2025 LIFE INSURANCE AND ANNUITY CONFERENCE

Reimagine Tomorrow

Transforming Mortality: The Future of Therapeutics

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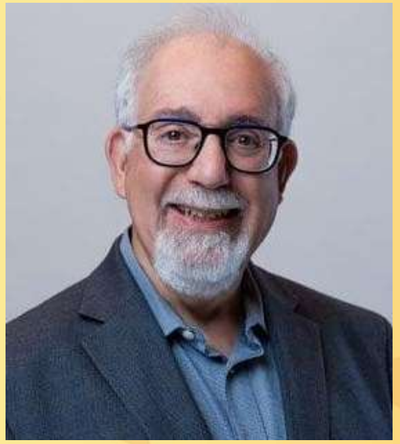

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There is no safe harbor under the antitrust law for professional association activities. Therefore, association meeting participants should refrain from discussing any activity that could potentially be construed as having an anti-competitive effect. Discussions relating to product or service pricing, market allocations, membership restrictions, product standardization or other conditions on trade could arguably be perceived as a restraint on trade and may expose the SOA and its members to antitrust enforcement procedures.

While participating in all SOA in person meetings, webinars, teleconferences or side discussions, you should avoid discussing competitively sensitive information with competitors and follow these guidelines:

- **Do not** discuss prices for services or products or anything else that might affect prices
- **Do not** discuss what you or other entities plan to do in a particular geographic or product markets or with particular customers.
- **Do not** speak on behalf of the SOA or any of its committees unless specifically authorized to do so.
- **Do** leave a meeting where any anticompetitive pricing or market allocation discussion occurs.
- **Do** alert SOA staff and/or legal counsel to any concerning discussions
- **Do** consult with legal counsel before raising any matter or making a statement that may involve competitively sensitive information.

Adherence to these guidelines involves not only avoidance of antitrust violations, but avoidance of behavior which might be so construed. These guidelines only provide an overview of prohibited activities. SOA legal counsel reviews meeting agenda and materials as deemed appropriate and any discussion that departs from the formal agenda should be scrutinized carefully. Antitrust compliance is everyone's responsibility; however, please seek legal counsel if you have any questions or concerns.

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Outline

Introduction: A Time of Wonder in Therapeutics — Loraine

- Introduction to Therapeutics, New Drug Development and AI
- The Complexity of Cancer and New Weight Loss Drugs

Cancer — Al

- New considerations

Cardiovascular Disease — David

- Data Analyses and Mortality Trends

New Weight Loss Drugs and Connections — Loraine

Future View of Therapeutics Impact — All

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Introduction: A Time of Wonder in Therapeutics – Loraine

