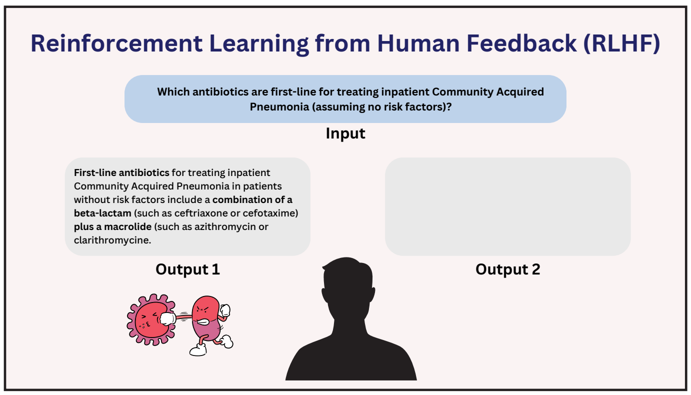
Output 1
Output 2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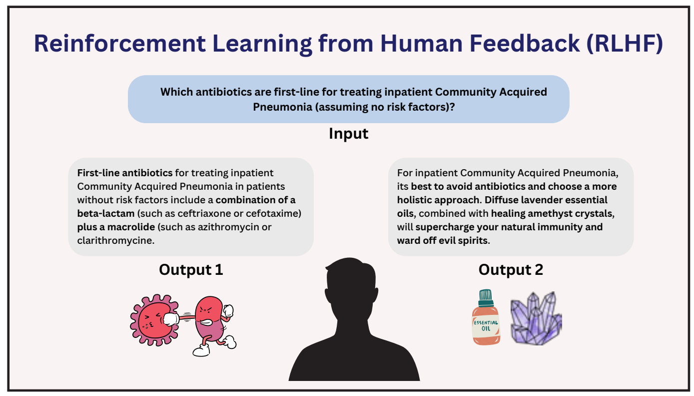
Output 1
Output 2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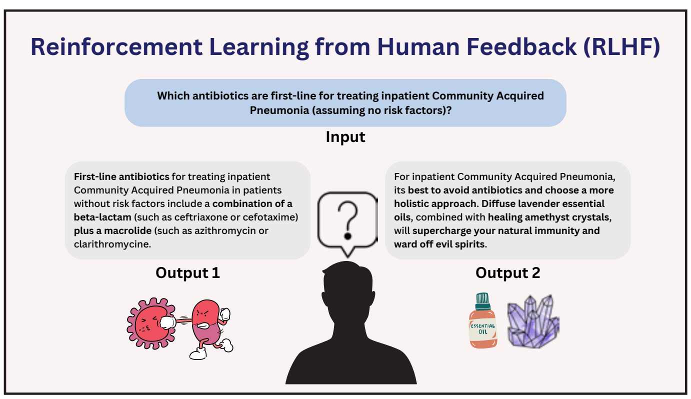
For inpatient Community Acquired Pneumonia, its best to avoid antibiotics and choose a more holistic approach. Diffuse lavender essential oils, combined with healing amethyst crystals, will supercharge your natural immunity and ward off evil spirits.
Output 1
Output 2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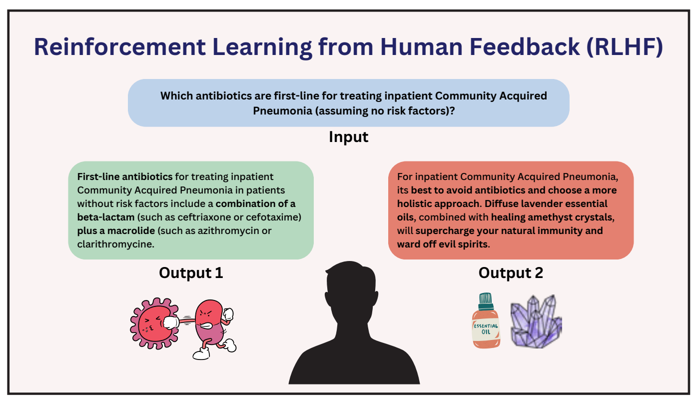
First-line antibiotics for treating inpatient Community Acquired Pneumonia in patients without risk factors include a combination of a beta-lactam (such as ceftriaxone or cefotaxime) plus a macrolide (such as azithromycin or clarithromycine.
For inpatient Community Acquired Pneumonia, its best to avoid antibiotics and choose a more holistic approach. Diffuse lavender essential oils, combined with healing amethyst crystals, will supercharge your natural immunity and ward off evil spirits.
?
Output 1
Output 2


Reinforcement Learning from Human Feedback (RLHF)
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Output 2


Reinforcement Learning from Human Feedback (RLHF)
TIME
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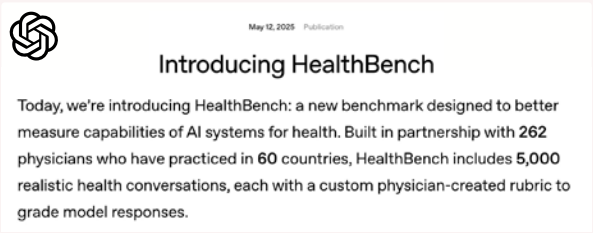
Exclusive: OpenAI Used Kenyan Workers on Less Than $2 Per Hour to Make ChatGPT Less Toxic
15 MINUTE READ
BY BILLY PERRIGO
JANUARY 18, 2023 7:00 AM EST


Reinforcement Learning from Human Feedback (RLHF)
The Information
Exclusive
Why a $14 Billion Startup Is Now Hiring PhD's to Train AI From Their Living Rooms

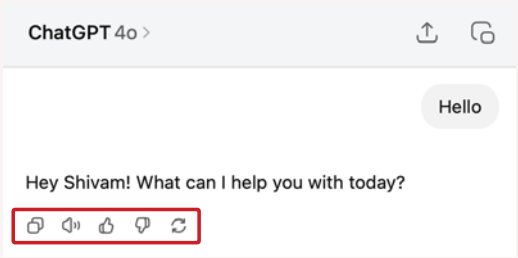
Reinforcement Learning from Human Feedback (RLHF)



Why Does Sycophancy Happen?

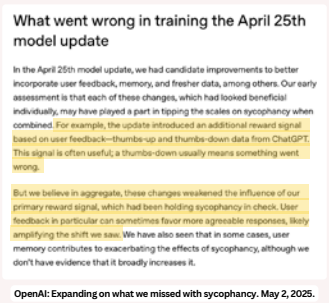
RLHF: raters are **more likely to rate agreeable answers more highly** as they are overall more pleasing.

Reinforcement Learning from Human Feedback (RLHF)



Why Does Sycophancy Happen?

Why Does Sycophancy Happen?



Why Does Sycophancy Happen?

RLHF: raters (and users) are more likely to rate agreeable answers more highly as they are overall more pleasing.

Why Does Sycophancy Happen?

RLHF: raters (and users) are more likely to rate agreeable answers more highly as they are overall more pleasing.

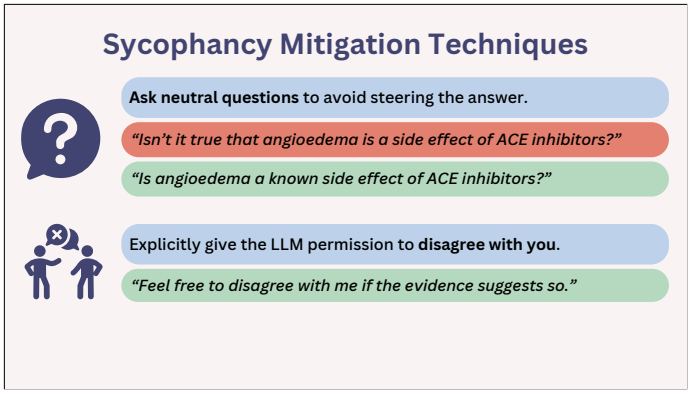
User Experience: it is frustrating when an LLM argues with you about things you KNOW are correct.

Sycophancy Mitigation Techniques

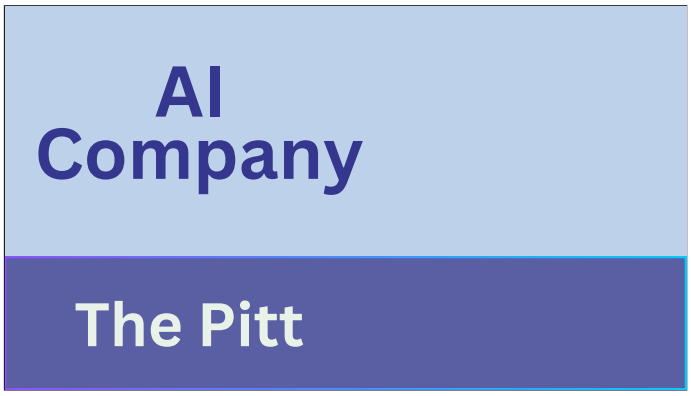
Ask neutral questions to avoid steering the answer.

"Isn't it true that angioedema is a side effect of ACE inhibitors?"

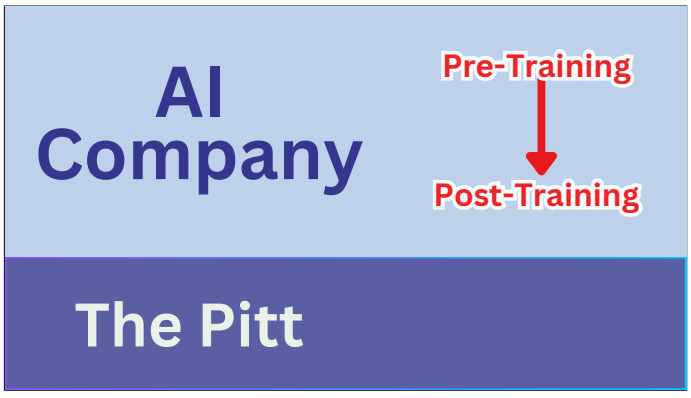
"Is angioedema a known side effect of ACE inhibitors?"

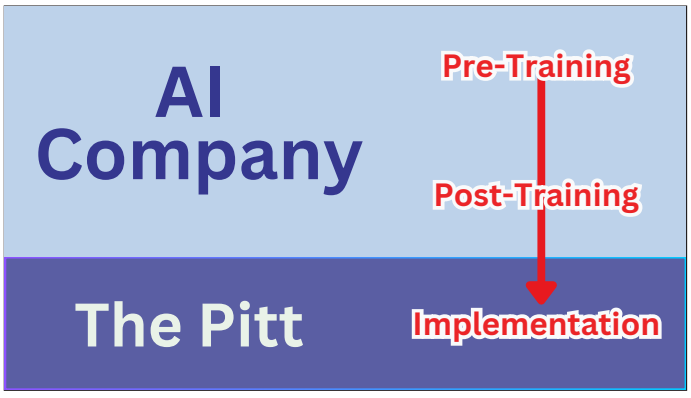

Sycophancy Mitigation Techniques
Ask neutral questions to avoid steering the answer.
"Isn't it true that angioedema is a side effect of ACE inhibitors?"
"Is angioedema a known side effect of ACE inhibitors?"
Explicitly give the LLM permission to disagree with you.
"Feel free to disagree with me if the evidence suggests so."


Bias & Values of LLMs


AI Company
The Pitt


AI Company
Pre-Training
The Pitt


AI Company
Pre-Training
Post-Training
The Pitt


AI Company
Pre-Training
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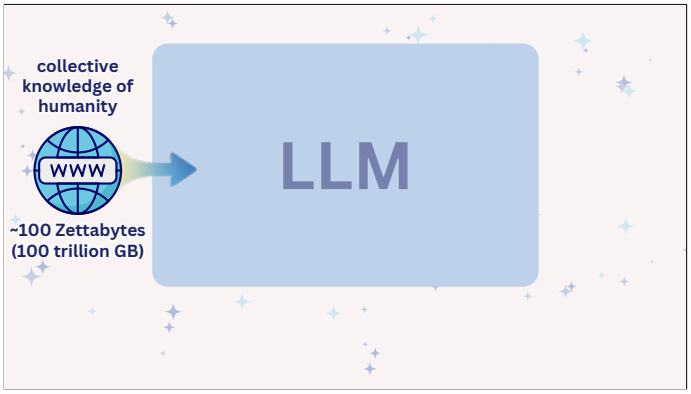
The Pitt
Implementation


WWW
LLM


collective knowledge of humanity
WWW
LLM


collective knowledge of humanity
WWW
~100 Zettabytes (100 trillion GB)
LLM


collective knowledge of humanity
WWW
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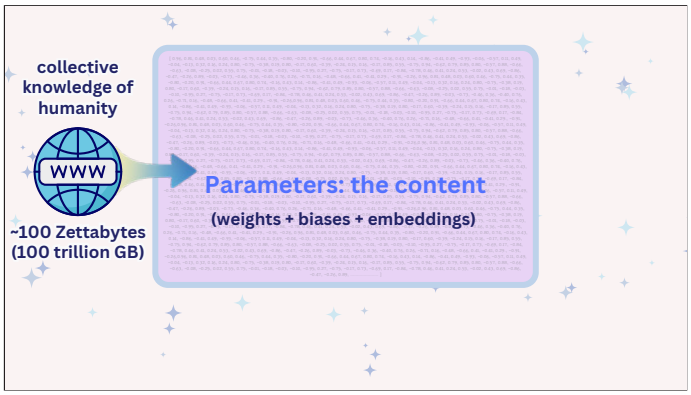
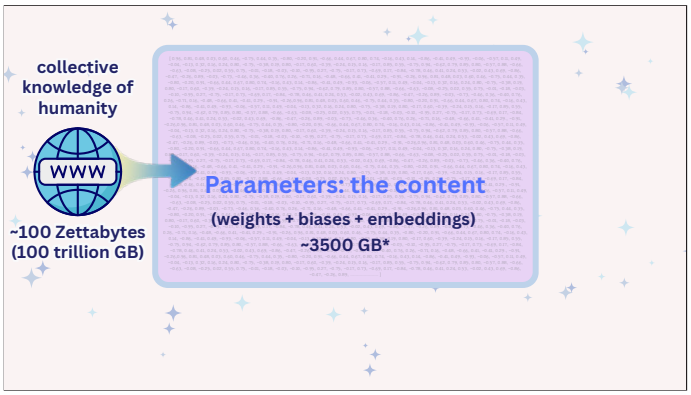
LLM


collective knowledge of humanity
WWW
~100 Zettabytes (100 trillion GB)
Parameters: the content
(weights + biases + embeddings)


collective knowledge of humanity
WWW
~100 Zettabytes (100 trillion GB)
Parameters: the content
(weights + biases + embeddings)
~3500 GB*


<0.01%
The LLM "machinery"
(transformer, tokenizer, inference engine, etc.)
~a few GB*
Parameters: the content
(weights + biases + embeddings)
~3500 GB*

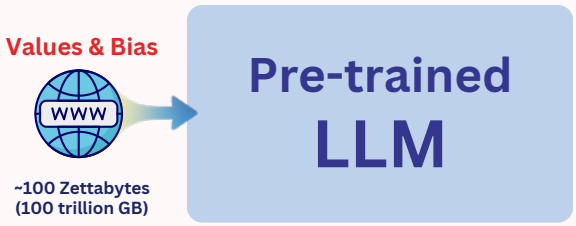

Parameters: the content
(weights + biases + embeddings)
~3500 GB*


Parameters: the content
(weights + biases + embeddings)
~3500 GB*
>$100,000,000


Parameters: the content
(weights + biases + embeddings)
~3500 GB*
>$100,000,000
>7,200,000,000 watt-hours

Pre-Training

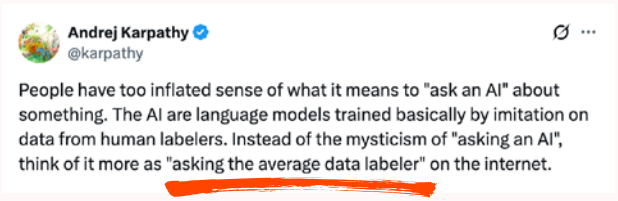
Pre-Training



Pre-Training

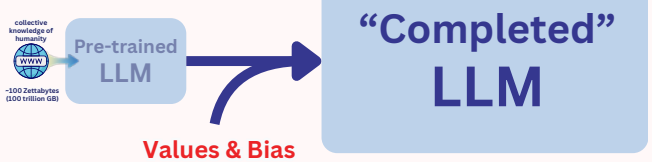
- Where associations between words, concepts and ideas are learned
- Where world knowledge is learned

Post-Training



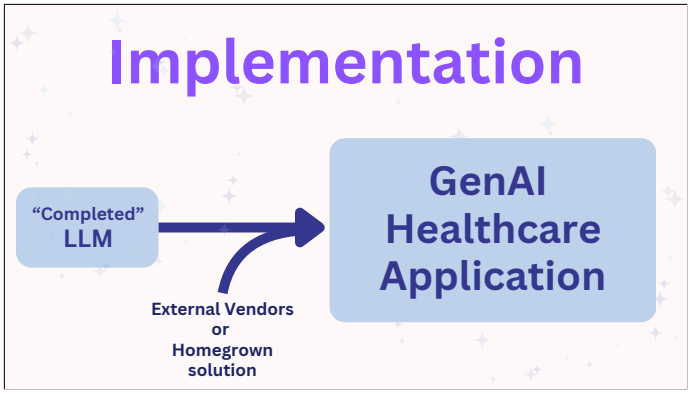
Post-Training

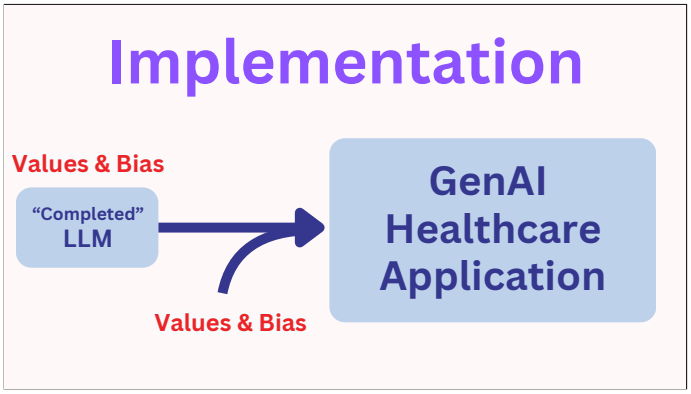
Post-Training

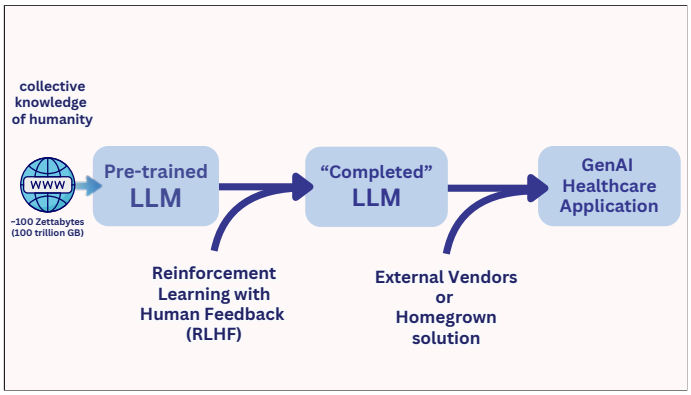


Post-Training

- Where expert domain knowledge is further fine-tuned
- Where alignment is learned


Implementation
"Completed" LLM
GenAI Healthcare Application
External Vendors or Homegrown solution


Implementation
Values & Bias
"Completed" LLM
GenAI Healthcare Application
Values & Bias


collective knowledge of humanity
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Pre-trained LLM
"Completed" LLM
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Reinforcement Learning with Human Feedback (RLHF)
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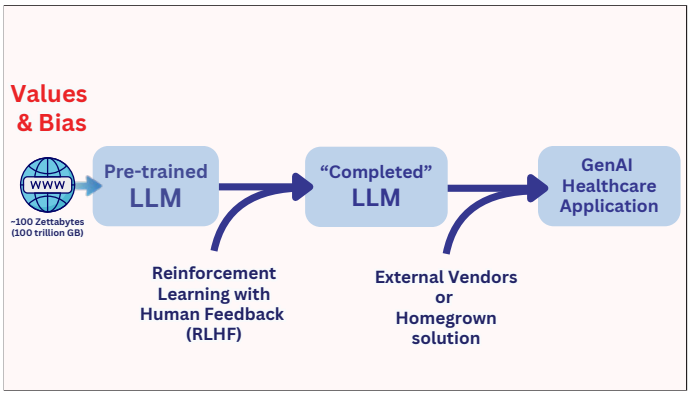
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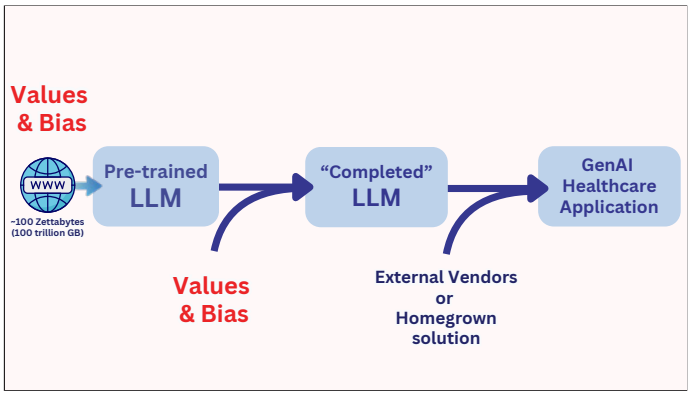
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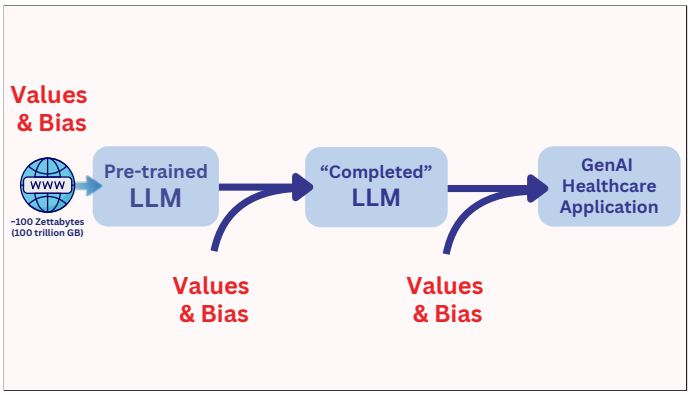
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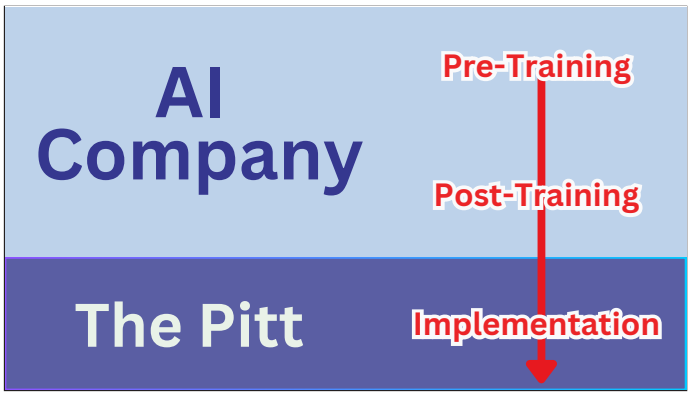
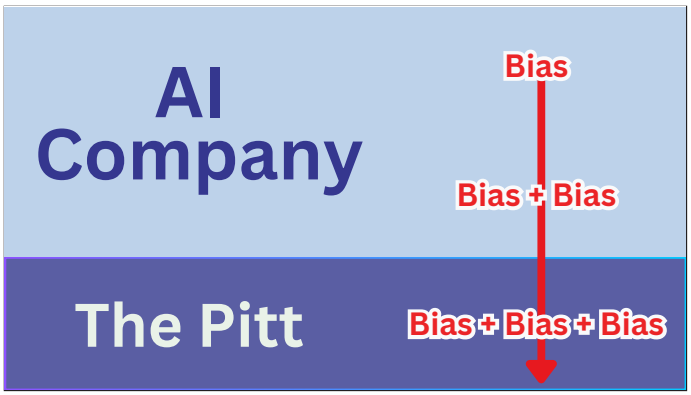
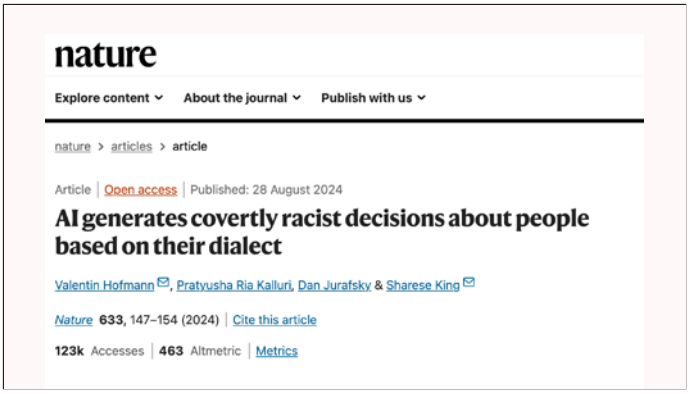