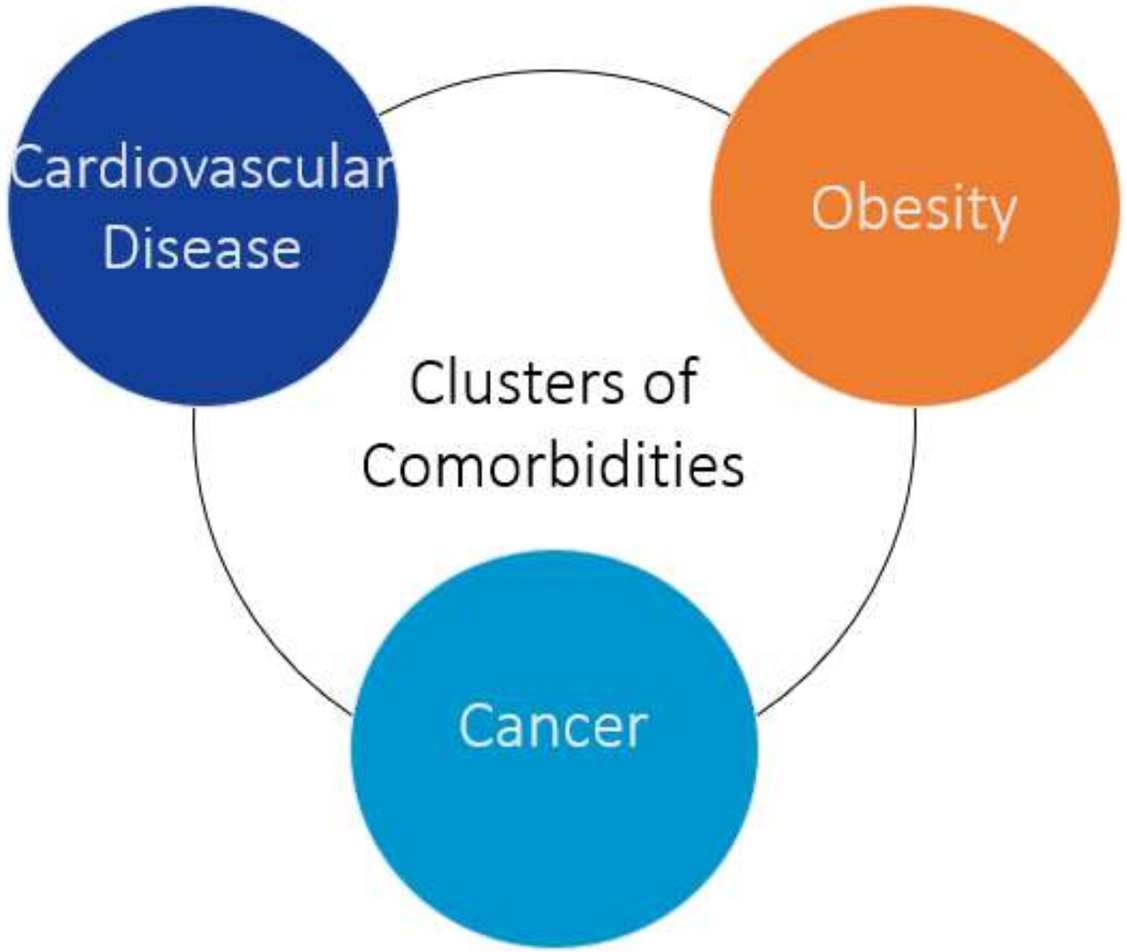
Which is most likely to decrease population mortality?

A. New Weight Loss Drugs

B. New Treatments for Cancer

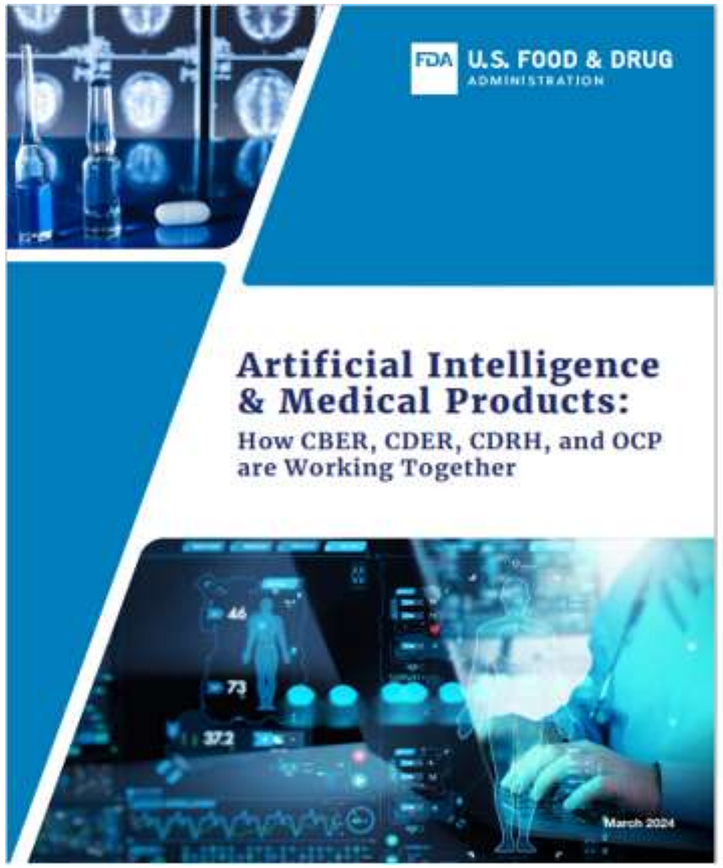
C. New Treatments for Cardiovascular Disease