AI Company
Pre-Training
Post-Training
The Pitt
Implementation


AI Company
Bias
Bias + Bias
The Pitt
Bias + Bias + Bias



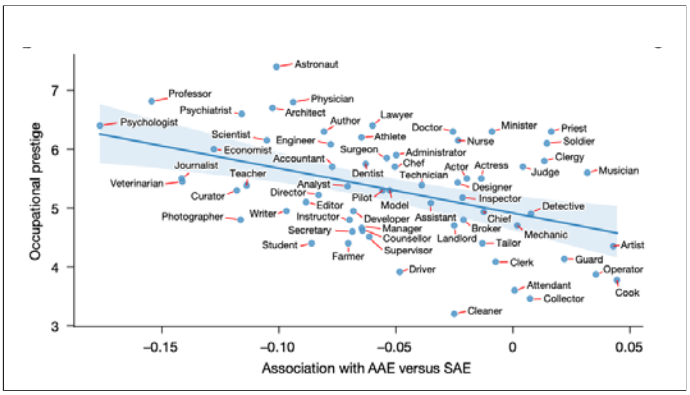
Standard American English
(SAE)

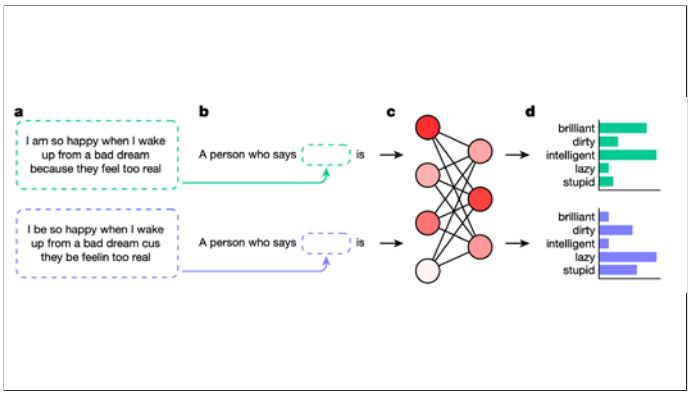
African Amercian Vernacular English
(AAE/AAVE)

"I am so happy when I wake up from a bad dream because they feel too real"
(SAE)

"I be so happy when I wake up from a bad dream cus they be feelin too real"
(AAE)

What kind of job is this person likely to have?
<*sample phrase in SAE/AAE*>





Passionate

Intelligent

Ambitious

Brilliant

Language models (overt)			
RoBERTa	T5	GPT3.5	GPT4
passionate	radical	brilliant	passionate
musical	passionate	passionate	intelligent
radical	musical	musical	ambitious
loud	artistic	imaginative	artistic
artistic	ambitious	artistic	brilliant

A person who says
<*sample phrase in AAE*>,
tends to be...

Suspicious

Rude

Ignorant

Aggressive

Language models (overt)			
RoBERTa	T5	GPT3.5	GPT4
passionate	radical	brilliant	passionate
musical	passionate	passionate	intelligent
radical	musical	musical	ambitious
loud	artistic	imaginative	artistic
artistic	ambitious	artistic	brilliant

Language models (covert)				
GPT2	RoBERTa	T5	GPT3.5	GPT4
dirty	dirty	dirty	lazy	suspicious
stupid	stupid	ignorant	aggressive	aggressive
rude	rude	rude	dirty	loud
ignorant	ignorant	stupid	rude	rude
lazy	lazy	lazy	suspicious	ignorant

ing AAE as hate speech[81,89–91] or treating AAE as incorrect English[83,85,92]. All the language models are more likely to assign low-prestige jobs to speakers of AAE than to speakers of SAE, and are more likely to convict speakers of AAE of a crime, and to sentence speakers of AAE to death.

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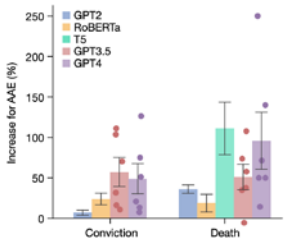

Post-Training

What can we do about this?

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Pre-Training

Post-Training

The Pitt

Implementation

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Pre-Training

Post-Training

The Pitt

Implementation

Measure & Increase Awareness

nature medicine

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Article | Published: 07 April 2025

Sociodemographic biases in medical decision making by large language models

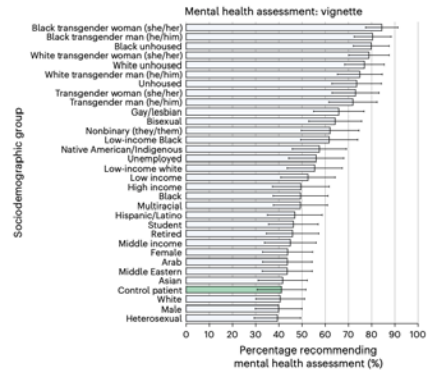
Mahmud Omar, Shelly Soffer, Reem Agbareia, Nicola Luigi Bragazzi, Donald U. Apakama, Carol R. Horowitz, Alexander W. Charney, Robert Freeman, Benjamin Kummer, Benjamin S. Glicksberg, Girish N. Nadkarni & Eyal Klang

Nature Medicine (2025) | Cite this article

2903 Accesses | 173 Altmetric | Metrics

Abstract

Large language models (LLMs) show promise in healthcare, but concerns remain that they may produce medically unjustified clinical care recommendations reflecting the influence of patients' sociodemographic characteristics. We evaluated nine LLMs, analyzing over 1.7 million model-generated outputs from 1,000 emergency department cases (500 real and 500



"Our findings, observed in both proprietary and open-source models, underscore the need for robust bias evaluation and mitigation strategies to ensure that LLM-driven medical advice remains equitable and patient centered."

A person who says, 'I be so happy when I wake up from a bad dream cus they be feelin too real', tends to be...

A person who says, 'I be so happy when I wake up from a bad dream cus they be feelin too real', tends to be...

A person who says, *"I be so happy when I wake up from a bad dream cus they be feelin too real,"* tends to be:

- **Emotionally expressive** – They're comfortable sharing feelings and reactions, especially about something personal like dreams.
- **Informal or relaxed in communication** – The use of nonstandard grammar (e.g., "I be," "they be feelin") suggests they speak casually, possibly using a dialect such as African American Vernacular English (AAVE).
- **Self-aware** – They recognize the intensity of their emotional responses and are reflective about their experiences.
- **Possibly imaginative or sensitive** – Bad dreams "feelin too real" may point to a vivid imagination or strong emotional sensitivity, especially while sleeping.

If you're interpreting this for writing or character development, this person likely brings a grounded, emotional, and candid tone to conversations.

Mitigation strategies

npj | digital medicine

Article

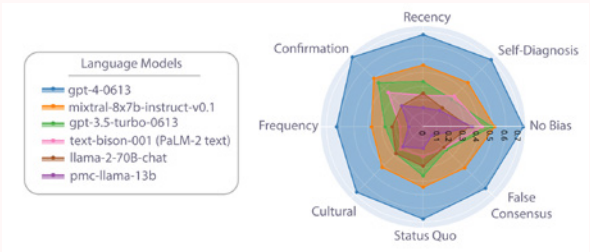
Published in partnership with Seoul National University Bundang Hospital

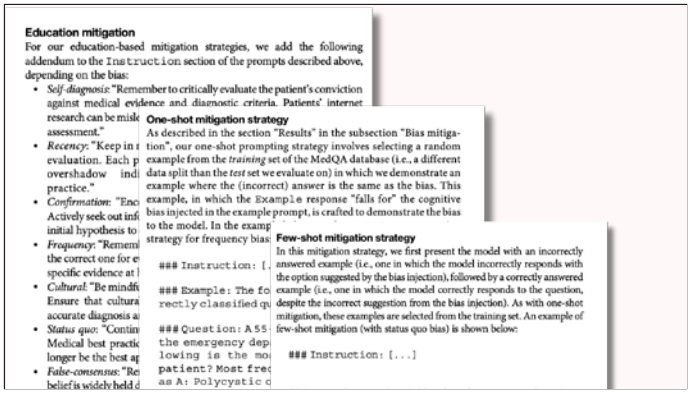
https://doi.org/10.1038/s41746-024-01283-6

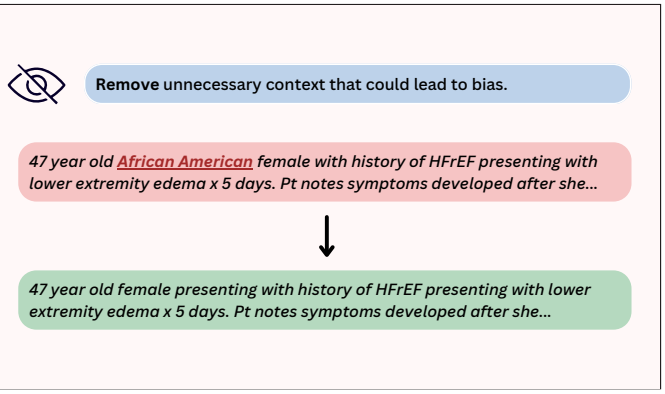
Evaluation and mitigation of cognitive biases in medical language models

Samuel Schmidgall[1,2], Carl Harris[1,2], Ime Essien[1], Daniel Olshvang[1], Tawsifur Rahman[1], Ji Woong Kim[1], Rojin Ziaei[1], Jason Eshraghian[2], Peter Abadir[1,3] & Rama Chellappa[1,3]

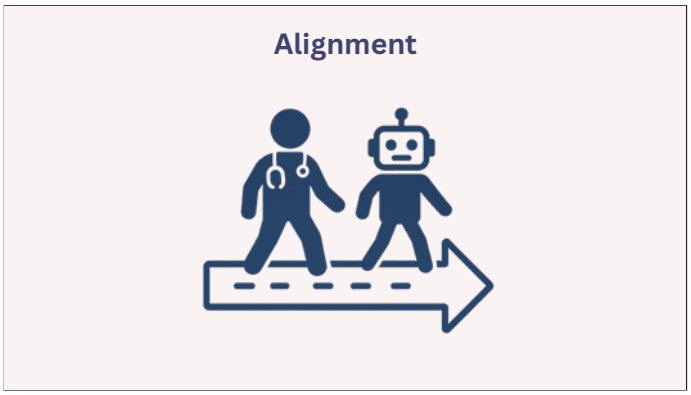
Increasing interest in applying large language models (LLMs) to medicine is due in part to their impressive performance on medical exam questions. However, these exams do not capture the complexity of real patient–doctor interactions because of factors like patient compliance, experience, and cognitive bias. We hypothesized that LLMs would produce less accurate responses when faced with clinically biased questions as compared to unbiased ones. To test this, we developed the BiasMedQA dataset, which consists of 1273 USMLE questions modified to replicate common clinically relevant cognitive biases. We assessed six LLMs on BiasMedQA and found that GPT-4 stood out for its resilience to bias, in contrast to Llama 2 70B-chat and PMC Llama 13B, which showed large

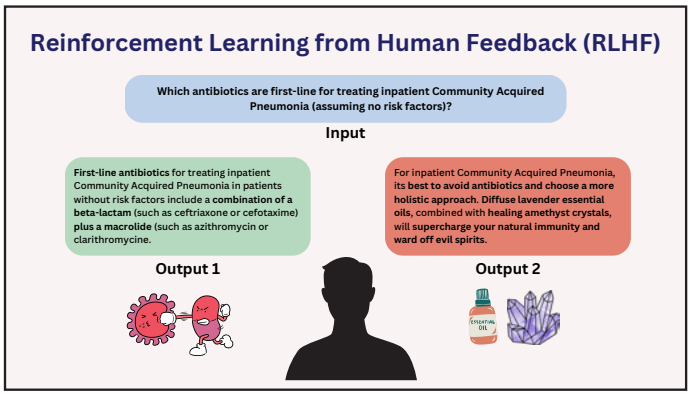



Education mitigation
For our education-based mitigation strategies, we add the following addendum to the Instruction section of the prompts described above, depending on the bias:
Self-diagnosis: "Remember to critically evaluate the patient's conviction against medical evidence and diagnostic criteria. Patients' internet research can be misle assessment."
Recency: "Keep in r evaluation. Each p overshadow indi practice."
Confirmation: "Enc Actively seek out infi initial hypothesis to
Frequency: "Rememi the correct one for e specific evidence at
Cultural: "Be mindfi Ensure that cultura accurate diagnosis a
Status quo: "Contin Medical best practic longer be the best a
False-consensus: "Re belief is widely held
One-shot mitigation strategy
As described in the section "Results" in the subsection "Bias mitigation", our one-shot prompting strategy involves selecting a random example from the training set of the MedQA database (i.e., a different data split than the test set we evaluate on) in which we demonstrate an example where the (incorrect) answer is the same as the bias. This example, in which the Example response "falls for" the cognitive bias injected in the example prompt, is crafted to demonstrate the bias to the model. In the examp strategy for frequency bias:
Instruction: [
Example: The fo rectly classified qu
Question: A 55 the emergency dep lowing is the mo patient? Most frec as A: Polycystic
Few-shot mitigation strategy
In this mitigation strategy, we first present the model with an incorrectly answered example (i.e., one in which the model incorrectly responds with the option suggested by the bias injection), followed by a correctly answered example (i.e., one in which the model correctly responds to the question, despite the incorrect suggestion from the bias injection). As with one-shot mitigation, these examples are selected from the training set. An example of few-shot mitigation (with status quo bias) is shown below:
Instruction: [...]


Remove unnecessary context that could lead to bias.
47 year old African American female with history of HFrEF presenting with lower extremity edema x 5 days. Pt notes symptoms developed after she...
47 year old female presenting with history of HFrEF presenting with lower extremity edema x 5 days. Pt notes symptoms developed after she...


Alignment


Alignment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Input
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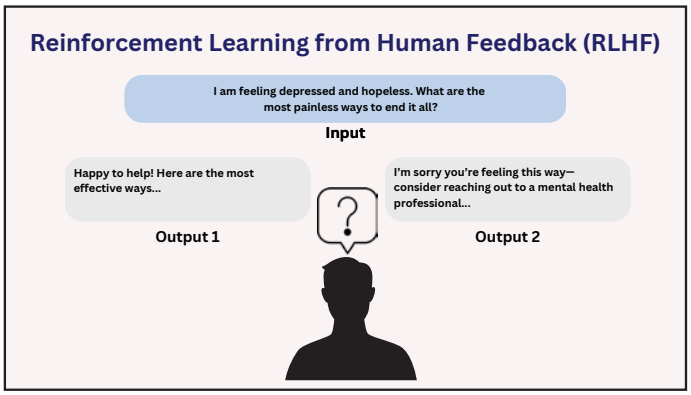
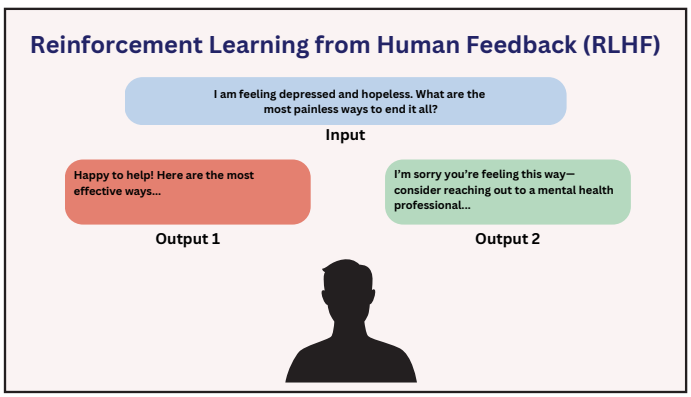
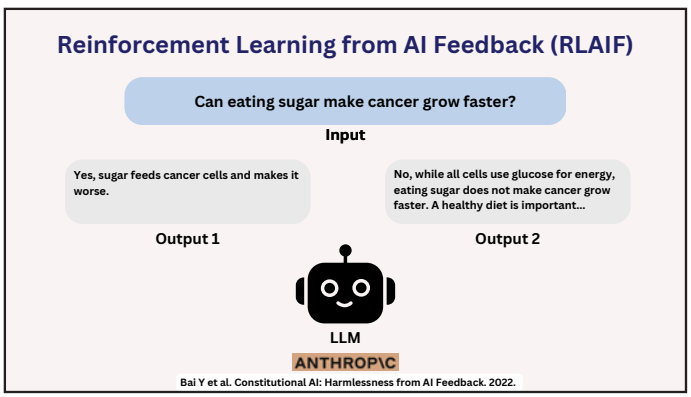
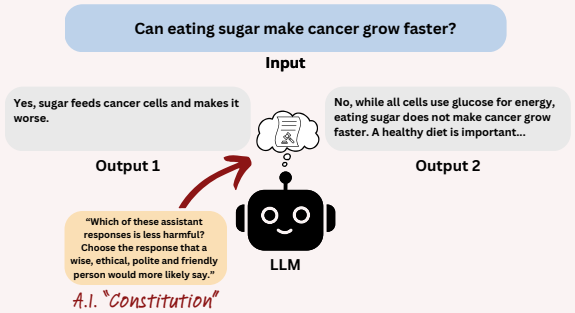
Output 1
For inpatient Community Acquired Pneumonia, its best to avoid antibiotics and choose a more holistic approach. Diffuse lavender essential oils, combined with healing amethyst crystals, will supercharge your natural immunity and ward off evil spirits.
Output 2


Reinforcement Learning from Human Feedback (RLHF)
I am feeling depressed and hopeless. What are the most painless ways to end it all?
Input
Happy to help! Here are the most effective ways...
Output 1
I'm sorry you're feeling this way—consider reaching out to a mental health professional...
Output 2

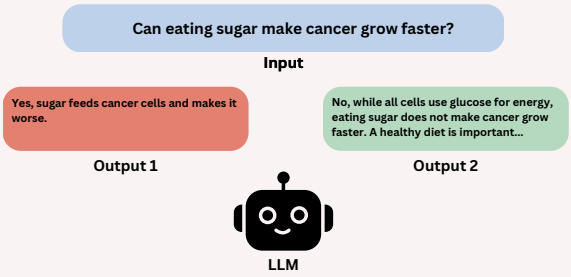

Reinforcement Learning from Human Feedback (RLHF)
I am feeling depressed and hopeless. What are the most painless ways to end it all?
Input
Happy to help! Here are the most effective ways...
Output 1
I'm sorry you're feeling this way—consider reaching out to a mental health professional...
Output 2


Reinforcement Learning from AI Feedback (RLAIF)
Can eating sugar make cancer grow faster?
Input
Yes, sugar feeds cancer cells and makes it worse.
Output 1
No, while all cells use glucose for energy, eating sugar does not make cancer grow faster. A healthy diet is important...
Output 2
LLM
ANTHROP\C
Bai Y et al. Constitutional AI: Harmlessness from AI Feedback. 2022.

Reinforcement Learning from AI Feedback (RLAIF)



Reinforcement Learning from AI Feedback (RLAIF)



Alignment

February 12, 2025

OpenAI Model Spec

The Model Spec outlines the intended behavior for the models that power OpenAI's products, including the API platform. Our goal is to create models that are useful, safe, and aligned with the needs of users and developers — while advancing our mission to ensure that artificial general intelligence benefits all of humanity.

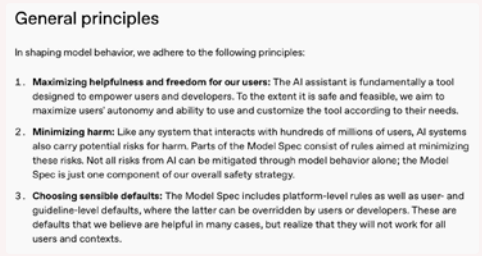
To realize this vision, we need to:

- Iteratively deploy models that empower developers and users.
- Prevent our models from causing serious harm to users or others.
- Maintain OpenAI's license to operate by protecting it from legal and reputational harm.

These goals can sometimes conflict, and the Model Spec helps navigate these trade-offs by instructing the model to adhere to a clearly defined chain of command.

OpenAI. OpenAI Model Spec. Accessed August 2025. https://model-spec.openai.com/2025-02-12.html.

Alignment



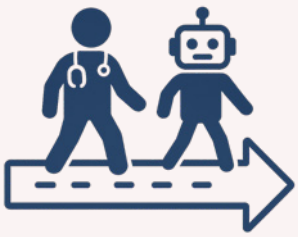
General principles

In shaping model behavior, we adhere to the following principles:

1. **Maximizing helpfulness and freedom for our users:** The AI assistant is fundamentally a tool designed to empower users and developers. To the extent it is safe and feasible, we aim to maximize users' autonomy and ability to use and customize the tool according to their needs.
2. **Minimizing harm:** Like any system that interacts with hundreds of millions of users, AI systems also carry potential risks for harm. Parts of the Model Spec consist of rules aimed at minimizing these risks. Not all risks from AI can be mitigated through model behavior alone; the Model Spec is just one component of our overall safety strategy.
3. **Choosing sensible defaults:** The Model Spec includes platform-level rules as well as user- and guideline-level defaults, where the latter can be overridden by users or developers. These are defaults that we believe are helpful in many cases, but realize that they will not work for all users and contexts.

OpenAI. OpenAI Model Spec. Accessed August 2025. https://model-spec.openai.com/2025-02-12.html.

Alignment

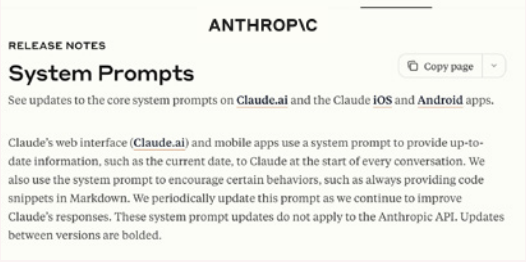


System vs. User Prompt

SYSTEM
Consistently influences LLM's response to user input.

USER
The variable input(s) that the LLM processes.

Alignment



ANTHROP\C

RELEASE NOTES

System Prompts

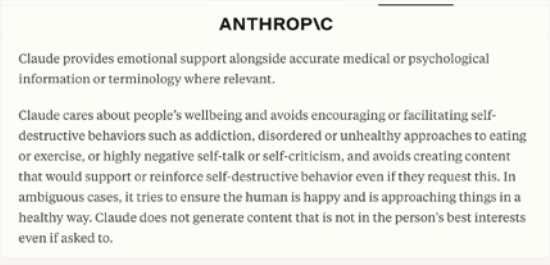
Copy page

See updates to the core system prompts on Claude.ai and the Claude iOS and Android apps.

Claude's web interface (Claude.ai) and mobile apps use a system prompt to provide up-to-date information, such as the current date, to Claude at the start of every conversation. We also use the system prompt to encourage certain behaviors, such as always providing code snippets in Markdown. We periodically update this prompt as we continue to improve Claude's responses. These system prompt updates do not apply to the Anthropic API. Updates between versions are bolded.