Therapeutics: The Transformation of Mortality



Therapeutics:
defined here as pharmaceuticals

Artificial Intelligence Transforms Medicine



March 2024: AI has emerged as a transformative force. It has the potential to revolutionize health care by:

- Advancing medical product development
- Improving patient care
- Augmenting capabilities of health care practitioners

Source: Artificial Intelligence and Medical Products | FDA

Drug Expenditures, USA

Am J Health Syst Pharm. 2024 Jul 8;81(14):583-598. doi: 10.1093/ajhp/zxae105.

National trends in prescription drug expenditures and projections for 2024

Eric M Tichy [1], James M Hoffman [2], Mina Tadrous [3 4], Matthew H Rim [5], Sandra Cuellar [6], John S Clark [7 8], Mary Kate Newell [9], Glen T Schumock [6]

2023: $722.5B

Increase since 2022: 13.6%

Driven by:
- Utilization
- New Drugs
- Price

Top Drug Expenditure in 2023:

Semaglutide $38B

GLP-1 Agonists for Weight Loss: Increasing Utilization

- GLP-1 Agonists: US **2024** spend **$53.5B**
- GLP-1 Market Growth: **CAGR 11.1%** 2024-2035
- KFF Poll 2024: **1 in 8 (12%)** of **adults** say they have taken a GLP-1 Agonist

Source: https://www.grandviewresearch.com/industry-analysis/glp-1-receptor-agonist-market
https://www.kff.org/health-costs/poll-finding/kff-health-tracking-poll-may-2024-the-publics-use-and-views-of-glp-1-drugs
https://www.globenewswire.com/news-release/2024/10/01/2955841/28124/en/49-3-Bn-GLP-1-Markets-2024-2035-with-Boehringer-Ingelheim-Eli-Lilly-Novo-Nordisk-Dominating.html

FDA New Drug Approvals 2024

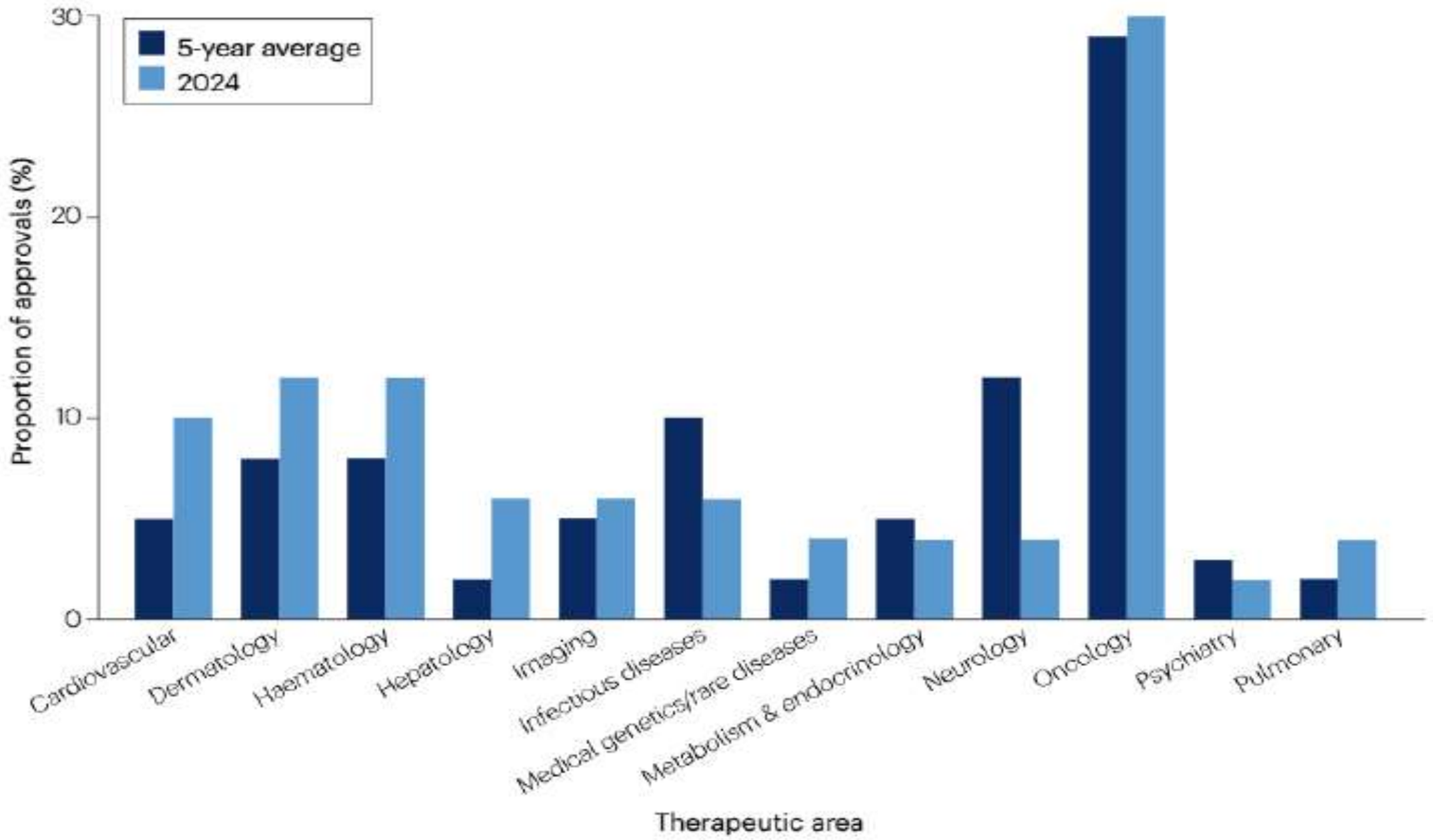


Fig. 2 | CDER approvals by therapeutic areas. Indications that span multiple disease areas are classified under only one, based on which FDA office and division reviewed the approval application. Source: *Nature Reviews Drug Discovery*, FDA.

2024:

- FDA's Center for Drug Evaluation and Research (CDER) approved 50 new small molecules, biologics and oligonucleotide therapeutics

- "**Cancer** remains the dominant focus of drug developers, with 15 (30%) novel approvals in 2024"