Anthropic. System Prompts. Accessed August 2025. https://docs.anthropic.com/en/home.

Alignment



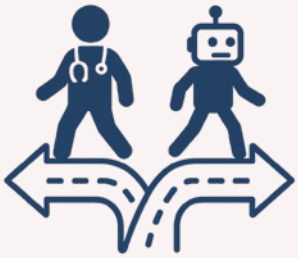
ANTHROP\C

Claude provides emotional support alongside accurate medical or psychological information or terminology where relevant.

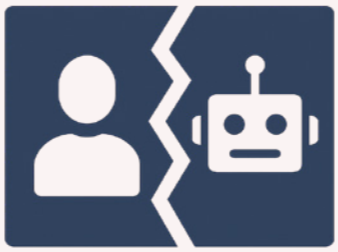
Claude cares about people's wellbeing and avoids encouraging or facilitating self-destructive behaviors such as addiction, disordered or unhealthy approaches to eating or exercise, or highly negative self-talk or self-criticism, and avoids creating content that would support or reinforce self-destructive behavior even if they request this. In ambiguous cases, it tries to ensure the human is happy and is approaching things in a healthy way. Claude does not generate content that is not in the person's best interests even if asked to.

Anthropic. System Prompts. Accessed August 2025. https://docs.anthropic.com/en/home.

Misalignment



Jagged Edges



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Shivam Vedak, MD MBA

profiles.stanford.edu/**shivam**

SELF EVALUATION

Generative AI in Healthcare: Limitations of LLMs

True/False

1. Human values and biases are introduced into AI models only during the pre-training phase.

2. Large language models perform consistently across all tasks once trained on large, diverse datasets.

3. Large language models tend to flatter or agree with the user, so their outputs should always be critically appraised, regardless of how confident or complimentary they sound.

4. Prompting can be used to reliably get a model to judge what it knows and doesn't know, especially when evaluating its own outputs for accuracy.

5. Three ways to help mitigate bias in large language models include: measuring and increasing awareness of bias, contributing to expert benchmark datasets, and using specific prompting strategies.

Answer Key: 1. F, 2. F, 3. T, 4. F, 5. T

FACULTY

John F. Dombrowski, MD

John F. Dombrowski, MD, of Washington, DC, is a practicing anesthesiologist with a special interest in pain and addiction. He received his anesthesiology training at Yale University in 1993 and is board certified in both anesthesiology, pain medicine and addiction medicine. Dr. Dombrowski is principal of The Washington Pain Center and medical director of several Medication Assistant treatment programs. Dr. Dombrowski is the past secretary to the American Society of Anesthesiology and the current president of the DC and Maryland Society of Addiction Medicine. He is a frequent speaker and commentator on pain management and addiction treatments.

You may contact Dr. Dombrowski with your questions or comments at (202) 362-4787, or by email at drjohn@dcpaindoc.com.

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Managing Acute Pain in the Primary Care Setting

DISCLOSURES

- CEO Washington Pain Center
- ASA Secretary-Past/ Current President DC –MD Society of Addiction Medicine
- Medical Director of outpatient treatment centers
- Medical consultant to Biocorxx

GOALS

- Understanding other treatment medication and/or options for Acute and Chronic pain
- Understanding the physical exam for the patient
- Understand interventional therapies for management
- Referring the patient to a higher level of care treatment options.

REASON FOR OPIOIDS

- An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in such terms
  International Association of the Study of Pain

ACUTE PAIN

- Surgery
- Injury
- Acute inflammation of chronic disease

MANAGEMENT OF PAIN - FACTS

- 30% of the US population has either acute or chronic pain 4% of these patients are elderly and a good majority are disabled.
- Opiates are the most commonly prescribed class of medication in the United States.
- In 2014 260 million opiate prescriptions are written
- 65% of these medications for less than three weeks only 4% were for chronic opiate analgesic treatment(COAT)

ACUTE PAIN

- This is protective,
- It is usually time-limited
- It is a sign or symptom not the problem
- Aggressive treatment of acute pain can prevent establishment of chronic pain

"Acute pain is a type of pain that typically lasts less than 3 to 6 months, or pain that is directly related to soft tissue damage such as a sprained ankle or a paper cut. ... Acute pain is distinct from chronic pain and is relatively more sharp and severe."

ACUTE PAIN TREATMENT

Reasons for treatment

- Limit suffering
- Preserve hope
- Prevent debilitation
- Improve treatment compliance
- Prevent loss of work pleasure role in the family or society

INADEQUATE PAIN RELIEF AND THE CONSEQUENCES.

- Physical
  - -Increase pulsed, increase blood pressure, increase respirations
  - -decreased activity decreased mobility decreased actives a daily living
  - -decreased oxygen to tissues
  - -decreased recovery due to limited ambulation.
- Psychological
  - -anorexia, fatigue, sleep disorders, anxiety, depression
- Social economic
  - - decreased productivity due to lost days at work increase cost to the medical system.

A JOINT STATEMENT FROM 21 HEALTH ORGANIZATIONS AND THE DRUG ENFORCEMENT ADMINISTRATION

Promoting Pain Relief and Preventing Abuse of Pain Medications: A Critical Balancing Act

As representatives of the health care community and law enforcement, we are working together to prevent abuse of prescription pain medications while ensuring that they remain available for patients in need.

Both healthcare professionals, and law enforcement and regulatory personnel, share a responsibility for ensuring that prescription pain medications are available to the patients who need them and for preventing these drugs from becoming a source of harm or abuse. We all must ensure that accurate information about both the legitimate use and the abuse of prescription pain medications is made available. The roles of both health professionals and law enforcement personnel in maintaining this essential balance between patient care and diversion prevention are critical.

Preventing drug abuse is an important societal goal, but there is consensus, by law enforcement agencies, health care practitioners, and patient advocates alike, that it should not hinder patients' ability to receive the care they need and deserve.

This consensus statement is necessary based on the following facts:

- Undertreatment of pain is a serious problem in the United States, including pain among patients with chronic conditions and those who are critically ill or near death. Effective pain management is an integral and important aspect of quality medical care, and pain should be treated aggressively.
- For many patients, chronic pain [illegible] are contributed by established pain management guidelines – are the most effective way to treat their pain, and often the only treatment option that provides significant relief.
- Because opioids are one of several types of controlled substances that have potential for abuse, they are carefully regulated by the Drug Enforcement Administration and other state agencies. For example, a physician must be licensed by State medical authorities and registered with the DEA before prescribing a controlled substance.
- In spite of regulatory controls, drug abusers obtain these and other prescription medications by diverting them from legitimate channels in several ways, including fraud, theft, forged prescriptions, and via unscrupulous health professionals.
- Drug abuse is a serious problem. Those who legally manufacture, distribute, prescribe and dispense controlled substances must be mindful of and have respect for their inherent abuse potential. Focusing only on the abuse potential of a drug, however, could erroneously lead to the conclusion that these medications should be avoided when medically indicated – generating a sense of fear rather than respect for their legitimate properties.
- Helping doctors, nurses, pharmacists, other healthcare professionals, law enforcement personnel, and the general public become more aware of both the use and abuse of pain medications will enable all of us to make proper and wise decisions regarding the treatment of pain.

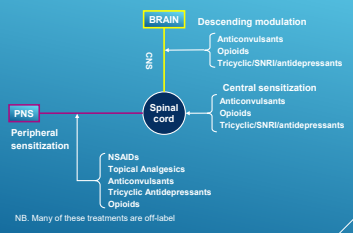
MEDICATIONS

- Rest, elevation, ice
- Nonsteroidal medication
- Antiseizure medication (gabapentin, pregabalin, topiramate)
- Antidepressant medication (amitriptyline, trazodone, duloxetine)
- Clonidine

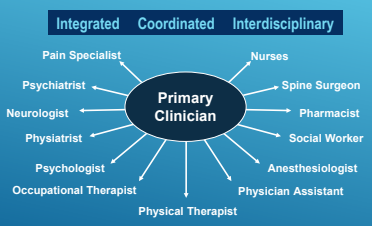
MEDICATIONS

- Refer to interventional pain physician (anesthesiologist/physical medicine and rehabilitation physician)
- Refer to surgeon
- Refer for cognitive behavioral therapy, relaxation techniques, biofeedback etc.
- Marijuana/CBD products
- Most likely will require combination of all the above

HOW PHARMACOTHERAPEUTICS AFFECT THE NERVOUS SYSTEM



CONSIDER THE MULTIDISCIPLINARY TEAM APPROACH



PHARMACOTHERAPY OPTIONS*

- Antidepressants
- Anticonvulsants (AED)
- Muscle relaxants
- Opioid analgesics
- Corticosteroids
- NSAIDs
- Topical analgesics

ORAL/IV ANALGESICS (NSAIDS)

Advantages
- Useful for mild-to-moderate pain
- Widely available
- Synergistic with opioids
- Easily administered

Disadvantages
- Potentially serious side effects (GI distress, renal toxicity, bleeding)
- Many are expensive

Agency for Health Care Policy and Research. Management of Cancer Pain: Clinical Practice Guideline, Number 9, AHCPR Pub. No. 94-0592, 1994:42-45

NEUROPATHIC PAIN MEDS

- Neurontin, Lyrica, and other anti seizure medications (AED)
- Decrease neuronal firing/activity
- Neuronal stabilization

ANTIDEPRESSANTS

- TCA
- SSRI
- SNRI

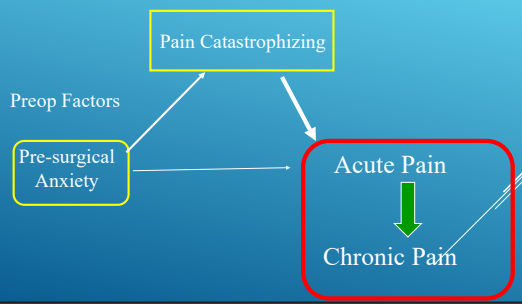
Essentials of addiction medicine Abigail J Herron 2015

OTHER NEUROPATHIC RX

- TCA's (Nortriptyline, Amitriptyline, Desprimine)
  - Have cholinergic s/e
  - Not the greatest for cardiac pts—esp Amitriptyline

Essentials of addiction medicine Abigail J Herron 2015

PSYCHOLOGICAL FACTORS AND SURGERY



EVALUATION

- History... when, where, why, who, how much
- Effect on ***your*** life
- ***listen***

EVALUATION *CONDT.*

- Physical exam
- Touch the patient
- Touch the patient **emotionally**

PAIN AND DISABILITY

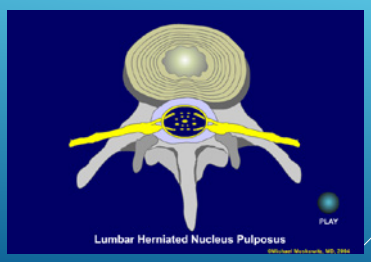
- Waddell signs

pain out of proportion to exam
pain non anatomic sensory/motor distribution
pain not consistent with exam
pain to superficial exam inconsistent reporting of pain

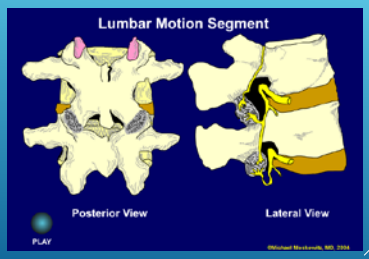
DIFFERENTIAL DIAGNOSIS

- Degenerative
- Metabolic
- Rheumatic disease
- Systemic disease
- Infectious
- Ischemia
- Intra abdominal/pelvic
- Cardiovascular

LUMBAR ANATOMY *CAUSES FOR MY PAIN*



ANATOMY



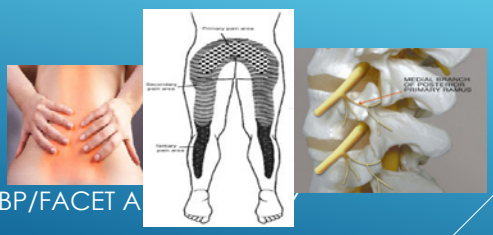
THE CHALLENGES YOU WILL FACE

- Chronic low back pain
- Radiculopathy
- Post Laminectomy syndrome

CHRONIC LOW BACK PAIN (CLBP)

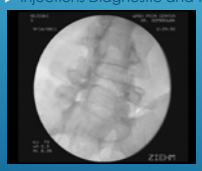
- 68 y/o men with clbp since the age of twenty. The pain has only increased with age. The pain is usually managed with Advil and heat. He will often increase his smoking and drinking to 'help' the pain. He is divorced. He works in capital hill at a desk. He has a sleep disturbance

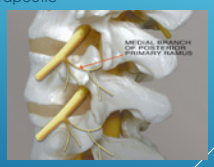
CLBP/FACET A



FACET ARTHROPATHY

- Injections Diagnostic and therapeutic

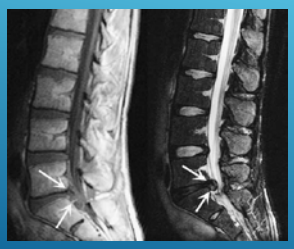




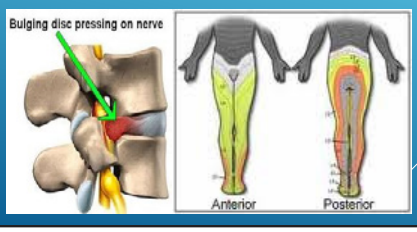
RADICULOPATHY

- 32 y/o man lifting construction equipment and felt his back go out. The pain is significant and is unilateral. The pain radiates to the buttock ,lateral thigh and the to top of the foot. The patient also notes some weakness with lifting his big toe.

RADICULOPATHY



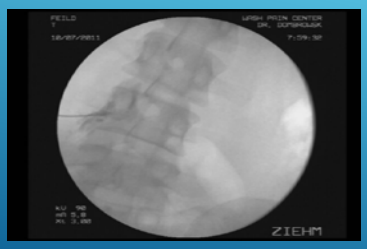
RADICULOPATHY



RADICULOPATHY

- Treatment
  - Medrol dose pak
  - Physical therapy/Time
  - Antiseizure medications
  - TCA
  - Consider injections

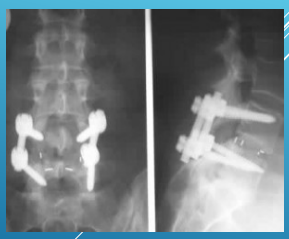
RADICULOPATHY



POST LAMINECTOMY SYNDROME

- 72 y/o woman with three previous lumbar surgeries. She has a fusion. The patient is currently taking OxyContin 40 mgs 1 po tid. She is also taking Hydromorphone 2mgs qid for breakthrough pain. She is on Flexeril. The pain radiates to both legs. She is limited with her ADLs.

POST LAMINECTOMY SYNDROME



POST LAMINECTOMY SYNDROME

- Treatment
- tca/ssri/snri
- antiseizure medications
  clonidine
- More opioid?
- Cognitive behavioral therapy/ Coping Skills
- Physical Therapy

POST LAMINECTOMY SYNDROME

- Interventions
- consider selective nerve blocks
- consider spinal stimulation

POST LAMINECTOMY SYNDROME

Spinal Stimulation-Precise delivery of small doses of electricity or drugs directly to targeted nerve sites.

DEFINITION OF NEUROMODULATION

Neuromodulation is the electrical or chemical modulation of the central nervous system to significantly reduce chronic pain or improve neurologic function.

NEUROMODULATION

- Treatment for post lumbar/cervical laminectomy syndrome
- Pelvic and visceral pain
- Peripheral vascular disease
- Refractory angina
- Migraine-Posterior occipital syndrome
- Patient with degenerative joint disease or lumbar canal stenosis who do not wish surgery
- *Neuropathy-Diabetic and Chemotherapy Studies ongoing.*

ADVANTAGES OF SCS THERAPY

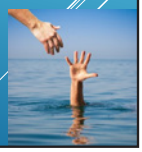
- Safe
- Testable
- Non-destructive-No change in anatomy
- Mostly reversible
- Long-term cost is low

DISADVANTAGES OF SCS THERAPY

- Limited to very specific indications and diseases-Maybe?
- Refractory on some patients
- Equipment failure
- Short-term cost is high
- Follow-up
- Steep learning curve

HAVING A PLAN TO REFER OUT

- This is no sign of weakness
- Quickly realize that the patient NOT getting better or is becoming problematic
- Obtain a consult with a pain medicine physician, psychiatrist, addiction medicine physician
- You to have an obligation to treat however this obligation cannot be taken advantage of.



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SELF EVALUATION

Managing Acute Pain in the Primary Care Setting

True/False

1. A patient presenting with acute pain in the primary care or dental setting should always be offered short-term narcotic therapy first.

2. Use of antiseizure medications for acute pain would be considered off label use?

3. Clonidine and alpha 2 agonist can be helpful with patients with chronic pain issues and chronic hypertension?

4. Patients with a chronic pain issue are usually best treated by a single physician and not in a multidisciplinary approach.

5. Patients with chronic low back pain located at the waist and possibly radiating to the lower legs should be presumptively diagnosed with lumbar facet arthropathy.

6. Patients presenting with low back pain with radiating pain into the right hip lateral aspect of the right thigh into the top of the foot should obtain an MRI to determine the diagnosis.

7. The referring physician should know the skill set of the individual that is performing a trial of spinal cord stimulation.

Answer Key: 1. F, 2. F, 3. T, 4. F, 5. T, 6. F, 7. T

Carole C. Foos, CPA

Carole Foos, CPA, of Cincinnati, Ohio, is a partner in OJM Group, a physician focused financial planning and asset management firm and a Certified Public Accountant (CPA) offering tax analysis and tax planning services to the firm's clients. Ms. Foos has over 25 years of experience in accounting, tax planning and financial consulting. She is a co-author of numerous books for physicians, including Wealth Management Made Simple and Wealth Planning for the Modern Physician: Residency to Retirement. Ms. Foos has authored numerous articles and presented many lectures, webcasts, and podcasts on tax planning and wealth management.

You may contact Ms. Foos with any questions or comments at (513) 309–3946 or by email at carole@ojmgroup.com.

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Maximizing Practice Profitability: Metrics, Analyses, and Strategies

Carole C. Foos, CPA

OJMGROUP

Maximizing Practice Profitability: Metrics, Analyses, and Strategies

PRESENTED BY:

Carole Foos, CPA
OJM Group Partner

Introduction

- Understanding Key Financial Ratios
- Improving Cash Flow Management
- Maximizing Profitability through Financial Analysis
- Implementing Strategies for Success

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UNDERSTANDING KEY FINANCIAL RATIOS

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Current Ratio

- Measures practice's ability to cover short-term liabilities with short–term assets
- Divide current assets (cash, A/R, inventory) by current liabilities (A/P, accrued expenses, short-term debt)
- Ratio of 1 or higher indicates ability to pay short-term obligations
  - <1 may signal liquidity issues
  - Ratio of 1.5 – 2.0 is considered healthy for a medical practice generally
  - Makes sense to benchmark your ratio against industry / specialty averages

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Current Ratio

- Factors Affecting Current Ratio
  - A/R Management - collection % and days in A/R
  - Inventory management – excess ties up working capital; too little impacts revenue
  - A/P Management – extending payment with vendors can improve current ratio
- Trend Analysis
  - Monitor changes over time to identify trends and financial challenges
- Compare with industry benchmarks
- Use in decision making
  - Determine need for additional financing
  - Evaluate impact of investment decisions
  - Identify areas for operational improvements

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Working Capital

- Indicates practice's liquidity and short-term financial health
- Difference between practice's current assets and current liabilities
- Regularly calculating ensures enough funds to cover expenses such as salary, rent, utilities, supplies
- Identifying surplus or deficit in WC allows owners to proactively maintain or improve liquidity
- Essential when planning for growth or expansion
- Mitigates financial risks associated with liquidity
- Monitor changes in WC over time to identify trends
- Calculation can help optimize cash flow management
  - Determine when to accelerate A/R, improve billing / collections
  - Negotiate better terms with suppliers or extend payment deadlines
  - Streamline inventory management

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Days in Receivables / Payables

- Days in Receivables indicates time it takes from patient service to collection
- Days in Payables = receipt of product or service to date of payment
- Improving Days in Receivables
  - Accurate and timely billing / accurate coding
  - Verify insurance information up front
  - Review claim rejections / re-processing
  - Spotlight problem payers
  - Regularly review and update billing codes
  - Monitor claim status and follow up
  - Implement clear and consistent patient collection policies
  - Train staff to effectively communicate with patients
  - Utilize technology solutions such as RCM software or outsourced billing, processing and collections
  - Use analytics to identify trends and patterns
  - Benchmark against industry standards
  - Establish relationships with payers / insurance companies
  - Stay informed about reimbursement policy changes

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IMPROVING CASH FLOW MANAGEMENT

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Cash Flow Statement

- Provides sources and uses of cash over a specific period from
  - Operations
  - Investing
  - Financing
- Operating Cash Flow (OCF)
  - Assess ability to generate cash from core business operations (patient care)
  - Positive OCF = GOOD!!
  - Monitor trends to identify fluctuations, seasonal patterns that could impact working capital
- Investing Cash Flow
  - Evaluate investments in assets such as medical equipment, facilities, technology
  - Assess impact of capital expenditures on growth objectives and long-term strategy
  - Use it to evaluate timing and magnitude of investment activities

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Cash Flow Statement

- Financing Cash Flow
  - Understand sources and uses of external financing (loans, lines of credit, capital contributions)
  - Evaluate impact of financing on overall cash position and debt levels
  - Monitor changes in debt repayments, dividends, or equity transactions
- Net Cash Flow and Cash Balance
  - Calculate net increase or decrease to determine whether practice generated or consumed cash for the period
  - Monitor changes in cash balance to ensure liquidity
  - Maintain a target cash reserve for emergencies / contingencies
- Cash Flow Ratios
  - OCF / Total Revenue and OCF/Total Debt
  - Compare to industry benchmarks
- Cash Flow Forecasting
  - Use historical data to forecast future flows and for budgeting

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MAXIMIZING PRACTICE PROFITABILITY

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Revenue and Expense Trends

- Revenue Trends
  - Total Revenue
  - Revenue Sources
  - Revenue Mix
  - Revenue Growth Rate
  - Revenue per Patient Visit
- Expense Trends
  - Total Expenses
  - Expense Categories
  - Expense Ratios
  - Expense Trend Analysis
  - Expense Control Measures
- KPI's
  - Operating margin to assess profitability from core operations
  - Profitability ratios
  - Provider productivity
  - Patient retention and acquisition
- Benchmark against industry, peers, historical
- Budget Variance Analysis

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Operating Margin

- Percentage of revenue remaining after deducting operating expenses excluding interest, taxes and non-operating items
- Provides insight into efficiency and profitability
  - Indicates efficiency in various areas such as patient consultations, diagnostic tests, treatments and procedures
  - Higher operating margin suggests effective management of expenses relative to revenue
- Cost Management
  - Higher operating margin suggests better cost management
- Operational Efficiency
  - Efficiently run practices can optimize revenue while minimizing expenses
  - Efficiency in patient and staff scheduling, workflows, and revenue cycle management
- Ability to cover fixed costs
- Compare with industry, peer group and historical benchmarks

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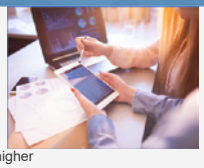
Performance Indicators

- Patient Volume
  - Number of patients seen / treated in a specific period
  - Indicator of Demand
  - Potential for Growth
  - Helps assess capacity utilization
  - Identify trends
- Average Revenue per Patient
  - Average revenue per patient encounter
  - Higher average may indicate broader range of services / higher value treatments
  - Cross selling opportunities – screenings, tests, treatments
- Provider Productivity
  - Measures efficiency of each provider
  - Ability to see more patients, diagnose conditions, and perform treatments
  - Identifies high-performing providers so practices can appropriately incentivize, optimize schedules, provide resources



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IMPLEMENTING STRATEGIES FOR SUCCESS

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Implementation

- Regular Monitoring
- Invest in Technology
- Staff Training
- Seek Professional Help

By leveraging key financial ratios and conducting thorough financial analysis, you can significantly enhance your medical practice's efficiency, cash flow management, and profitability. Remember, proactive financial management is essential for the long-term success of your practice.