Source: Nature Reviews Drug Discovery Vol. 24, Feb. 2025, 75-82; FDA

FDA: Accelerated Pathways to New Drug Approval

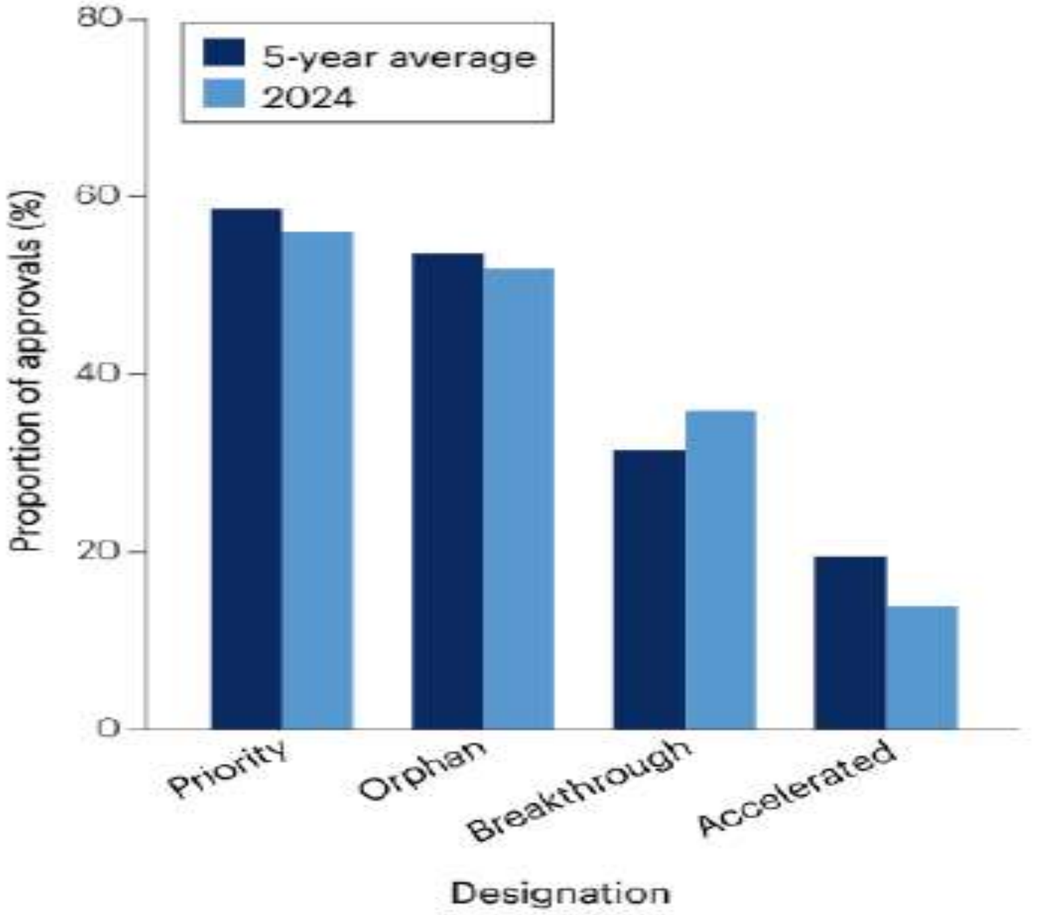


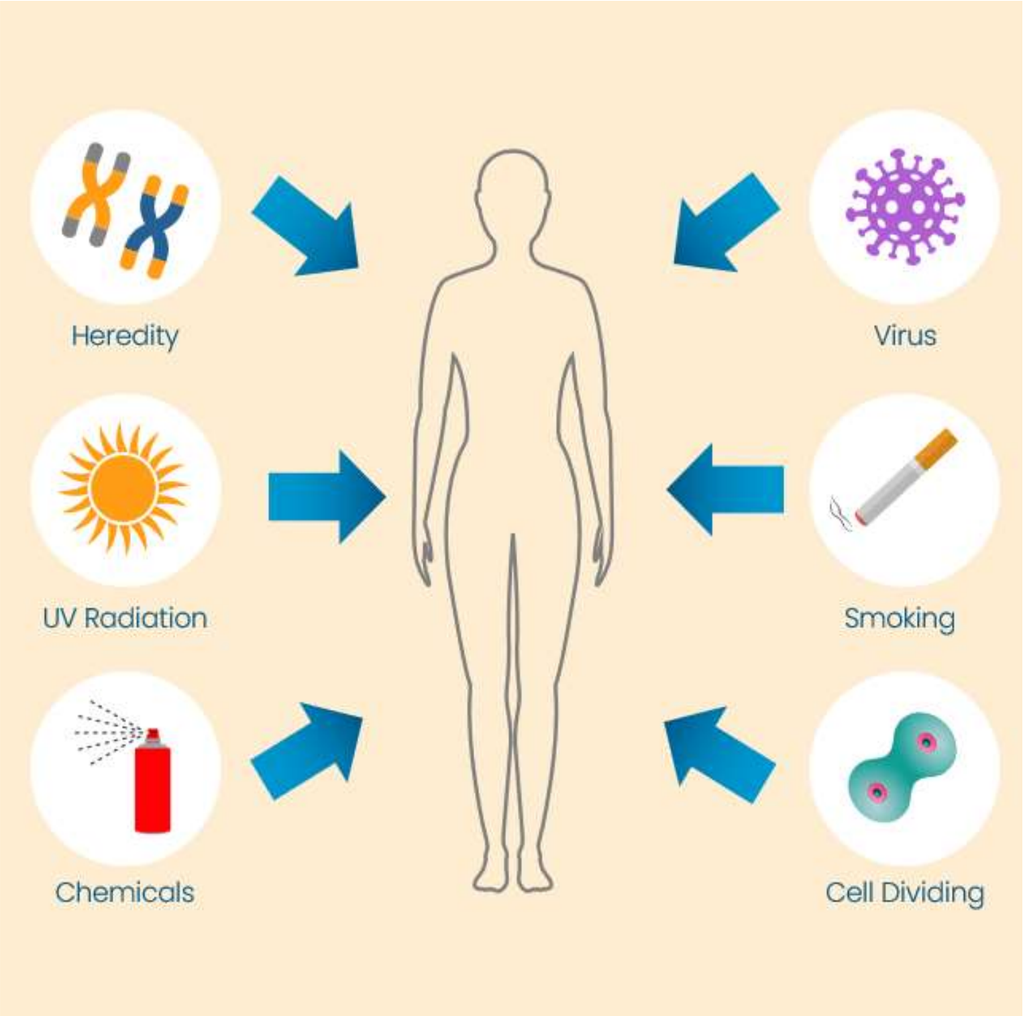
Fig. 4 | CDER approvals by regulatory designation.
Source: *Nature Reviews Drug Discovery*, FDA.