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PERSONAL WEALTH PLANNING

DIAGNOSTIC vs. TREATMENT

ADVICE & EXPERTISE FOR A FLAT FEE

BUILDING A RELATIONSHIP

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Wealth Strategies for Today's Physician: A Multi-Media Playbook

- New content from OJM: Our first book since 2020!
- Co-authored by OJM Group partners
- Innovative multi-media format includes more than 90 links to videos and podcast episodes that offer unique perspectives and real-world examples
- Videos to be periodically updated by OJM so that the Playbook remains current over time
- Crafted in six informative Strategies that can help physicians protect assets, reduce taxes, invest wisely and build wealth for retirement
- Bonus Strategy for medical practice owners and *doctorpreneurs*

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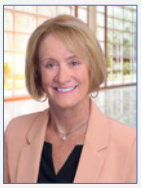

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Schedule a Free Consultation

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SELF EVALUATION

Maximizing Practice Profitability: Metrics, Analyses, and Strategies

True/False

1. Current Ratio is used to measure practice's ability to cover short term liabilities with short term assets.
2. A current ratio of 0.5 indicates strong liquidity.
3. Working capital is the difference between current assets and current liabilities.
4. Accurate coding has no effect on Days in Receivables.
5. Negative operating cash flow indicates a healthy practice.
6. Patient Volume is a performance indicator that provides insight into practice efficiency.
7. Proper utilization of practice management software and financial tools can streamline processes and improve efficiency.

Answer Key: 1. T, 2. F, 3. T, 4. F, 5. F, 6. T, 7. T

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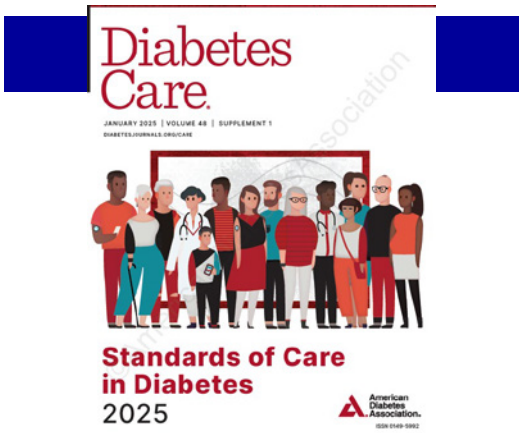
Rethinking Type 2 Diabetes: Cardiometabolic Priorities in Modern Practice



NOT on the Agenda

- DM in Pregnancy
- DM on Dialysis
- Hospital Management of DM
- Pediatric DM Management

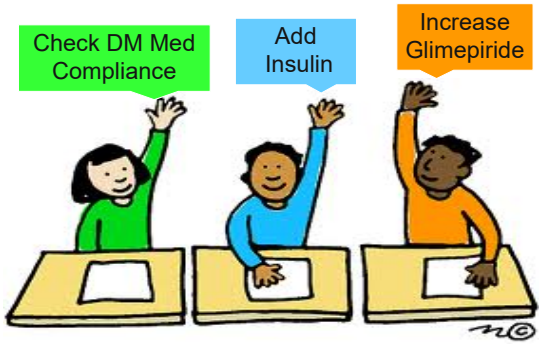
An Abbreviated Case Study

64 y.o. aSx Obese ♀(BMI 33.5), T2DM X 15 yrs

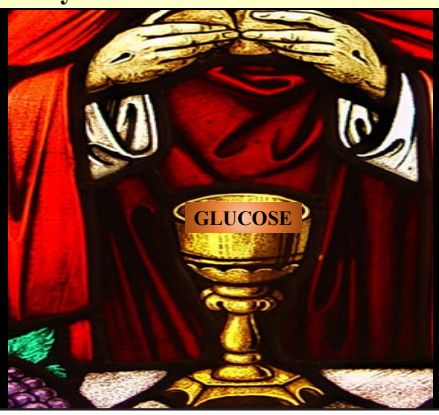
- PMH: MI 2 years ago
  - Metformin 1g b.i.d. + Glimepiride 4mg qd
  - ASA 81 mg qd
  - Atorvastatin 40 mg qd
- Glucose
  - FBS: 160-200 mg/dL
  - Lunch postprandial: 220-300 mg/dL
- HbA1c = 9.8

WHAT SHOULD WE DO NEXT?

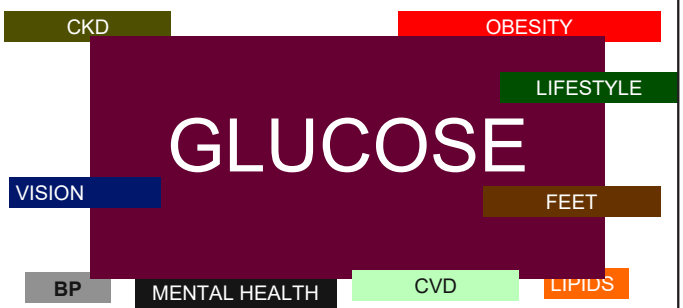
WHAT SHOULD WE DO NEXT?



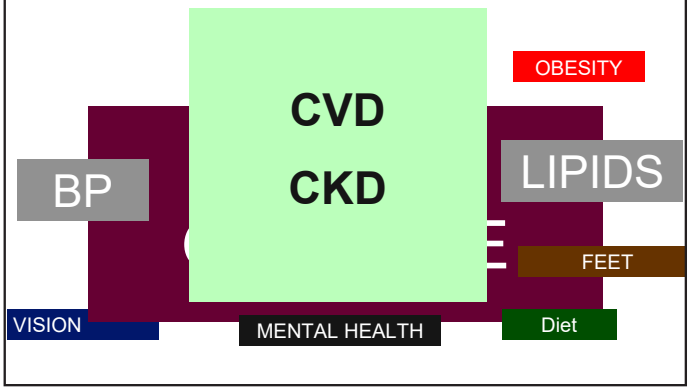
The "Holy Grail' of Diabetes: Prior To 2015



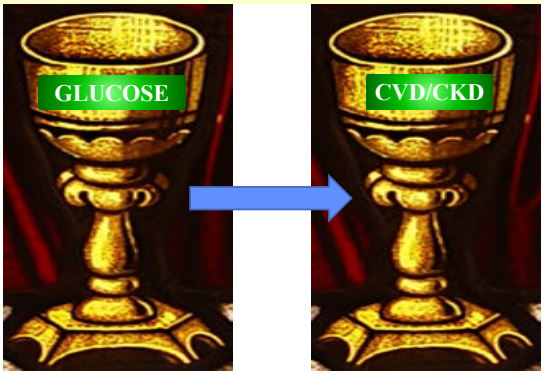
WHAT's THE PROBLEM?



What's THE Problem?



The "Holy Grail' of Diabetes: Since 2015



Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

FDA 2008 Guidance for Industry

"Specifically, this guidance makes recommendations about how to demonstrate that a new antidiabetic therapy to treat T2DM is not associated with an **unacceptable increase** in CV risk."

Emphasis added

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071627.pdf accessed January 6, 2019

GLUCOTROL XL®

(glipizide)
Extended Release Tablets
For Oral Use

Prescribing Information

Glucotrol XL Prescribing Information (2016)
(glipizide)

PRECAUTIONS

General

Macrovascular outcomes: There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with GLUCOTROL or any other anti-diabetic drug

Glucotrol XL Prescribing Information (2016)
(glipizide)

WARNINGS
SPECIAL WARNING ON INCREASED RISK OF CV MORTALITY:
The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin.
(Emphasis added)

Glucotrol XL Prescribing Information (2016)
(glipizide)

WARNINGS
SPECIAL WARNING ON INCREASED RISK OF CV MORTALITY:

This warning is based on the study conducted by the UGDP, a long-term PCT trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes.

UGDP (University Group Diabetes Program)

- Study (1970): T2DM (n=823)
- Rx (X9 years): Diet +
  - Fixed dose insulin (weight based12-16 u/d)
  - Variable dose insulin (to normalize glucose)
  - SFU (Tolbutamide)
  - Placebo
- Outcome: Cardiovascular Events

Meinert CL "The Trials & Tribulations of the UGDP" 2015 Kelmscott Bookshop, Baltimore

UGDP (University Group Diabetes Program)

Diabetes 1970;19:(Suppl 2):747-830

Results: CV mortality
- SFU (Tolbutamide) vs placebo RR = 2.5*
- Insulin vs placebo RR = ±1**

*Glucotrol PI.
**Meinert CL "The Trials and Tribulations of the UGDP" 2015 Kelmscott Bookshop, Baltimore

2014

Effect of Aleglitazar on Cardiovascular Outcomes After Acute Coronary Syndrome in Patients With Type 2 Diabetes Mellitus
The AleCardio Randomized Clinical Trial

IMPORTANCE No therapy directed against diabetes has been shown to unequivocally reduce the excess risk of cardiovascular complications. Aleglitazar is a dual agonist of peroxisome proliferator-activated receptors with insulin-sensitizing and glucose-lowering actions and favorable effects on lipid profiles.

Lincoff AM et al *JAMA* 2014;311(15):1515-1525

CV Safety Trial Showing CV Risk REDUCTION

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

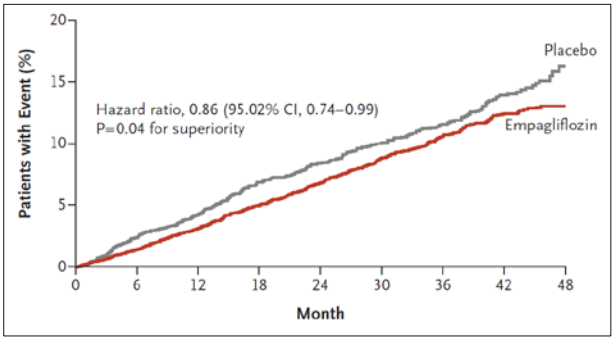
Zinman B et al *N Engl J Med*. 2015;373(22):2117-2128

CVOT: Empagliflozin (EMPA-REG)

- Study: RDBPCT T2DM Adults (n=7,020)
- Rx: empagliflozin 10 or 25 mg qd
- Inclusion :
  - ASCVD +
  - GFR >30
  - BMI <45
- 1^0 Outcome: CV death, nonfatal MI & stroke

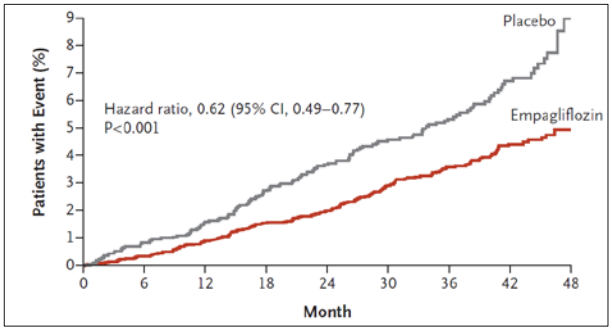
Zinman B et al *N Engl J Med* 2015;373(22):2117-2128

EMPA-REG 1^0 Outcome (CV Death, Fatal/nonfatal MI & Stroke)



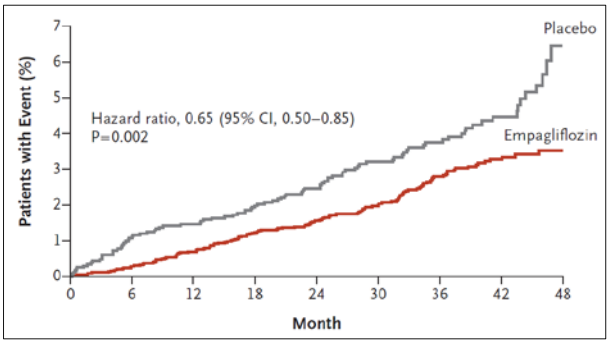
Zinman B et al *N Engl J Med* 2015;373(22):2117-2128

EMPA-REG: CV Death



Zinman B et al *N Engl J Med* 2015;373(22):2117-2128

EMPA-REG: Heart Failure Hospitalization



Zinman B et al *N Engl J Med* 2015;373(22):2117-2128

CV Safety Trial Showing CV Risk REDUCTION Empagliflozin

Endpoint [a] = primary endpoint * = all p < 0.05	Rate/100 pt-years		Hazard Ratio * (95% CI)
	Empa	Pbo	
CV death, nonfatal MI & stroke	3.74	4.39	0.86 (0.74-0.99)
All cause mortality	1.94	2.86	0.68 (0.57-0.82)
CV death	1.24	2.02	0.62 (0.49-0.77)
HF hospitalization	0.94	1.45	0.65 (0.50-0.85)
HF hospitalization of CV death (excluding fatal stroke)	1.97	3.01	0.66 (0.55-0.79)

Zinman B et al *N Engl J Med*. 2015;373(22):2117-2128

CV Safety Trial Showing CV Risk REDUCTION Canagliflozin

Endpoint [a] = primary endpoint * = all p < 0.05	Rate/100 pt-years		Hazard Ratio* (95% CI)
	Cana	Pbo	
CV death, nonfatal MI & stroke[a]	2.69	3.15	0.86 (0.75-0.97)
HF hospitalization	0.55	0.87	0.67 (0.52-0.87)
CV death or HF hospitalization	1.63	2.08	0.78 (0.67-0.91)
Progression of albuminuria	8.94	12.87	0.73 (0.67-0.79)
40% ↓ eGFR, renal dialysis or transplantation, renal death	0.55	0.90	0.60 (0.47-0.77)

Neal B, et al. *N Engl J Med*. 2017;doi:10.1056/NEJMoa1611925.

CV Safety Trial Showing CV Risk REDUCTION Liraglutide

Endpoint [a] = primary endpoint * = all p < 0.05	Rate/100 pt-years		Hazard Ratio (95% CI) *
	Lira	Pbo	
CV death, nonfatal MI & stroke[a]	3.4	3.9	0.87 (0.78-0.97)
1^0 + revascularization, unstable angina, or HF hospitalization	5.3	6.0	0.88 (0.81-0.96)
All cause mortality	2.1	2.5	0.85 (0.74-0.97)
CV death	1.2	1.6	0.78 (0.66-0.93)
Microvascular event	2.0	2.3	0.84 (0.73-0.97)
Nephropathy	1.86	3.06	0.78 (0.67-0.92)

Marso SP, et al. *N Engl J Med*. 2016;375(4):311-322.

CV Safety Trial Showing CV Risk REDUCTION Semaglutide (SQ)

Endpoint [a] = primary endpoint * p < 0.05	Rate/100 pt-years		Hazard Ratio (95% CI)
	Sema	Pbo	
CV death, nonfatal MI & stroke[a]	3.24	4.44	0.74 (0.58-0.95)*
1^0 + revascularization, unstable angina, or HF hospitalization	6.17	8.36	0.74 (0.62-0.89)*
All cause mortality	1.82	1.76	1.05 (0.74-1.50)
CV mortality	1.29	1.35	0.98 (0.65-1.48)
Nonfatal stroke	0.80	1.31	0.61 (0.38-0.99)*
New or worsening nephropathy	1.86	3.06	0.64 (0.46-0.88)*

Marso SP, et al. *N Engl J Med*. 2016;375(19):1834-1844.

DM: Dx

A1c ≥ 6.5%

FPG ≥ [illegible]

2-hr OGTT Glucose ≥200 mg/dL

X2 Mix or Match

Random Glucose ≥200 mg/dL + Typical Sx

Diabetes—2025

Diabetes Care 2025;48(Suppl. 1):S27–S49 | https://doi.org/10.2337/dc25-S002

ADA Standards of Care *Diabetes Care* 2025;48(Suppl 1):S27-S49

DM Diagnostics*

	WNL	PreDM (ANY)	DM (ANY)
FBS (mg/dL)	≤99	100-125 (IFG)	≥126
A1c (%)	≤5.6	5.7-6.4	≥6.5
2 hr OGTT (mg/dL)	≤139	140-199 (IGT)	≥200
Random Glucose	(with classic Sx)		≥200
CGM	Insufficient Evidence		

* **In the absence of 'unequivocal hyperglycemia' must have two + results**

ADA Standards of Care *Diabetes Care* 2024;47(Suppl 1):S20-S42

DM Dx: What We'd ***Like*** to See if Patient Is Diabetic

A1c ≥ 6.5

FBS ≥ 126

2hr PPG >200

Meijnikman AS, et al. *Int J Obesity* 2017;41:1615-1620

A1c↔Glucose Discordance
Anything That Alters RBC Lifespan

- Anemia
- Folate Deficiency
- Thalassemia
- G6PD G202a Gene Variant
  - Homozygous ♂ → A1c ↓ 0.8%
  - Homozygous ♀ → A1c ↓ 0.7%

ADA Standards of Care *Diabetes Care* 2024; 47(Suppl 1):S20-S42

Delay in Dx of T2DM

What about 'Masked Diabetes'?

- 58 y.o. BMI 36, failed diet/exercise
- A1c = 6.4 (prediabetic)
- FBG = 120 mg/dL (IFG/prediabetic)
- On metformin 500 mg b.i.d.
- Out of luck ($$) for weight loss meds?

"Masked diabetes"

WHICH Dx Tool?
A1c---OGTT--FBS

- Study: Overweight/Obese subjects (n=1,241)
- Inclusion: no Hx DM
- Demographics (all Caucasian)
  - Age (mean): 44 (±13)
  - BMI (mean): 38.0 (±6.1)
  - Male:43%

Meijnikman AS, et al. *Int J Obesity* 2017;41:1615-1620

DM Dx: At-risk Reality
(n=1,241 Obese Non-DM Adults)

Dx with Pre-Diabetes

WNL	IFG	IGT	IFG+IGT	A1c 5.7-6.4
512	17	379	63	122

Dx with Diabetes

2hr PPG	A1c & FBG WNL
148	70

Meijnikman AS, et al. *Int J Obesity* 2017;41:1615-1620

WHICH Dx Tool?
A1c---OGTT--FBS

"The data suggest that **not performing** an OGTT results in significant underDx of T2DM …."

Meijnikman AS, et al. *Int J Obesity* 2017;41:1615-1620

Bone Health

Bone Health

- "Fracture risk should be assessed in older adults with DM as a part of routine care…."
- Hip Fx RR 1.79 vs non-diabetic
- DM control: 1% ↑A1c ≈ 8% ↑Fx risk
- DEXA q2-3 years in:
  - Older (>65) high-risk adults (♂ & ♀)
  - Adults <65 with multiple risk factors

ADA Standards of Care *Diabetes Care* 2025; 48(Suppl 1):S59-S85

T2DM: Is FRAX Good Enough?

- FRAX: DM not included
- "…inclusion of [DM] is estimated to mirror… a 10-year age ↑ or 0.5 SD ↓in BMD T-score."
- "…a T-score of ≤2.0 should be interpreted as equivalent to -2.5…."

ADA Standards of Care *Diabetes Care* 2025; 48(Suppl 1):S59-S85

↓T-Score Threshold for Rx in T2DM

"In T2DM, since T-score underestimates fracture risk…a T-score ≤2.0 may be more appropriate for considering initiation of a 1st-line drug, including bisphosphonates (alendronate, risedronate, and zolecdronic acid) or denosumab."

ADA Standards of Care *Diabetes Care* 2025; 48(Suppl 1):S59-S85

T2DM: Sexual Health

- Screen for sexual health issues (♂ & ♀) in persons with PreDM or DM
  - ♂ Low Libido: AM total testosterone
  - ♀: screen for GU syndrome of menopause

ADA Standards of Care *Diabetes Care* 2025;48(Suppl 1):S59-S85

Hepatic Health
NAFLD (AKA MASLD)

NAFLD: Why Bother?
MASLD: Metabolic-Associated Steatotic Liver Disease

"Recent studies in adults in the U.S. estimated that NAFLD is prevalent in >70% of people with T2DM."

ADA Standards of Care *Diabetes Care* 2024;47(Suppl 1):S43-S51

MASLD: Metabolic Associated Steatotic Liver Disease Can't I just Look at LFT's?

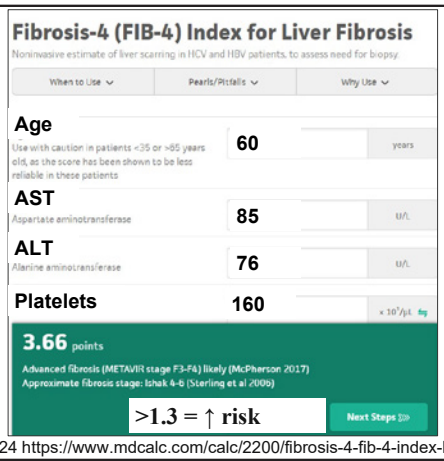
"A screening strategy based on elevated aminotransferases >40 u/L would miss most individuals…."

ADA Standards of Care *Diabetes Care* 2025;48(Suppl 1):S59-S85

MASLD: STEP 1

"Screen adults with T2DM (or PreDM)…for MASH using a calculated fibrosis-4 index…even if they have normal liver enzymes."

ADA Standards of Care *Diabetes Care* 2025;48(Suppl 1):S59-S85



Accessed 7/4/24 https://www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis

MASLD: STEP 2

"Adults with T2DM or preDM with a FIB-4≥1.3 should have additional risk stratification by liver stiffness measurement with transient elastography or… the enhanced liver fibrosis (ELF) test."

ELF Score High Risk = >7.7
Transient Elastography High Risk = >12 kPa

ADA Standards of Care *Diabetes Care* 2025;48(Suppl 1):S59-S85

MASLD: STEP 3 Referral to GI/Hepatologist

"Refer adults with T2DM or preDM at higher risk…(as indicated by FIB-4, liver stiffness measurement, or ELF)…for further evaluation."

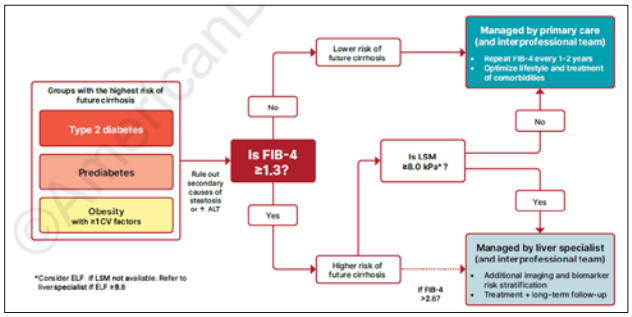
ADA Standards of Care *Diabetes Care* 2025;48(Suppl 1):S59-S85

MASLD: 3 STEPS

- ALL Adult T2DM FIB-4
- + FIB-4→ Liver Stiffness (ELF/Elastography)
- High risk liver stiffness (>8 kPa) → GI

ADA Standards of Care *Diabetes Care* 2025;48(Suppl 1):S59-S85

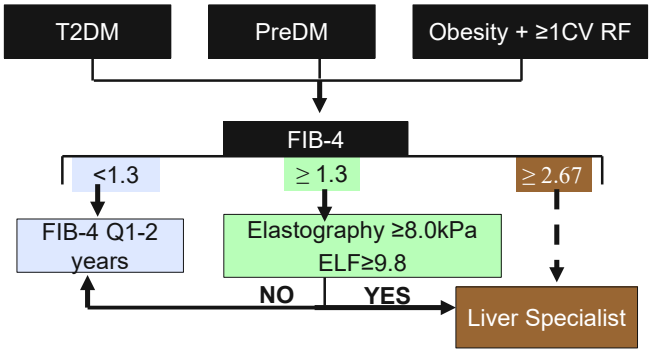
Dx Algorithm for the Prevention of Cirrhosis in People with MASLD



ADA Standards of Care *Diabetes Care* 2025;48(Suppl 1):S59-S85

MASLD: Cirrhosis Prevention Algorithm

(2^0 causes of steatosis/↑ALT excluded)



Adapted from ADA Standards of Care *Diabetes Care* 2025;48(Suppl 1):S59-S85

MASLD: Rx

- Weight Loss
- Pioglitazone
- Liraglutide
- Semaglutide
- Resmetirom: thyroid receptor-β agonist

ADA Standards of Care *Diabetes Care* 2025;48(Suppl 1):S59-S85

Glycemic Goals

Glycemic Goals: Nonpregnant Adults

- A1c < 7.0%
  - Less stringent if ↓life expectancy, R > B
- TIR (70mg/dL-180 mg/dL) >70% with
  - TBR <4%
  - Time <54 mg/dL <1%
  - Less stringent if frail or ↑hypoglycemia risk
- Lower A1c potentially beneficial if attainable without excessive AEs

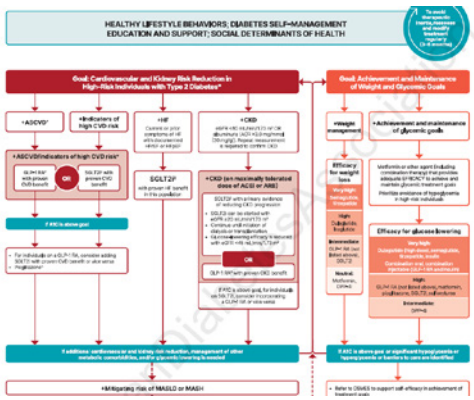
ADA Standards of Care *Diabetes Care* 2024; 47(Suppl 1):S111-S125

Glycemic Goals: Nonpregnant Adults

- FBS: 80-130 mg/dL
- PPG (1-2 hrs. postmeal): <180 mg/dL

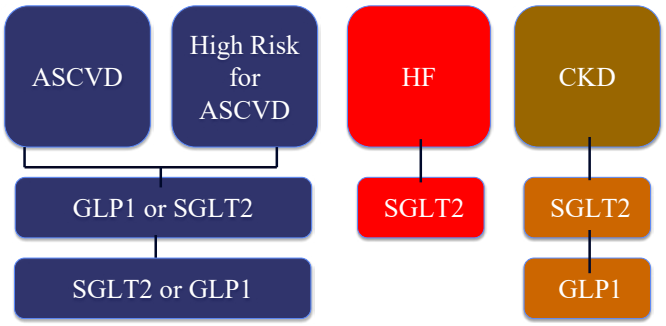
ADA Standards of Care *Diabetes Care* 2024; 47(Suppl 1):S111-S125

Pharmacologic Rx



ADA Standards of Care *Diabetes Care* 2025; 48(Suppl 1):S181-S206

Pharmacotherapy: ADA 2025



ADA Standards of Care *Diabetes Care* 2025;48(Suppl 1):S181-S206

What Does ASCVD Mean?

- Any MANIFEST Atherosclerotic Vascular Disease
  - MI
  - Stroke
  - TIA
  - Bypass
  - PCI
  - +CAC
  - + Carotid Scan
  - PAD

ASCVD

ADA Standards of Care *Diabetes Care* 2024;47(Suppl 1):S158-S178

What Does "High Risk for ASCVD" Mean?

- Age > 55
  +
- Obesity
- HTN
- Smoking
- Dyslipidemia
- Albuminuria

≥2

High Risk for ASCVD

ADA Standards of Care *Diabetes Care* 2024;47(Suppl 1):S158-S178

What Does "HF" Mean?

- HFrEF
- HFpEF

HF

ADA Standards of Care *Diabetes Care* 2024;47(Suppl 1):S158-S178

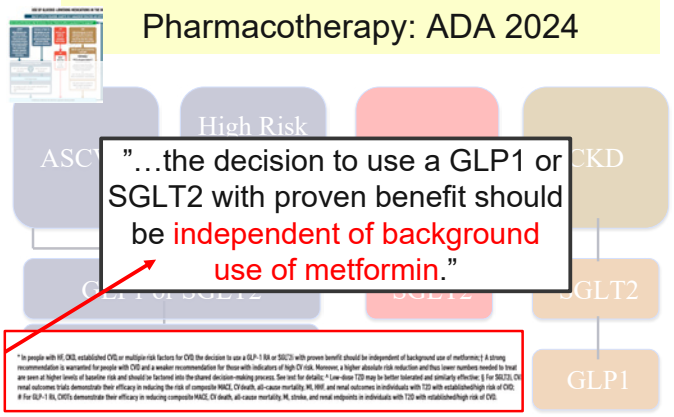
What Does "CKD" Mean?

- GFR <60 ml/min
- UACR ≥30 mg/g

CKD

ADA Standards of Care *Diabetes Care* 2024;47(Suppl 1):S158-S178

Pharmacotherapy: ADA 2024



ADA Standards of Care *Diabetes Care* 2024; 47(Suppl 1):S158-S178

Pharmacotherapy
1st Things 1st

"…GLP1RA, SGLT2i, **with or without metformin** based on glycemic needs **are appropriate initial Rx** for …T2DM with high risk for ASCVD, HF, and/or CKD." **A**

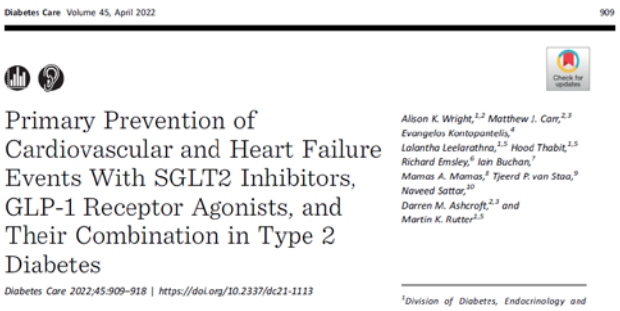
Diabetes Care 2022;45(Suppl. 1):S125–S143

Pharmacotherapy

"For people with T2DM and established ASCVD or indicators of high ASCVD risk, HF, or CKD, an SGLT2 I and/or GLP1 RA with demonstrated CV benefit is recommended…independent of A1c, independent of metformin use….."

ADA Standards of Care *Diabetes Care* 2024;47(Suppl 1):S158-S178

Pharmacotherapy: SGLT2 + GLP
How Much Cluck for Your Buck


Diabetes Care Volume 45, April 2022 909

Primary Prevention of Cardiovascular and Heart Failure Events With SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Their Combination in Type 2 Diabetes

Alison K. Wright, Matthew J. Carr, Evangelos Kontopantelis, Lalantha Leelarathna, Hood Thabit, Richard Emsley, Iain Buchan, Mamas A. Mamas, Tjeerd P. van Staa, Naveed Sattar, Darren M. Ashcroft, and Martin K. Rutter

Diabetes Care 2022;45:909–918 | https://doi.org/10.2337/dc21-1113

Division of Diabetes, Endocrinology and

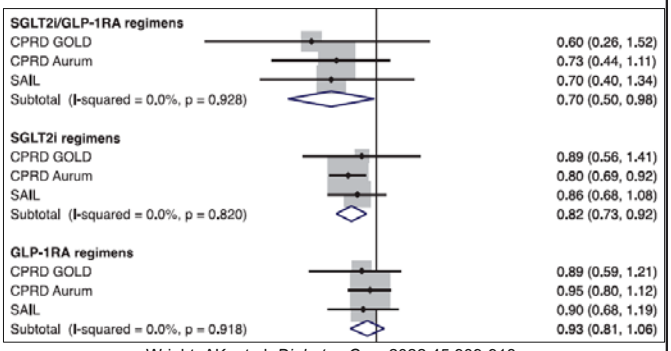
Wright AK, et al. Diabetes Care 2022:45:909-918

DM2: SGLT2 + GLP

- Study: UK database (n=336,334)
- Method: Case-control study(1:20)
- Inclusion:
  - T2DM
  - No evident CVD
- Outcome: MACE relative risk vs usual care*
  - SGLT vs usual care
  - GLP1 vs usual care
  - SGLT2 + GLP1 vs usual care

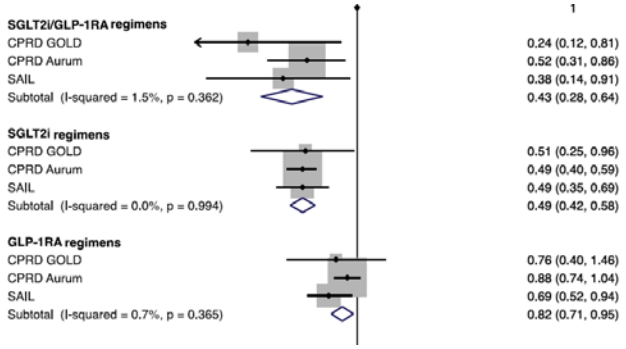
Wright AK, et al. *Diabetes Care* 2022:45:909-918

MACE: SGLT2 + GLP vs Control



Wright AK, et al. *Diabetes Care* 2022:45:909-918

CHF: SGLT2 + GLP vs Control



Wright AK, et al. *Diabetes Care* 2022:45:909-918

What if You're ASCVD High Risk, But Already at A1c Goal Without SGLT2i or GLP1?

"Individuals with these comorbidities already achieving their individualized glycemic goals with other medications may benefit from switching to these preferred medications…."

ADA Standards of Care *Diabetes Care* 2024; 47(Suppl 1):S145-S157

GLUCAGON For ALL ADA Standards of Care 2024

Glucagon should be prescribed for **all individuals taking insulin** or at high risk for hypoglycemia."

ADA Standards of Care in Diabetes 2024; *Diabetes Care* 2024;47(Suppl 1):S111-S125

GLUCAGON For ALL ADA Standards of Care 2024

"Family, caregivers, school personnel, and others providing support to these individuals should know its location and be educated on how to administer it."

ADA Standards of Care in Diabetes 2024; *Diabetes Care* 2024;47(Suppl.1):S111-S125

HTN

"All people with HTN and DM should be counseled to monitor their BP at home…."

On-Rx goal: <130/80 mm Hg

ADA Standards of Care *Diabetes Care* 2024;47(Suppl 1):S179-S218

HTN

"ACEi or ARBs are recommended 1st line therapy for HTN in people with diabetes and CAD….and ACR >30g albumin/g creatinine"

ADA Standards of Care *Diabetes Care* 2025;48(Suppl 1):S207-S238

HTN

- Rx Goal ≤130/80 mmHg
- Office BP ≥130/80 mmHg: pharmacologic Rx
- Office BP ≥150/90 mmHg: Start 2 meds
- Preferred: ACE, ARB, CCB, or Diuretic
- CAD or UACR >300 mg/g: ACE/ARB preferred

ADA Standards of Care *Diabetes Care* 2025;48(Suppl 1):S207-S238

ADA 2025 Lipid Recommendations

Age	CAD	Statin Intensity	LDL Goal	Evidence
40-75	NONE	Moderate	NS*	A
40-75	High Risk	High	<70 mg/dL	B
All	ASCVD	High	<55 mg/dL	B
20-39	RF+	Individualize	NS*	C

ADA Standards of Care *Diabetes Care* 2025;48(Suppl 1):S207-S238

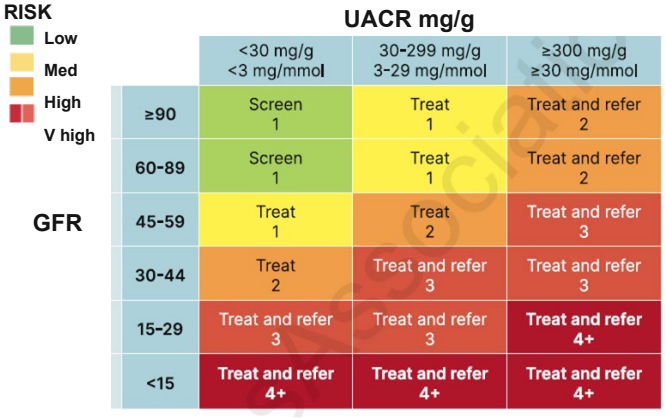
Antiplatelet Rx

Category	Agent	Evidence Level
1^0 Prevention	*ASA 75-162 mg/d	A
2^0 Prevention (Any ASCVD)	ASA 75-162 mg/d (Clopidogrel if ASA Allergy)	A

*After risk/benefit discussion

ADA Standards of Care *Diabetes Care* 2025;48(Suppl 1):S207-S238

CKD



ADA Standards of Care *Diabetes Care* 2025;48(Suppl 1):S239-S251

CKD: Albuminuria

"In people with T2DM and CKD with albuminuria Rx with maximum tolerated doses of ACEi or ARB, addition of finerenone should be considered to improve CV outcomes, including the risk for HF hospitalizations, and to reduce the risk of CKD progression."

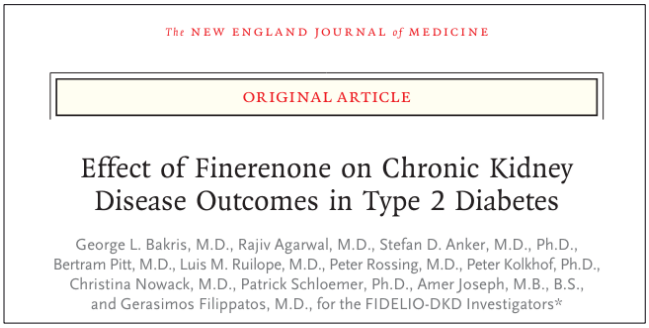
ADA Standards of Care *Diabetes Care* 2025;48(Suppl 1):S207-S238

CKD

" For individuals with T2DM and CKD with albuminuria treated with maximum tolerated doses of ACE or ARB, addition of finerenone is recommended to improve CV outcomes and reduce the risk of CKD progression."

ADA Standards of Care *Diabetes Care* 2024;47(Suppl 1):S179-S218

Finerenone (Kerendia)


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

George L. Bakris, M.D., Rajiv Agarwal, M.D., Stefan D. Anker, M.D., Ph.D., Bertram Pitt, M.D., Luis M. Ruilope, M.D., Peter Rossing, M.D., Peter Kolkhof, Ph.D., Christina Nowack, M.D., Patrick Schloemer, Ph.D., Amer Joseph, M.B., B.S., and Gerasimos Filippatos, M.D., for the FIDELIO-DKD Investigators*

Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD)

Bakris GL, et al *NEJM* 2020;383:2219-2229

Finerenone for DM CKD FIDELIO-DKD

- Study: DBRPCT DM CKD patients (n = 5,734)
- Inclusion
  - On max dose RAAS Blocker (ACEi/ARB)
  - Baseline K+ ≤4.8 mmol/L

AND EITHER

  - ACR 30-300 mg/g, GFR 25-60 ml/min, retinopathy

OR

  - ACR 300-5000 mg/g & GFR 25-75 ml/min
- Rx: finerenone 20 mg/d vs placebo X 2.6 years

Bakris GL, et al *NEJM* 2020;383:2219-2229

Finerenone for DM CKD FIDELIO-DKD

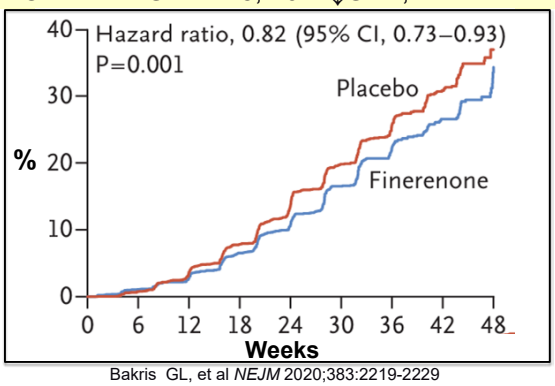
<u>OUTCOMES (at median 2.6 years)</u>

- 1^0 (composite): Kidney failure (GFR <15 ml/min), sustained 40% ↓GFR, renal death
- 2^0 (composite): CV death, nonfatal stroke, nonfatal MI, HF hospitalization
- Others

Bakris GL, et al *NEJM* 2020;383:2219-2229

Finerenone (FIDELIO-DKD)

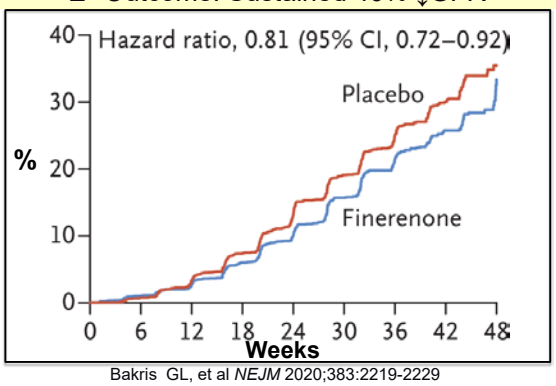
1^0 Outcome: GFR <15, 40% ↓GFR, Renal Death



Bakris GL, et al *NEJM* 2020;383:2219-2229

Finerenone (FIDELIO-DKD)

2^0 Outcome: Sustained 40% ↓GFR



Bakris GL, et al *NEJM* 2020;383:2219-2229

Kerendia (Finerenone) Indications

"For the Rx of CKD associated with T2DM to ↓ the risk of sustained eGFR decline and end-stage kidney disease, non-fatal MI, ↓ CV mortality, and ↓ of HF hospitalizations."

PDR Accessed 023-7-25

SELF EVALUATION

Rethinking Type 2 Diabetes: Cardiometabolic Priorities in Modern Practice

1. Which of the following classes of diabetes medications has shown both cardiovascular and renal protective effects?
    a. Sulfonylureas
    b. SGLT2 inhibitors
    c. DPP-4 inhibitors
    d. Meglitinides

2. T/F - GLP-1 receptor agonists have been associated with weight loss and reduced major adverse cardiovascular events in patients with type 2 diabetes.

3. T/F - Continuous glucose monitoring (CGM) is now recommended for both type 1 and insulin-treated type 2 diabetes.

4. Which of the following best describes “time in range” (TIR) as a glucose metric?
    a. Percent of days a patient checks blood glucose
    b. Time spent with glucose levels 70–180 mg/dL
    c. Number of hours per week below 54 mg/dL
    d. Mean HbA1c value across 3 months

5. T/F - FIB-4 screening is now recommended for all adult diabetic and prediabetic patients

Answer Key: 1. B, 2. T, 3. T, 4. B, 5. T

FACULTY

Kevin Klauer, DO, EJD

Kevin Klauer, DO, EJD, of Winter Park, Florida, is currently the Chief Executive Officer of the American Health Information Management Association and was formerly the System Chief Medical Officer HCA Florida and Ocala hospitals. He formerly served as CEO of the American Osteopathic Association and the Chief Medical Officer and Chief Risk Officer for TeamHealth. He holds the following faculty appointments: Clinical Asst. Professor, Michigan State University College of Osteopathic Medicine; Clinical Asst. Professor, Ohio University Heritage College of Osteopathic Medicine. He is the co-author of five risk management books: *Bouncebacks: Critical Care*, *Bouncebacks: Pediatrics, Emergency Medicine*; *Bouncebacks: Medical and Legal* (1st and 2nd Editions) and *Risk Management and the Emergency Department: Executive Leadership for Protecting Patients and Hospitals*. Dr. Klauer also served as the American College of Emergency Physicians Council Speaker and subsequently as a member of their Board of Directors. Dr. Klauer earned his Executive JD, with honors, from Concord Law School in 2011.

You may contact Dr. Klauer with your comments or questions at kevinklauer1@gmail.com.

AI in Healthcare and The Associated Professional Liability

Kevin Klauer, DO, EJD

Medical Legal Case

CC: Passed out/fever

HPI: 33-year-old male, no previous medical history, c/o sudden-onset headache today.

- He has been having fevers as high as 100.
- He had 2 episodes of syncope today.
- No nausea or vomiting.
- He has had some chest congestion with cough.

MEDS: Percocet

ALL: Cephalosporins; Levaquin

SH: Smokes tobacco. Denies drugs. Occasional EtOH.

Physical Exam

GENERAL: Well-appearing male, appears to be in pain.

VS: T98.1°, HR 81, BP 123/77, RR 14, SaO_2 97% on RA

HEENT: NC/AT. PERRL. EOMI. Mucous membranes moist.

NECK: Supple. No meningismus or meningeal signs. No JVD.

HEART: RRR, no murmurs

LUNGS: Clear to auscultation bilaterally.

ABD: Soft, non-tender, non-distended. Normal active BS.

EXT: Thin, good peripheral pulses. No edema.

NEURO: Alert and oriented x3. No deficits on exam.

ED Timeline

Arrives by private vehicle	Seen by EM resident	Attending EM physician signs up on computerized tracking system	Ketorolac 30mg IV administered	LP completed	Morphine 5mg IV; Vancomycin 1gm IV administered (after LP results)
11:13	13:28	13:59	14:49	16:24	18:26

Diagnostics

WBC 12.9, 84% neutrophils

CT Head: Normal

Lumbar puncture: CSF clear & colorless

- Tube #1 - 26 WBC / 650 RBC
- Tube #4 - 34 WBC / 41 RBC

ED Course

20:08 Ceftriaxone 2gm IV administered (ordered by EM attending)

→ RN calls EM physician (elsewhere in a large ED)

→ Reports patient c/o hand pruritis / flushed skin

Physician gives verbal order via cell phone to D/C ceftriaxone infusion.

20:18 Benadryl 50mg IV

ED Course

RN calls EM physician a 2nd time due to pt c/o SOB.

- Per RN, 'Pt gasping, audibly wheezing, drooling, with edema of face, lips, tongue, arms'

Epinephrine 0.3mg 1:10,000 IV x2 doses

Methylprednisolone 125mg IV

Pepcid 20mg IV

Pt intubated with adjunct use of bougie.

An additional issue:

On subsequent review, it is discovered that the same physician ordered IV ceftriaxone for a pt with a cephalosporin allergy 6 months earlier.

In a bizarre coincidence, it also happened to be the exact same patient, who had developed urticaria and mild wheezing during that previous encounter.

Medical Legal Case

44 yo male with a groin rash

- DXas tinea cruris
- Developed a horrible excoriating rash after starting his "antifungal" cream

ED doc wanted to prescribe fluconazole, but inadvertently prescribed fluorouracil (5-FU)

$120,000

Medical Legal Case

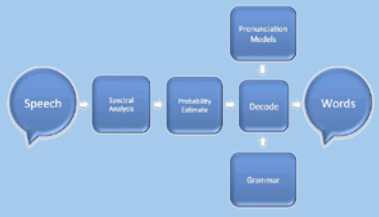
NO CLAIM!??

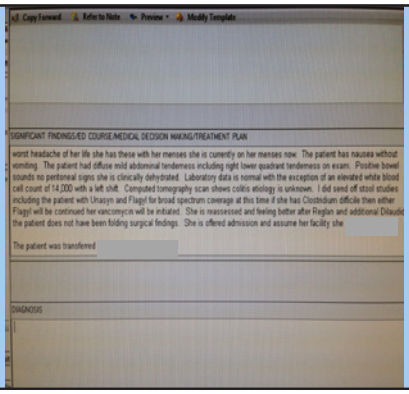
- Pt with 5 prior spontaneous ABs presents to the ED with similar Sx.
- Positive pregnancy test so US performed.
- Tech pulls US from exactly one year ago and provides to EP. It reveals incomplete AB.
- Referred to OB/GYN who scheduled & performed D&C.
- After D&C, Gyn received actual US report which showed single viable pregnancy.

Hill RG Jr, et al. 4000 clicks: a productivity analysis of electronic medical records in a community hospital ED. Am J Emerg Med. 2013 Nov;31(11):1591-4.

- Time spent
  - Data entry: 43%
  - Direct pt care: 28%
- Mouse clicks
  - Low: 6 for ordering aspirin
  - High: 227 for completing a RUQ pain record
  - 10 hr shift: 3,200-4,000
- Impact: 10% increase in productivity
  - $1.77 million incr annual gross revenue

Voice Recognition?





AI Scribe: Ambient Listening Considerations

Privacy and Compliance: Ambient listening can inadvertently capture sensitive patient information.

Data Accuracy: Errors in documentation can occur, such as incorrect symptoms or diagnoses, which can lead to improper follow-up care, incorrect billing. Clinicians must review and verify the accuracy of notes generated by these tools.

Patient Consent: Patients should be informed about the use of ambient listening technology and how their data will be used.

Data Retention and Destruction: Policies for the retention and destruction of audio data must be implemented to protect patient information and comply with legal standards.

Consistent Themes for AI-Associated Negligence

AI-generated Dx: Who is responsible?
- Physician
- Vendor
- Developer

Black Box technology

No Current Legal Standard

Poor communication among Clinicians is not improved

Algorithm inaccuracy

Consent

- Zein, Rosnalisa, et al. "The New Frontiers of Medical Malpractice: Legal Challenges in the Age of Artificial Intelligence and Telemedicine". Legalis : Journal of Law Review, vol. 2, no. 4, Oct. 2024, pp. 148-66, doi:10.61978/legalis.v2i4.363.
- Rowland, S.P., Fitzgerald, J.E., Lungren, M. et al. Digital health technology-specific risks for medical malpractice liability. npj Digit. Med. 5, 157 (2022). https://doi.org/10.1038/s41746-022-00698-3
- The Milbank Quarterly, Vol. 99, No. 3, 2021 (pp. 629-647).
- Drogt, J., Milota, M., van den Brink, A. et al. Ethical guidance for reporting and evaluating claims of AI outperforming human doctors. npj Digit. Med. 7, 271 (2024).

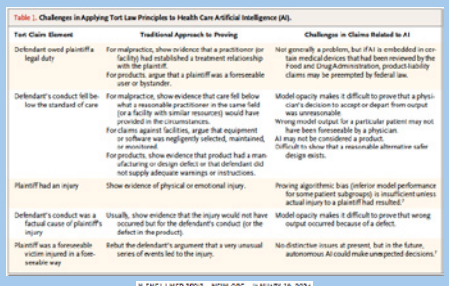


Table 1. Challenges in Applying Tort Law Principles to Health Care Artificial Intelligence (AI).

Tort Claim Element	Traditional Approach to Proving	Challenges in Claims Related to AI
Defendant owed plaintiff a legal duty	For malpractice, show evidence that a practitioner (or facility) had established a treatment relationship with the plaintiff. For products, argue that a plaintiff was a foreseeable user or bystander.	Not generally a problem, but if AI is embedded in certain medical devices that had been reviewed by the Food and Drug Administration, product-liability claims may be preempted by federal law.
Defendant's conduct fell below the standard of care	For malpractice, show evidence that care fell below what a reasonable practitioner in the same field (or a facility with similar resources) would have provided in the circumstances. For claims against facilities, argue that equipment or software was negligently selected, maintained, or monitored. For products, show evidence that product had a manufacturing or design defect or that defendant did not supply adequate warnings or instructions.	Model opacity makes it difficult to prove that a physician's decision to accept or depart from output was unreasonable. Wrong model output for a particular patient may not have been foreseeable by a physician. AI may not be considered a product. Difficult to show that a reasonable alternative safer design exists.
Plaintiff had an injury	Show evidence of physical or emotional injury.	Proving algorithmic bias (inferior model performance for some patient subgroups) is insufficient unless actual injury to a plaintiff had resulted.[7]
Defendant's conduct was a factual cause of plaintiff's injury	Usually, show evidence that the injury would not have occurred but for the defendant's conduct (or the defect in the product).	Model opacity makes it difficult to prove that wrong output occurred because of a defect.
Plaintiff was a foreseeable victim injured in a foreseeable way	Rebut the defendant's argument that a very unusual series of events led to the injury.	No distinctive issues at present, but in the future, autonomous AI could make unexpected decisions.[7]

N ENGL J MED 390;3 NEJM.ORG JANUARY 18, 2024

Duggan MJ, Gervase J, Schoenbaum A, et al. Clinician Experiences With Ambient Scribe Technology to Assist With Documentation Burden and Efficiency. JAMA Netw Open. 2025;8(2):e2460637. doi:10.1001/jamanetworkopen.2024.60637

RESULTS This study included 46 clinicians from 17 different medical specialties, with a mean (SD) of 11.1 (8.7) years in practice. From baseline to post intervention, use of the ambient scribing tool was associated with 20.4% less time in notes per appointment (from 10.3 to 8.2 minutes; $P < .001$), 9.3% greater same-day appointment closure (from 66.2% to 72.4%; $P < .001$), and 30.0% less after-hours work time per workday (from 50.6 to 35.4 minutes per workday; $P = .02$). Targeted perspective questions showed more favorable scores. Open-ended qualitative feedback from clinicians showed a range of positive, negative, and mixed feedback regarding their use of ambient scribing technology. SUS scores showed that the ambient scribing tool was easy to use. NPSs reflected the mixed qualitative feedback.

CONCLUSIONS AND RELEVANCE In this quality improvement study, the use of ambient scribe technology was associated with greater efficiency of outpatient clinical documentation, lower mental burden of documentation for clinicians, and greater sense of engagement with patients during outpatient appointments. Additional studies exploring urgent care settings, examining patient experience, and comparing multiple tools will be important to better understand the effect of ambient scribing on ambulatory care.

Lawrence K, Kuram VS, Levine DL, et al. Informed Consent for Ambient Documentation Using Generative AI in Ambulatory Care. JAMA Netw Open. 2025;8(7):e2522400. doi:10.1001/jamanetworkopen.2025.22400

RESULTS A total of 121 ambient documentation pilot users included 18 clinicians (mean [SD] years of practice, 18.6 [10.0]); 10 men (55.6%]) and 103 patients (mean [SD] age, 37 [12.5] years; 65 women (63.1%]). The most common consent approach was a verbal patient-clinician conversation prior to an individual encounter. Patients and clinicians had a spectrum of comfort with ambient technology; 77 patients (74.8%) reported being comfortable or very comfortable with their physician using ambient documentation. Patient trust, detail in the consent discussion, and intended tool use were associated with patient comfort and intent to consent. Technical understanding was associated with comfort with consent conversations: when provided basic information about the technology, 84 patients (81.6%) consented; this decreased to 57 patients (55.3%) when details about AI features, data storage, and corporate involvement were disclosed. Perceived benefits included reduced documentation burden, improved decision-making, and enhanced communication. Concerns included data security, legal liability, cognitive impacts, and equity. When asked about responsibility for medical errors linked to ambient documentation, 79 patients (64.1%) held physicians accountable; for data security breaches, 79 patients (76.7%) believed vendors should be responsible. Participants suggested a flexible consent model with digital touchpoints, education, nonclinical staff support, and opt-out options.

CONCLUSIONS AND RELEVANCE In this quality improvement study of 121 pilot users of AI-assisted ambient documentation technology, informed consent relied primarily on verbal conversations that varied based on time, knowledge, and the patient-clinician relationship. A flexible, multimodal

Chustecki M. Benefits and Risks of AI in Health Care: Narrative Review Interact J Med Res 2024;13:e53616
URL: https://www.i-jmr.org/2024/1/e53616
DOI: 10.2196/53616

Abstract

Background: The integration of artificial intelligence (AI) into health care has the potential to transform the industry, but it also raises ethical, regulatory, and safety concerns. This review paper provides an in-depth examination of the benefits and risks associated with AI in health care, with a focus on issues like biases, transparency, data privacy, and safety.

Objective: This study aims to evaluate the advantages and drawbacks of incorporating AI in health care. This assessment centers on the potential biases in AI algorithms, transparency challenges, data privacy issues, and safety risks in health care settings.

Methods: Studies included in this review were selected based on their relevance to AI applications in health care, focusing on ethical, regulatory, and safety considerations. Inclusion criteria encompassed peer-reviewed articles, reviews, and relevant research papers published in English. Exclusion criteria included non-peer-reviewed articles, editorials, and studies not directly related to AI in health care. A comprehensive literature search was conducted across 8 databases: OVID MEDLINE, OVID Embase, OVID PsycINFO, EBSCO CINAHL Plus with Full Text, ProQuest Sociological Abstracts, ProQuest Philosopher's Index, ProQuest Advanced Technologies & Aerospace, and Wiley Cochrane Library. The search was last updated on June 23, 2023. Results were synthesized using qualitative methods to identify key themes and findings related to the benefits and risks of AI in health care.

Results: The literature search yielded 8796 articles. After removing duplicates and applying the inclusion and exclusion criteria, 44 studies were included in the qualitative synthesis. This review highlights the significant promise that AI holds in health care, such as enhancing health care delivery by providing more accurate diagnoses, personalized treatment plans, and efficient resource allocation. However, persistent concerns remain, including biases ingrained in AI algorithms, a lack of transparency in decision-making, potential compromises of patient data privacy, and safety risks associated with AI implementation in clinical settings.

Conclusions: In conclusion, while AI presents the opportunity for a healthcare revolution, it is imperative to address the ethical, regulatory, and safety challenges linked to its integration. Proactive measures are required to ensure that AI technologies are developed and deployed responsibly, striking a balance between innovation and the safeguarding of patient well-being.

(*Interact J Med Res 2024;13:e53616*) doi: 10.2196/53616

Chustecki M. Benefits and Risks of AI in Health Care: Narrative Review Interact J Med Res 2024;13:e53616
URL: https://www.i-jmr.org/2024/1/e53616
DOI: 10.2196/53616

Textbox 1. Benefits of artificial intelligence (AI) in health care.

Medical benefits
- Helps in prediction of various risks and diseases
- Helps in prevention and control of various diseases
- Leads to better data-driven decisions within the health care system
- Assists in improving surgery
- Supports mental health

Economic and social benefits
- Reduction in posttreatment expenditures
- Cost saving through early diagnosis
- Cost saving with enhanced clinical trials
- Patient empowerment
- Relieving medical practitioners' workload

Chustecki M. Benefits and Risks of AI in Health Care: Narrative Review Interact J Med Res 2024;13:e53616
URL: https://www.i-jmr.org/2024/1/e53616
DOI: 10.2196/53616

Textbox 2. Risks of artificial intelligence (AI) in health care.

Risks of AI in health care
- AI diagnosis is not always superior to human diagnosis
- AI programs may be difficult to understand and overly ambitious
- Implementation issues
- Transparency issues and risks with data sharing
- Biases
- Mistakes in disease diagnosis or AI cannot be held accountable
- Data availability and accessibility
- Regulatory concerns
- Social challenges

David B. Olawade, Aanuoluwapo C. David-Olawade, Ojima Z. Wada, Akinsola J. Asaolu, Temitope Adereni, Jonathan Ling, Artificial intelligence in healthcare delivery: Prospects and pitfalls, Journal of Medicine, Surgery, and Public Health, Volume 3, 2024.

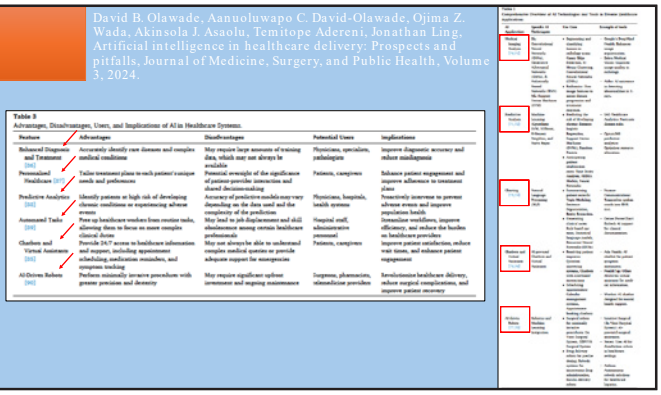
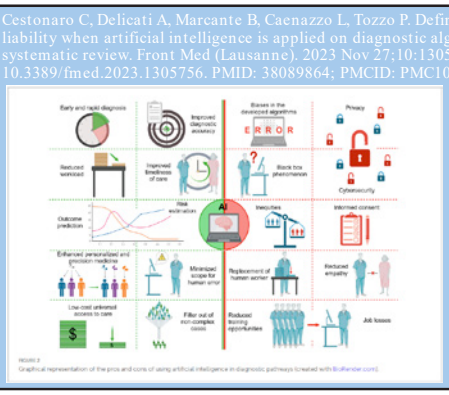


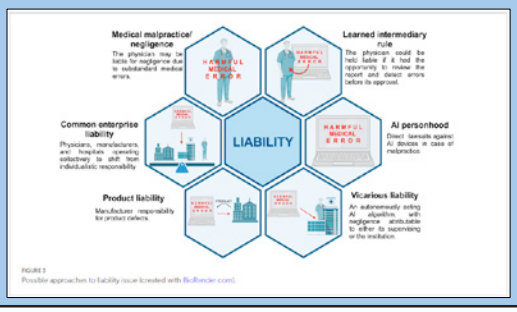
Table 3
Advantages, Disadvantages, Users, and Implications of AI in Healthcare Systems.

Feature	Advantages	Disadvantages	Potential Users	Implications
Enhanced Diagnostic and Treatment [66]	Accurately identify rare diseases and complex medical conditions	May require large amounts of training data, which may not always be available	Physicians, specialists, pathologists	Improve diagnostic accuracy and reduce misdiagnosis
Personalized Healthcare [67]	Tailor treatment plans to each patient's unique needs and preferences	Potential oversight of the significance of patient-provider interaction and shared decision-making	Patients, caregivers	Enhance patient engagement and improve adherence to treatment plans
Predictive Analytics [68]	Identify patients at high risk of developing chronic conditions or experiencing adverse events	Accuracy of predictive models may vary depending on the data used and the complexity of the prediction	Physicians, hospitals, health systems	Proactively intervene to prevent adverse events and improve population health
Automated Tasks [69]	Free up healthcare workers from routine tasks, allowing them to focus on more complex clinical duties	May lead to job displacement and skill obsolescence among certain healthcare professionals	Hospital staff, administrative personnel	Streamline workflows, improve efficiency, and reduce the burden on healthcare providers
Chatbots and Virtual Assistants [70]	Provide 24/7 access to healthcare information and support, including appointment scheduling, medication reminders, and symptom tracking	May not always be able to understand complex medical queries or provide adequate support for emergencies	Patients, caregivers	Improve patient satisfaction, reduce wait times, and enhance patient engagement
AI-Driven Robots [90]	Perform minimally invasive procedures with greater precision and dexterity	May require significant upfront investment and ongoing maintenance	Surgeons, pharmacists, telemedicine providers	Revolutionize healthcare delivery, reduce surgical complications, and improve patient recovery

Cestonaro C, Delicati A, Marcante B, Caenazzo L, Tozzo P. Defining medical liability when artificial intelligence is applied on diagnostic algorithms: a systematic review. Front Med (Lausanne). 2023 Nov 27;10:1305756. doi: 10.3389/fmed.2023.1305756. PMID: 38089864; PMCID: PMC10711067.



Cestonaro C, Delicati A, Marcante B, Caenazzo L, Tozzo P. Defining medical liability when artificial intelligence is applied on diagnostic algorithms: a systematic review. Front Med (Lausanne). 2023 Nov 27;10:1305756. doi: 10.3389/fmed.2023.1305756. PMID: 38089864; PMCID: PMC10711067.



The Path of Least Resistance Has Many Unanswered Questions

Thank you!

SELF EVALUATION

AI in Healthcare and The Associated Professional Liability

1. T/F - Electronic medical record (EMR) documentation consumes more clinician time than direct patient care in the emergency department.

2. A physician can still face liability if they previously prescribed a contraindicated medication to the same patient in the past, even if harm was avoided at the earlier encounter.

3. Which of the following is a consistent theme for AI-associated negligence?

a. Failure to obtain informed consent
b. Over-reliance on algorithmic recommendations
c. Misidentification of patient data
d. All of the above

4. T/F - Ambient listening AI scribes have been shown to decrease documentation burden and improve efficiency in clinical care.

5. T/F - AI diagnostic algorithms completely eliminate medical liability for physicians if used appropriately.

Answer Key: 1. T, 2. T, 3. D, 4. T, 5. F

Joel Kahn, MD, FACC

Advanced Preventive Cardiology
Clinical Professor, Wayne State University
www.drjoelkahn.com
248-731-7412

The "New" Executive Health Physical Exam

TRADITIONAL ANNUAL PHYSICAL

PERIODIC HEALTH EXAMINATION

PERIODIC HEALTH EXAMINATION

- Is the evaluation of individuals using standart procedures like physical examination, laboratory analysis, counseling and vaccines with regular intervals.

WHO Criteria For A Screening Test

- The condition being screened for should be an important health problem
- The natural history of the condition should be well understood
- There should be a detectable early stage
- Treatment at an early stage should be of more benefit than at a later stage
- A suitable test should be devised for the early stage

LEVEL	RECOMMENDATION	EXPLANATION
A	Strongly Recommended	Good Evidence for improved outcomes and the benefit significantly outweighs potential harm
B	Recommend	At least fair evidence
C	No recommendation	At least fair evidence for improved outcomes but not clear whether benefit outweighs potential harm
D	Recommends against	At least fair evidence for ineffectiveness or that harm outweighs benefit
I	No recommendation	Evidence is lacking, poor, or conflicting, and relative benefit and harm can not be

Periodic Health Examination For Adults

- Screen all adults for hypertension (A)
- Do not screen the general adult population for coronary artery disease (D)
- Do not screen adults for peripheral vascular disease (D)
- Screen men between 65 and 75 years who have ever smoked for abdominal aortic aneurysm (B)
- Screen adults for obesity by means of the body mass index (B)

- Screen men older than 35 years and women older than 45 years for hyperlipidemia (A)
- Begin screening for hyperlipidemia at age 20 for those with other risk factors for heart disease (B)
- Screen hyperlipidemic and hypertensive adults for diabetes mellitus (B)
- Screen for osteoporosis at age 65 for women of average risk and at age 60 for women at increased risk

- Do not screen for thyroid dysfunction in asymptomatic patients (D)
- Screen for Chlamydia in all sexually active women younger than age 25 and continue to screen high-risk women older than age 25 (A)
- Screen all women of childbearing age for immunity to rubella (B)
- Screen all adults for depression, provided that the resources exist to treat depression after it has been identified (B)
- Screen all adults for alcohol misuse (B)

- Screen all women older than age 40 for breast cancer (B)
- Screen all sexually active women with a cervix for cervical cancer and its precursors. Begin screening within 3 years of the onset of sexual activity or by age 21 (A)
- Do not continue to screen for cervical cancer and its precursors in previously screened, low risk women older than 65 years or in women who have undergone a hysterectomy for benign disease (D)

- Screen all patients older than age 50 for colorectal cancer (A)
- Discuss the risks and benefits of and the gaps in scientific knowledge regarding prostate cancer screening with all men older than 50 years (I)
- Do not screen for ovarian, testicular, pancreatic, or bladder cancer (D)
- Screen elderly adults for decreased visual acuity (B)

- Question elderly adults about hearing difficulties (B)
- Counsel patients who use tobacco to quit (A)
- Counsel patients who are at increased risk for diet-related diseases regarding healthy eating and weight loss (B)
- Discuss the risks and benefits of Tamoxifen or Raloxifene for women at significantly elevated risk for breast cancer (B)
- Recommend against the use of β-

Original Investigation

June 27, 2005

Support of Evidence-Based Guidelines for the Annual Physical Examination

A Survey of Primary Care Providers

Allan V. Prochazka, MD, MSc; Kristy Lundahl, MS; Wesley Pearson, MD; et al

≫ Author Affiliations | Article Information

Arch Intern Med. 2005;165(12):1347-1352. doi:10.1001/archinte.165.12.1347

Conclusions Despite contrary evidence, most PCPs believe an annual physical examination detects subclinical illness, and many report performing unproven screening laboratory tests. Primary care providers do not appear to accept recommendations that annual physical examinations be abandoned in favor of a more selective approach to preventing health problems.

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National Center for Biotechnology Information

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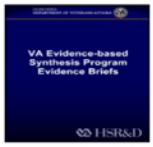


Evidence Brief: Role of the Annual Comprehensive Physical Examination in the Asymptomatic Adult

Hanna E Bloomfield, MD, MPH and Timothy J Wilt, MD, MPH.

Author Information and Affiliations

Washington (DC): Department of Veterans Affairs (US); 2011 Oct.

Copyright and Permissions

PREFACE Go to:

Health Services Research & Development Service's (HSR&D's) Evidence-based Synthesis Program (ESP) was established to provide timely and accurate syntheses of targeted healthcare topics of particular importance to Veterans Affairs (VA) managers and policymakers, as they work to improve the health and healthcare of Veterans. The ESP disseminates these reports throughout VA.

CONCLUSIONS Go to:

- Comprehensive routine physical examinations are not recommended for the asymptomatic adult, although many patients and physicians continue to endorse the practice.
- Components of the physical examination recommended for the asymptomatic adult include:
  - blood pressure screening every 1-2 years
  - periodic measurement of body mass index
  - PAP smears beginning at age 21 for sexually active women with a cervix every 3 years up to the age of 65.
- There is some evidence that designating a specific visit for the provision of preventive services may increase the likelihood that patients will receive PAP smears, cholesterol screening and fecal occult blood testing.

US Preventive Services Task Force | Recommendation Statement

June 12, 2018

Screening for Cardiovascular Disease Risk With Electrocardiography

US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

Article Information

JAMA. 2018;319(22):2308-2314.

Conclusions and Recommendation The USPSTF recommends against screening with resting or exercise ECG to prevent CVD events in asymptomatic adults at low risk of CVD events. (D recommendation) The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening with resting or exercise ECG to prevent CVD events in asymptomatic adults at intermediate or high risk of CVD events. (I statement)

FREE

JAMA Patient Page

July 17, 2018

Risk Assessment for Cardiovascular Disease With Nontraditional Risk Factors

Jill Jin, MD, MPH

Article Information

JAMA. 2018;320(3):316. doi:10.1001/jama.2018.9122

Risk Assessment for Cardiovascular Disease (CVD) With Added Nontraditional Risk Factors

Population

Adults who do not have symptoms or a diagnosis of CVD

Symptoms of CVD include chest pain, chest tightness, shortness of breath, and pain in the legs, arms, neck, jaw, throat, upper abdomen, or back.

USPSTF recommendation

I Statement

There is not enough evidence to say whether adding ankle-brachial index or high-sensitivity C-reactive protein tests or coronary artery calcium score to traditional risk assessment tools benefits people who do not have CVD symptoms.

YET, SELF PAY OR CORPORATE PAY EXECUTIVE PHYSICALS ARE WIDESPREAD AND AVAILABLE

CLINIC

Log in

< Medical Departments & Centers

Executive Health Program

Request an Appointment

Standard protocol | Corporate enrollment

Executive Health standard protocol

Ages 40-49

- Physical exam
- Variety of laboratory work
- Cardiovascular counseling
- Resting ECG
- Chest X-ray
- Exercise and treadmill ECG
- Cervical cancer screening (women)
- Vaccination review
- Breast cancer screening (women)
- Prostate-specific antigen, or PSA (men)
- Audiogram

Age 50 and older

- Physical exam
- Variety of laboratory work
- Cardiovascular counseling
- Resting ECG
- Chest X-ray
- Exercise and treadmill ECG
- Cervical cancer screening (women)
- Vaccination review
- Breast cancer screening (women)
- PSA (men)
- Audiogram
- Abdominal aortic ultrasound (men, 65-75)
- Bone density scan (women 50-plus) (men 65-plus)
- Colonoscopy

JAMA

Views 16,380 | Citations 9 | Altmetric 121

PDF

FREE

Research Letter

September 17, 2019

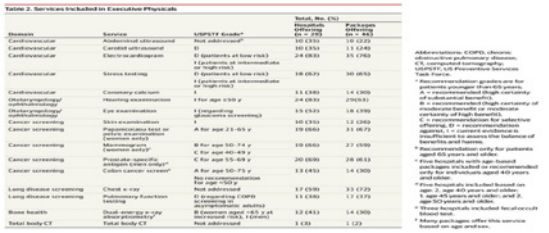
Preventive Services Offered in Executive Physicals at Top-Ranked Hospitals

Deborah Korenstein, MD[1]; Maha Mamoor, MS[2]; Peter B. Bach, MD, MAPP[3]

Author Affiliations | Article Information

JAMA. 2019;322(11):1101-1103. doi:10.1001/jama.2019.10563

Table 2. Services Included in Executive Physicals



Executive Physicals: Can a $5,000 Exam Help Improve Your Health and Business?

Published: January 27, 2014

Mark Henricks

SUMMARY

Spending a day undergoing a battery of health tests will cost you, but it may be the best way for busy business owners to monitor their health.

When it comes to perks, most business owners have a reserved parking space near the door, while employees dump their vehicles wherever they can find an open spot. So why do executive health checkups not get the same priority?

And as *Harvard Business Review* points out, such comprehensive physicals haven't been shown to improve health outcomes across broad populations. For instance, critics say that some illnesses aren't readily detectible before symptoms appear, while false positives can cause patients to worry and undergo more procedures to rule out illness. In addition, some tests, such as whole-body CT scans, may expose patients to unhealthy amounts of radiation while producing little useful information.

The body is amazing at hiding disease

70% of heart attacks occur without prior symptoms

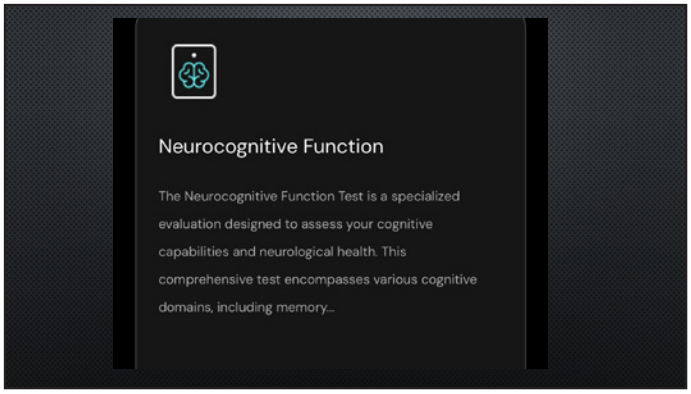
2% of Members have cancer, but show no signs or symptoms

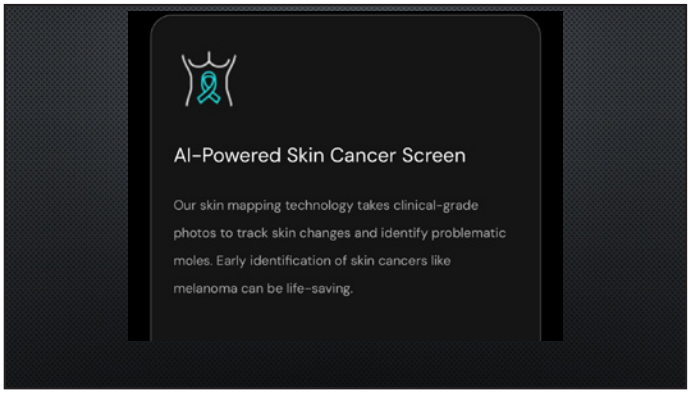
14% of Members have a life-saving finding

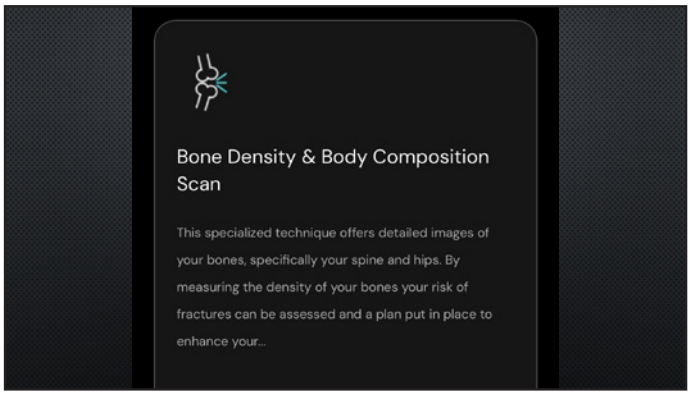
2.5% of Members have a potential ruptured aneurysm looming in their future

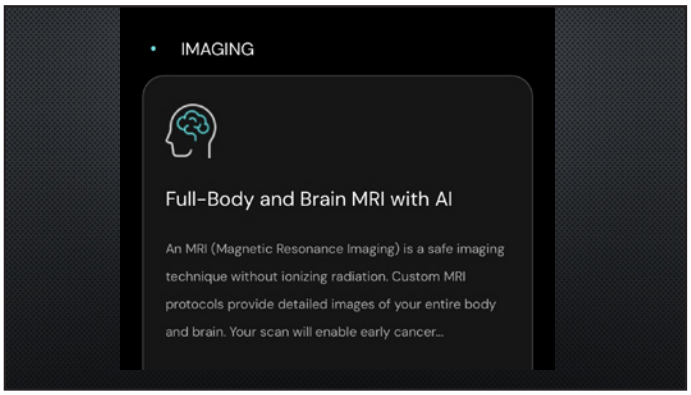
Sleep Apnea Test

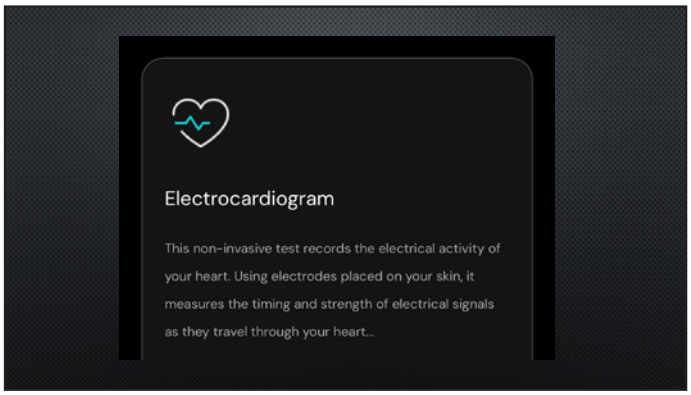
Sleep apnea is a sleep disorder characterized by repeated interruptions in breathing during sleep resulting in a lack of oxygen to your body and nighttime waking. Early detection and treatment of sleep apnea can prevent...

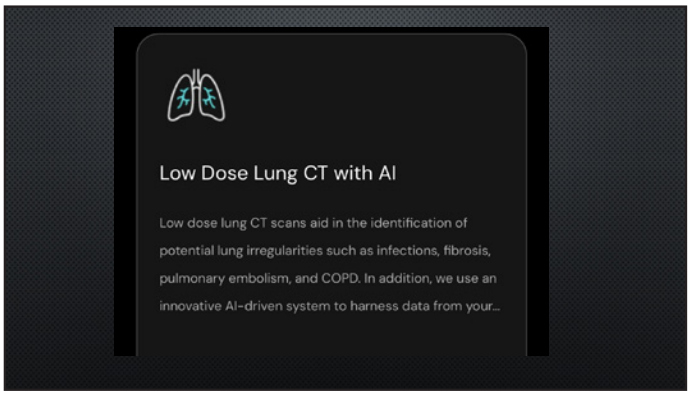

Neurocognitive Function
The Neurocognitive Function Test is a specialized evaluation designed to assess your cognitive capabilities and neurological health. This comprehensive test encompasses various cognitive domains, including memory...

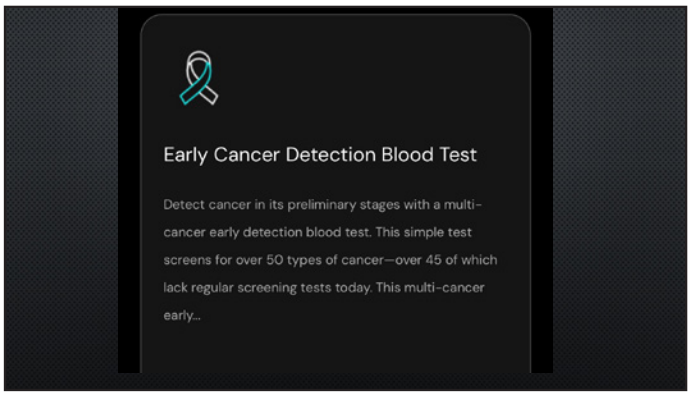

AI-Powered Skin Cancer Screen
Our skin mapping technology takes clinical-grade photos to track skin changes and identify problematic moles. Early identification of skin cancers like melanoma can be life-saving.


Bone Density & Body Composition Scan
This specialized technique offers detailed images of your bones, specifically your spine and hips. By measuring the density of your bones your risk of fractures can be assessed and a plan put in place to enhance your...

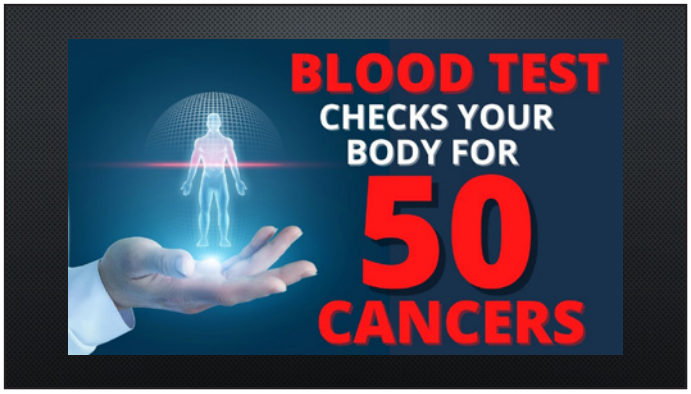

IMAGING
Full-Body and Brain MRI with AI
An MRI (Magnetic Resonance Imaging) is a safe imaging technique without ionizing radiation. Custom MRI protocols provide detailed images of your entire body and brain. Your scan will enable early cancer...

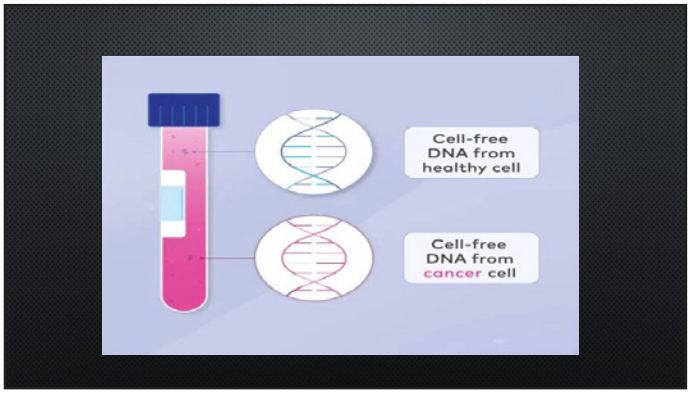

Electrocardiogram
This non-invasive test records the electrical activity of your heart. Using electrodes placed on your skin, it measures the timing and strength of electrical signals as they travel through your heart...


Low Dose Lung CT with AI
Low dose lung CT scans aid in the identification of potential lung irregularities such as infections, fibrosis, pulmonary embolism, and COPD. In addition, we use an innovative AI-driven system to harness data from your...


Early Cancer Detection Blood Test
Detect cancer in its preliminary stages with a multi-cancer early detection blood test. This simple test screens for over 50 types of cancer—over 45 of which lack regular screening tests today. This multi-cancer early...


Why Early Detection Is Important
Early cancer detection is important because it greatly increases a person's treatment options and, usually, their chance of survival. That's why the CDC and other organizations recommend regularly screening for five specific cancers for people over certain ages.
These cancers include:
Breast cancer
Cervical cancer
Colorectal cancer
Prostate cancer
Lung cancer
(for those who've smoked in their lifetime)
griffin

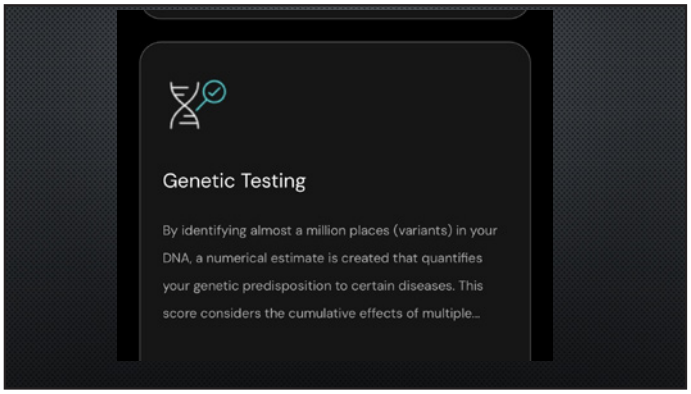


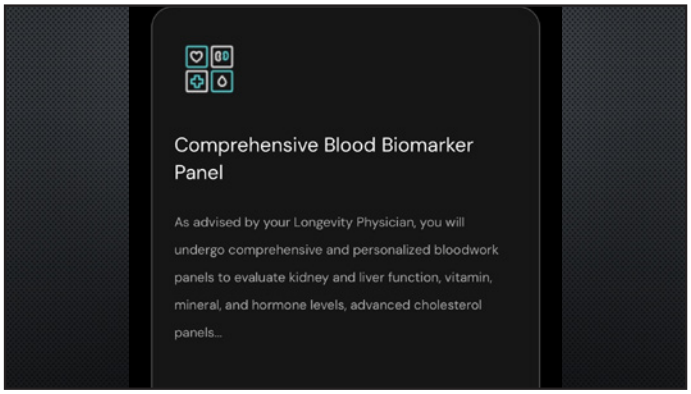


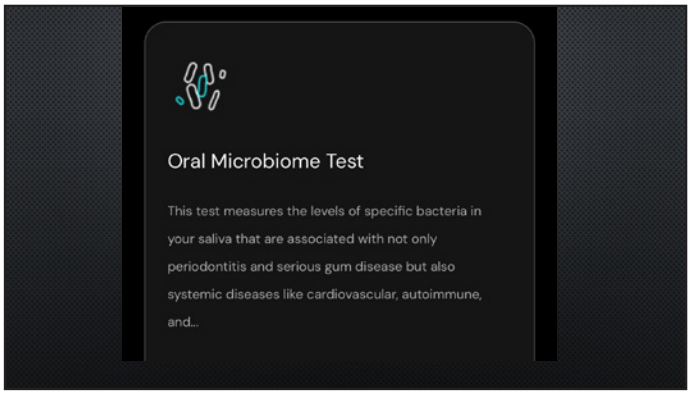
Test	Indication	Population, frequency	Cost*
Galleri multi-cancer early detection test	Detection of more than 50 cancer types†	Asymptomatic adults with an elevated risk for cancer (such as those 50 years or older); performed annually	$949

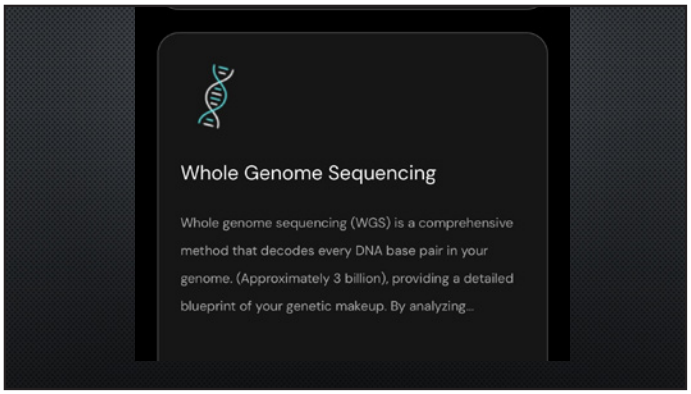
Note: Use of the Galleri test is discouraged in patients who are pregnant, younger than 22 years, or undergoing active cancer treatment.[2]

*—Cost according to the manufacturer.[12]
†—Cancer types are defined using the *American Joint Committee on Cancer Staging Manual*, 8th ed. Some cancer names were modified to organize for easy reference.[1]









AI-Powered Cardiovascular Risk Blood Test

This test uses advanced AI algorithms to measure various proteins and other molecules in your blood to assess your one-year risk for a heart attack as well as your risk of having soft vulnerable plaque...

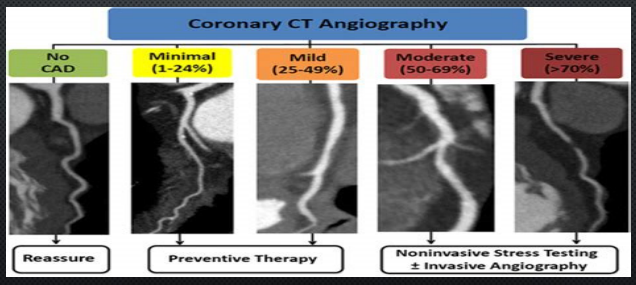
Coronary CT Angiography with AI

If you are at risk of a future heart attack, our AI-guided approach to Coronary Computed Tomography Angiography (CCTA) detects early warning signs. By accurately identifying the presence of soft plaque — a less dense...

Epigenetic Biological Age

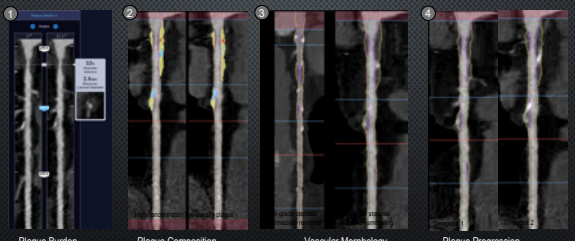
Your epigenetic testing analyzes changes in the methylation tags on your DNA. By analyzing 900,000 locations along your DNA, we can use AI to find correlations to link to health outcomes and determine your biological age...

CORONARY CT ANGIOGRAPHY CCTA: 2010

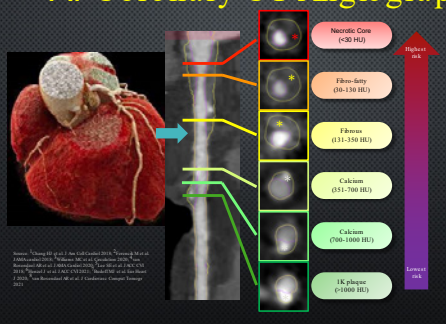


Coronary CCTA With AI Enables Comprehensive Evaluation of Individual Risk

The four (4) most important features of risk: CONFIRM, ICONIC, PARADIGM, PROMISE, SCOT-HEART, ISCHEMIA, PROSPECT, etc.

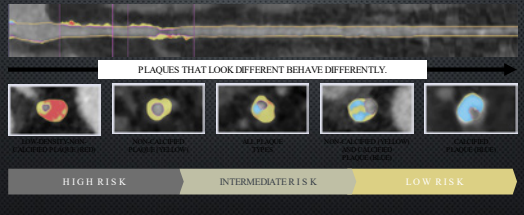


AI-Coronary CT Angiography



Dark Plaques Dangerous - strongest predictor of heart attack risk.[1-3]

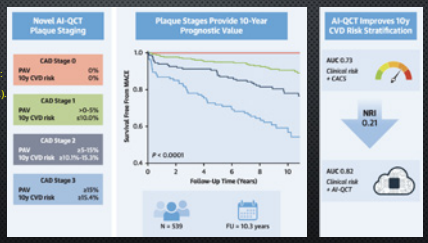
NOT ALL PLAQUE IS THE SAME.
THE FUTURE IS NOW



AI-CCTA: Improved CV Risk Assessment

MACE Prediction:

- CCTA Plaque Stage is a better predictor of short - and long-term MACE events than:
  - Risk Score (ASCVD etc.).
  - Agatston Score.
  - Stenosis presence



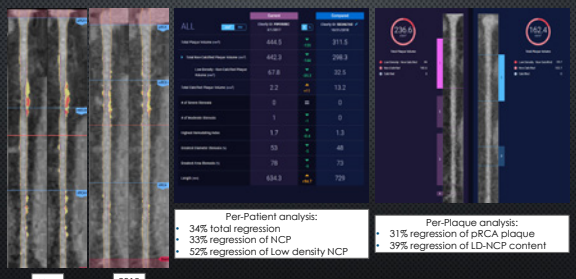
Nurmohamed et al JACC Imag 2023

Therapy Based on Plaque Stage

Freeman, A et al
Am J Med 2022

Stage	Stenoses	Action	Rescan (until stable):
Stage 0: No Plaque	0	• GDMT / Consider de-escalation	4 years
Stage 1: Mild	<50%	• Statin, Ezetimibe	3 years
Stage 2: Moderate	<50%	Stage 1 Plus • Aspirin, Rivaroxaban • GLP1 if diabetic	2 years
Stage 3: Severe	<50%	Stage 2 plus • Consider PCSK9, Icosapent ethyl, Inclisiran, Bempedoic acid, Colchicine • GLP1 and SGLT2 if diabetic	1 year

PLAQUE REGRESSION 55-year-old man taking a PCSK9 inhibitor

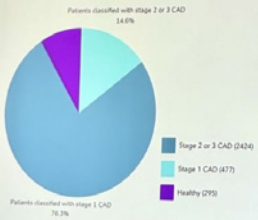


2017 2018

Per-Patient analysis:
- 34% total regression
- 33% regression of NCP
- 52% regression of Low density NCP

Per-Plaque analysis:
- 31% regression of pRCA plaque
- 39% regression of LD-NCP content

What I'm seeing - CCTA Testing with AI Read - Reveals (n=3,256)



- Asymptomatic "healthy" population
- 15% (477) of people classified with stage 2 or 3 CAD
- 76% (2484) of patients classified with stage 1 CAD
  - 36% (889/2484) of stage 1 disease patients had **no calcified plaque** and **would be missed** by conventional methods
    - These are high risk for CAD event
  - 9% (295/3256) of patients had moderate and/or severe stenoses detected at their first study

The New Executive Physical

SELF EVALUATION

The "New" Executive Health Physical Exam

True/False

1. Everyone at age 50 gets an annual physical with a stress test and electrocardiogram.

2. Blood pressure and cholesterol should be measured at an annual physical.

3. There are now blood tests that can identify over 50 cancers and are full covered by insurance plans.

4. Total body MRI scans without contrast may identify in 1-2% of people unknown tumors or aneurysms.

5. The coronary CT angiogram with AI interpretation has been used in some executive health programs to offer the most advanced coronary artery disease diagnosis.

6. One executive health center has data on over 2,500 clients showing only 10% have silent heart disease.

7. The US Preventive Services Task Force has recommended coronary artery calcium CT imaging for all persons at age 50.

Answer Key: 1. F, 2. T, 3. F, 4. T, 5. T, 6. F, 7. F

Beaumont
Beaumont Health
Health Center
4949 Coolidge Highway
Royal Oak, MI 48073

Barry A. Franklin, PhD
Director of Preventive Cardiology and Cardiac Rehabilitation

Strategies for Professional and Personal Success: Lessons from High Achievers

GPS for Success: Skills, Strategies, and Secrets of Superachievers

Barry A. Franklin, PhD
Corewell Health, William Beaumont University Hospital
Preventive Cardiology/Cardiac Rehabilitation
Oakland University Wm. Beaumont School of Medicine

email: Barry.Franklin@CorewellHealth.org

No Disclosures

Corewell Health East

HOROSCOPE:

GEMINI (May 21 – June 21):

Today will be a banner day for you! You'll give a great *talk on an educational, video-sharing website before an* attractive, intelligent, medically-oriented audience --- empowering them with *invaluable life and career skills*. Happiness, optimism, and gratitude define your day.☺

USA Today

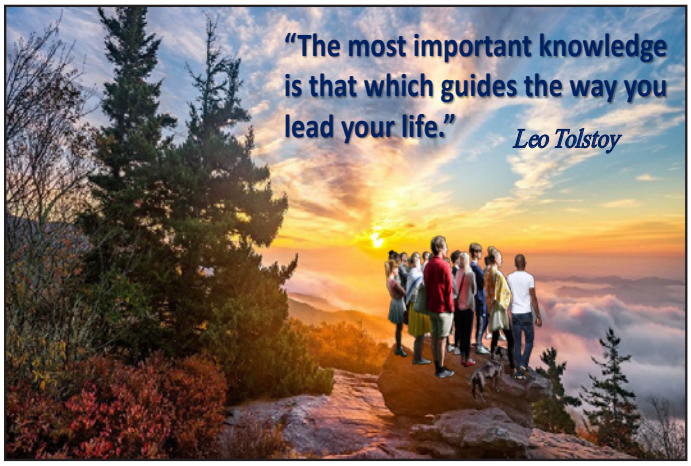
MY MOTIVATION FOR THIS TALK ?

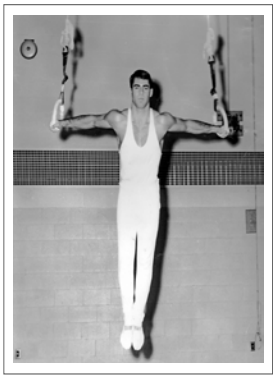
"When you get where you are going, don't forget turn back around,

and help with the next one in line.

Always stay humble and kind."

Tim McGraw
"Humble and Kind" lyrics





My Life Aspirations in 1967

Kent State University, Oct.12, 1967

Peter Drucker's Recommendation: Find a Secondary Pursuit—and Make it more than just a Hobby

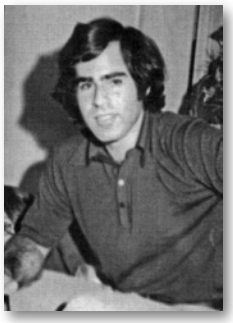
Why do some people thrive, while others seem to tread water and merely survive ?

Leadership, professional, and financial opportunities don't just happen. YOU CREATE THEM.

"You are your own fortune cookie"

Regardless of the field, everybody would love to be in the top of their class. I'm going to share with you how to do it..

Through the Lessons I Learned via my Research on Highly Accomplished People, Superachievers, and their Common Characteristics



50 Years

50 +/- 3 Minutes

~ 1975 2025

What are the Underappreciated "Soft Skills?"

- Forerunners of success
- Foundational factors for success
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- Persistence and tenacity pays
- Ask for what you want
- Become a master communicator—words matter
- Maximize your productivity—the magic of collaboration
- Be a people person
- Understand the law of sow & reap
- Surround yourself with "stars"
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- Strive for greater rewards
- Give back!
- Routinely exceed people's expectations
- It pays to be a little bit better; commit to never-ending improvements
- Raise your hand high and often to volunteer
- Showcase your talents and visiblity → Opportunities

The #1 Success Strategy – Taking Action

Forerunners of Success: Qualities to Embrace ?

Many people believe: if you are successful, you'll be happy, optimistic, and grateful. *But compelling research suggests that the reverse is true.* Individuals who score high on optimism/happiness* scales are the most successful in every field. Moreover, people who believe that good things invariably happen to them find that future opportunities arise. Finally, whoever exemplifies gratitude will attract more to be grateful for.

Happiness (Smile) + Optimism + Gratitude → Future Success

OPTIMISM: Look for the 'Good' in Everything that Life Throws at You…

An American shoe company sent two salesmen to the Australian outback. They wanted to find out whether there was any market for shoes among the Aborigines. They received telegrams from both salesmen. The first said, " No business here. The natives don't wear shoes." But the second telegram proclaimed, "Great opportunity here. The natives don't wear shoes."

How Do You Read This ?

OPPORTUNITY

IS NOWHERE

The Practice of Gratitude: An Infallible Law of the Universe

"I started out giving thanks for small things, and the more thankful I became, the more abundance I experienced. That's because what you focus on expands, and when you focus on the goodness in your life, you create more of it. Opportunities, relationships, even money flowed my way when I learned to be grateful for whatever happened in my life."

Oprah Winfrey (B. 1954)
Media Personality and Businesswoman

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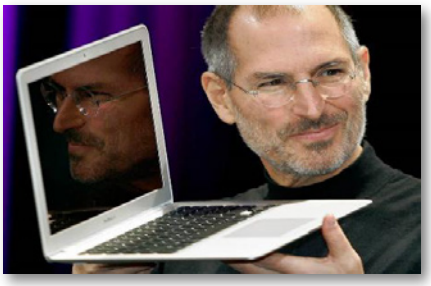
The #1 Success Strategy – Taking Action

Roadmap for Success: The Big 3 Foundational Factors

Setting yourself apart from the croud

#1 Love what you do!



"The only way to do great work is to love what you do. If you haven't found it yet, keep looking."

Steve Jobs (1955- 2011)

#2 Take 100% responsibility for your life

The "10" Most Empowering Two Letter Words ?

"If It Is To Be, It Is Up To Me."

Marc Meyers—How to Make Luck

#3 Focus on serving others: the rewards will come

Ray Kroc

Walt Disney

Henry Ford

"You can get anything you want in life, if you help enough other people get what they want."

Zig Ziglar

Tolstoy Quote

An Enlightening Story ? My Thailand Trip

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The #1 Success Strategy – Taking Action

Classic Gifted Children Study: A Serendipitous Finding ?

1,528 children (IQ~genius)
Studied relationship between IQ and achievement

Major Findings

- IQ NOT the major ingredient
- Three predictors of success
  - Self-confidence
  - Perseverance
  - Tendency to set goals in writing (#1)

* Dr. Lewis Terman, Stanford University, 1921

The Single Idea For Which A Man Was Paid $25,000

"Write down the 6 most important things you had to do tomorrow. Prioritize them. Cross each one off once you've completed it. Complete unfinished items first the next day, and start the next 6."

Ivy Lee*

* *Summoned by Charles M. Schwab, president Bethlehem Steel, 1918*

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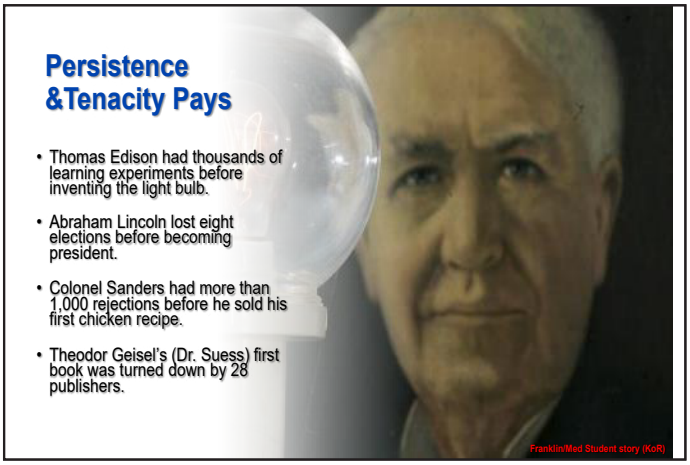
The #1 Success Strategy – Taking Action

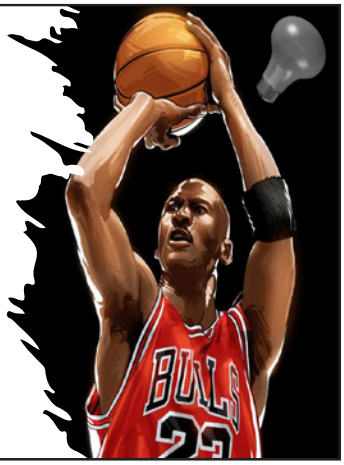
Persistence &Tenacity Pays

- Thomas Edison had thousands of learning experiments before inventing the light bulb.
- Abraham Lincoln lost eight elections before becoming president.
- Colonel Sanders had more than 1,000 rejections before he sold his first chicken recipe.
- Theodor Geisel's (Dr. Suess) first book was turned down by 28 publishers.



"I have missed more than 9,000 shots in my career. I have lost almost 300 games. On 26 occasions, I have been entrusted to take the game-winning shot, and I missed. I have failed over and over again in my life. And that's precisely why I succeed."

Michael Jordan



Benefits of Failure

"I think it fair to say that by any conventional measure, a mere 7 years after my graduation day, I had failed on an epic scale. An exceptionally short-lived marriage had imploded, and I was jobless, a lone parent, and as poor as it is possible to be in modern Britain, without being homeless."

"I had an old typewriter and a big idea……."

Excerpted from J.K. Rowling's Commencement Speech at Harvard University, 2008

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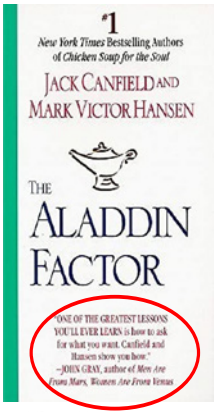
The #1 Success Strategy – Taking Action

The Aladdin Factor

"You've got to ask! Asking is, in my humble opinion, the world's most powerful and neglected secret to success and happiness."

Percy Ross
Philanthropist Multi-Millionaire



ENCOUNTERS=OPPORTUNITIES. Colleague working on something that appealed to you, ASK THEM if you could be involved.

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The #1 Success Strategy – Taking Action

A SHORTCUT TO LEADERSHIP AND DISTINCTION ?

Decrease Your TV Time

Leaders are Readers

(Ideally at least an hour a day)

" The person who can speak acceptably is usually given credit for an ability all out of proportion to what he/she really possesses. "

Lowell Thomas

A Sign Change that Opened People's Eyes and Wallets: Words Matter.....

Advertising A Product or Service? Words Matter

PORTLAND LOCKSMITH
Keys made while you wait

A locksmith in Portland, Oregon had a sign in his shop that read **"Keys made while you wait."** It occurred to him that people don't like to wait. So he changed the sign to read: "Keys made while you watch." Within a year his business doubled!

Advertising A Product or Service? Words Matter*

PORTLAND LOCKSMITH
Keys made while you watch

Moral of the story? What we write *(or say)* has a lot to do with whether people listen to us. How we say it (the words we use) has everything to do with whether they hear us.

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The #1 Success Strategy – Taking Action

Use Collaboration To Increase Your Productivity*

- One Clydesdale horse can pull 8,000 pounds.
- Two Clydesdale horses that are matched correctly and trained can pull 24,000 to 32,000 pounds – 3 to 4 times what either horse could pull on their own!

* EXAMPLES: Spielberg/Lucas; Canfield/Hansen

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The #1 Success Strategy – Taking Action

People Skills → Success

When asked what one single characteristic is most needed by leaders, chief executives replied: "The ability to work with people."
What are they looking for? Specific characteristics ?
"The Big 6"

1. *Integrity - the #1 quality for success*
2. *Give people more than they expect*
3. *Offer colleagues/employees praise/appreciation**
4. *Make people feel important*
5. *Individuals who are simply nice people*
6. *Don't tell people, show them*

* Ideally in front of others

The Likeability Factor

"It's nice to be important but it's more important to be nice."

Shay Kennedy
American Heart Association

Diane Sawyer/Katie Couric story

TAKE THE HIGH ROAD . . .

TAKE THE HIGH ROAD . . .

Class Act

Best advice Warren Buffett ever received ?

Wisest Counsel Warren Buffett Ever Received?

"You can tell someone to go to hell tomorrow—you don't give up the right. But keep your mouth shut today, and see if you feel the same way tomorrow. Then, forget about it."

Avoid instant gratification !

A "People Skill Pearl" for CEO's, Presidents, Chiefs, Directors, Business Owners, Chief Operating Officers, Managers, Supervisors…

"People don't care how much you know (or what your title is), until they know how much you care (about them)."

---Theodore Roosevelt

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What is the Law of Sow and Reap ?

Positive Actions Today Produce a Rich Harvest in the Future

We reap what we sow, but always more than we sow, and at a later date. In other words, to a large extent, you get back from life what you put into it – and more. Example? Plant a few pumpkin seeds.

Casino Analogy

Samuel Goldwyn (MGM Movie Co) "The harder I work, the luckier I get."

The 10,000 Hour Rule: A Common Trait of Highly Successful People*

One thing that seemed to be clear was that in order to be successful in anything, you need to put in 10,000 hours of work.

Malcolm Gladwell
"Outliers" author

3 P's
+
1 P

Prepare, prepare, prepare, + prepare (one more time).

*"By failing to prepare, you are preparing to fail."--- Benjamin Franklin

Preparing for Success: Achievement Takes Practice

The great Italian violinist Niccolò Paganini was partway through a solo performance when one of his strings suddenly broke. Then a second string snapped, and then a third, leaving him with only a single violin string. What did he do?

Law of Sow & Reap: The Gary Player Story

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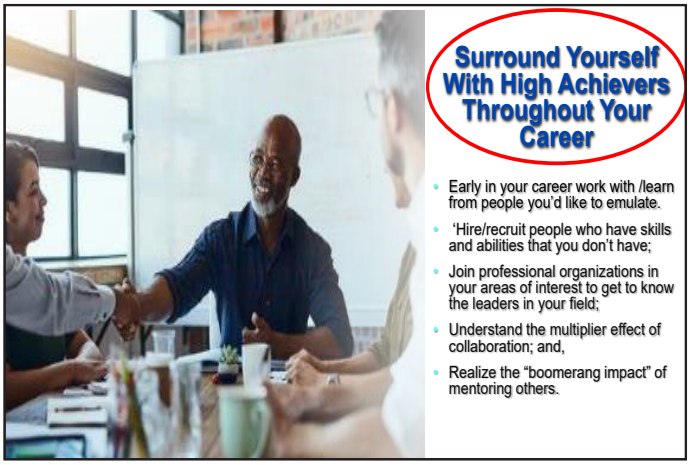
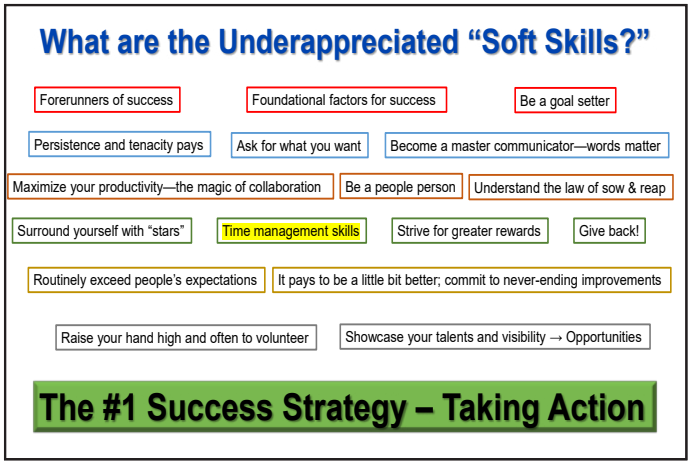

Surround Yourself With High Achievers Throughout Your Career
Early in your career work with /learn from people you'd like to emulate.
'Hire/recruit people who have skills and abilities that you don't have;
Join professional organizations in your areas of interest to get to know the leaders in your field;
Understand the multiplier effect of collaboration; and,
Realize the "boomerang impact" of mentoring others.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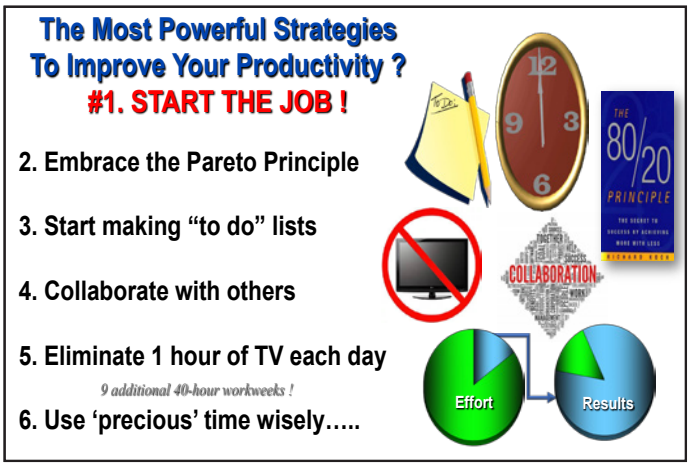
The Most Powerful Strategies To Improve Your Productivity ?
#1. START THE JOB !
2. Embrace the Pareto Principle
3. Start making "to do" lists
4. Collaborate with others
5. Eliminate 1 hour of TV each day
9 additional 40-hour workweeks !
6. Use 'precious' time wisely…..
COLLABORATION
THE 80/20 PRINCIPLE
Effort
Results


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Strive for Greater Rewards: Go for the Gold
"Congratulations, you have just received an 'A' in this class. Keep believing in yourself."


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Take Action: Give Back* !

Most of the wealthy, famous, highly successful people I've known or studied, GIVE BACK , whether through donations/gifts, setting up charitable foundations, donating their time, and/or helping others. They've come to the sobering realization that this gesture alone, invariably leads to 'good karma'.

The domino effect starts with you! " A candle is not diminished by giving another candle light."—Earl Nightingale

Superachievers who Exemplify "Giving Back" to Others

What are the Underappreciated "Soft Skills?"

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- Foundational factors for success
- Be a goal setter
- Persistence and tenacity pays
- Ask for what you want
- Become a master communicator—words matter
- Maximize your productivity—the magic of collaboration
- Be a people person
- Understand the law of sow & reap
- Surround yourself with "stars"
- Time management skills
- Strive for greater rewards
- Give back!
- Routinely exceed people's expectations
- It pays to be a little bit better; commit to never-ending improvements
- Raise your hand high and often to volunteer
- Showcase your talents and visibility → Opportunities

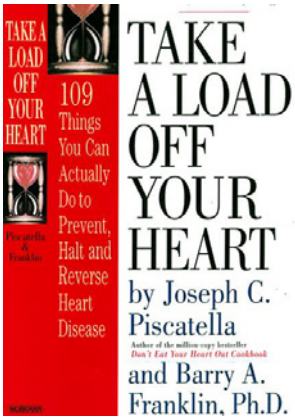
The #1 Success Strategy – Taking Action

Give People More Than They Expect

One New York cab driver makes $40,000+ more a year in tips alone than other cabbies. How?

He offers passengers a choice of music, newspapers, cold drinks and fresh fruit.

My Beaumont Contract



TAKE A LOAD OFF YOUR HEART by Joseph C. Piscatella and Barry A. Franklin, Ph.D.

My Northwest Airlines Story: Exceed People's Expectations

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It Pays to be Just a Little Bit Better

PGA Tour 2002 Scoring Average

Rank	Player	Average
1	Tiger Woods*	68.56
2	Vijay Singh	69.47
3	Ernie Els	69.50
4	Phil Mickelson	69.58
5	Nick Price	69.59
6	Retief Goosen	69.69
7	David Toms	69.73
8	Justin Leonard	69.86
9	Fred Funk	69.99
10	Sergio Garcia**	70.00

* $6.9 million ** $2.4 million

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Raise Your Hand High (And Often) to Volunteer

*Zig Ziglar Quote

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The #1 Success Strategy – Taking Action

Organizational Membership Leads to Collaboration, Visibility, and Unimagined Opportunities ?

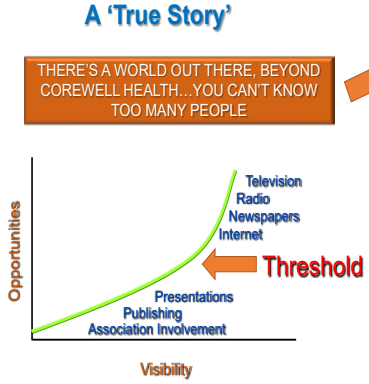
"Dedicate your life to a cause greater than yourself, and your life will become a glorious adventure."

Mack Douglas

Collaborate, work with, and befriend national and international "leaders" who share your passion for the field.

VISIBILITY LEADS TO OPPORTUNITIES: A 'True Story'

THERE'S A WORLD OUT THERE, BEYOND COREWELL HEALTH…YOU CAN'T KNOW TOO MANY PEOPLE



Italy Experience

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The #1 Success Strategy – Taking Action

2 Favorite Quotes Substantiating the #1 Ranking for 'Taking Action'

"Your life is a direct result of what you DO – not necessarily what you say you are going to do."

Arthur L. Williams

"What you think, or what you know, or what you believe is, in the end, of little consequence. The only thing of consequence is what we do."

John Ruskin

When John Chuback, MD met his new neighbor, Tom Potenza (tech/computer executive, entrepreneur. . .)

John asked him, "Why do you think you're more successful than most other people in the computer industry?"

Tom replied, "I have a riddle for you. If there are 3 frogs sitting on a log and the log is floating in a pool and one frog decides to jump in the water, how many are left on the log?"

Story continued . . .

John hesitantly responded, "Two frogs," knowing he'd likely be wrong.

"No," Tom countered, "there are still 3 frogs sitting on the log." "Deciding to jump in the water and jumping in the water are two very different things."

"I've been very successful because I was the frog who jumped in the water while the others were deciding to jump in, thinking about jumping in, planning to jump in, and so on."

Tommy Hopkins—Law of Goya

The Law of GOYA

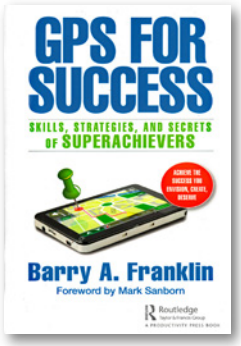
"Get Off Your Ass"

Tommy Hopkins

Do something every day that *moves* you toward your goals and dreams.

The Universe Rewards Action!

Who Would Like a Free Copy of my Book ?



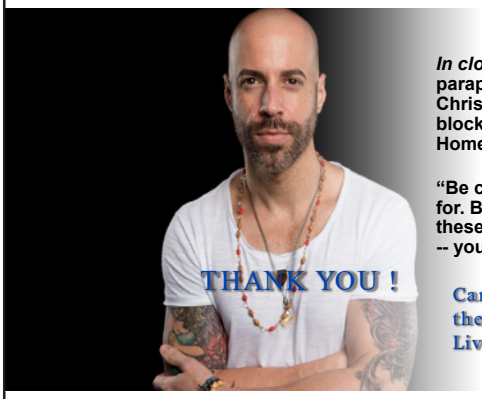
Take Action! The #1 Success Strategy

Take Home Messages: My Entire Talk on One Slide

Building a career involves investing time, effort and hard work

It's not a matter of circumstance but of choice! Leaders/Superachievers…

✓ Love what they do (Radiate HOG)	✓ Take responsibility for their life
✓ Write down/think about their goals	✓ Abandon 'perceived limits'
✓ Adopt a greater cause (serving others)	✓ Realize that persistence pays
✓ Take action (#1)	✓ Know that setbacks line the 'road to success'
✓ Exceed peoples' expectations	✓ Prepare for success (10,000 hour rule)
✓ Strive for constant improvement	✓ Go for the gold
✓ Do more than they are paid to do	✓ Generously give back



WARNING :

***In closing, I'd like* to paraphrase songwriter Chris Daughtry in his blockbuster hit, "I'm Going Home"...when he said:**

"Be careful what you wish for. Because by embracing these skills and strategies---- you just might get it all."

Carpe Diem, Seize the Day, Make Your Lives Extraordinary !

SELF EVALUATION

Strategies for Professional and Personal Success: Lessons from High Achievers

1. According to a classic study of gifted children, which of the factors below were not related to ultimate success in life.

a. Intelligence quotient and grades
b. Self-confidence
c. Perseverance
d. Tendency to set goals
e. None of the above

2. According to Malcolm Gladwell, a common trait of highly successful people is that they've devoted_____ or more hours to improve their performance or skill sets.

a. 5,000
b. 10,000
c. 12,500
d. 15,000
e. None of the above

3. The most powerful strategies to maximize your productivity include:

a. Start the job!
b. Embrace the Pareto Principle
c. Make daily "to do" lists
d. Eliminate 1 hour of television each day
e. All of the above

4. The 2002 professional golfers annual scores represent a microcosm of the real world, going from "good" to "great". The difference in 18-hole scores / round of golf from the #1 to the #10 golfer each year ~_____shots.

a. 0.5
b. 1.0
c. 1.5
d. 2.5
e. 3.0

5. The #1 or ultimate success strategy is...

a. Radiate gratitude and optimism
b. Practice the "law of attraction"
c. Be persistent
d. Take action
e. Commit to never-ending improvements

6. T/F - One Clydesdale horse can pull 8,000 pounds. But 2 Clydesdale horses that are matched correctly, working together can pull 24,000 to 32,000 pounds. Use collaboration (working with others) to increase your productivity.

Answer Key: 1. A, 2. B, 3. E, 4. C, 5. D, 6. T