Source: Nature Reviews Drug Discovery Vol. 24, Feb. 2025, 75-82; FDA

Cancer: A Dynamic, Complex Group of Genetic Diseases

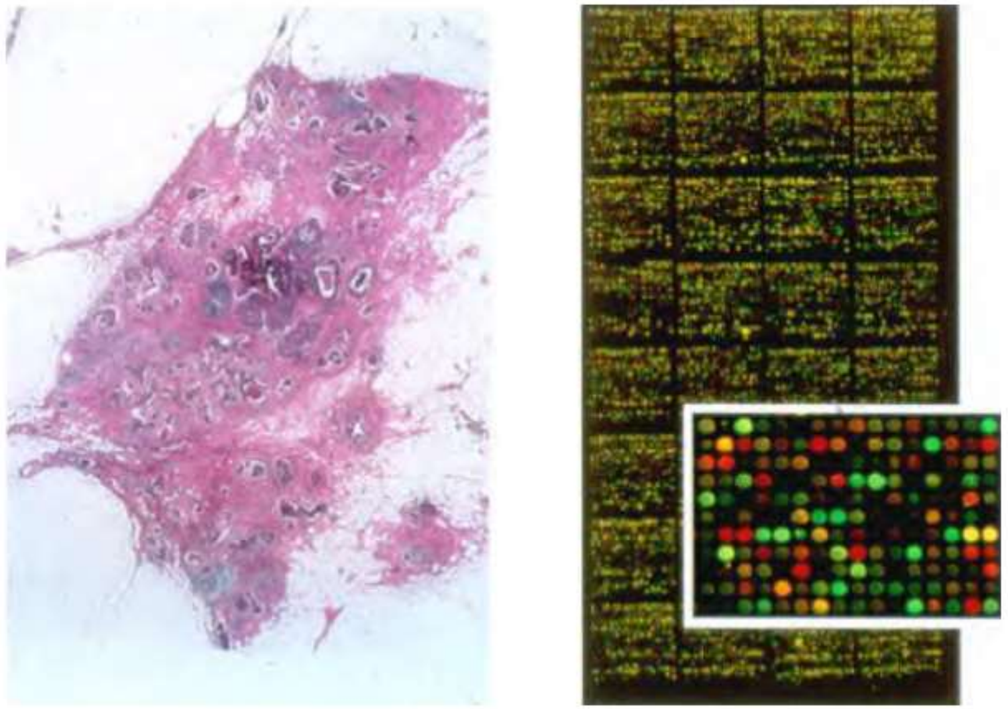
All Cancer is Genetic

- Multiple factors including genetic, nongenetic contribute to cause
- Key risk factor: **Aging**
- **Cancers change** with time to evade treatment
- **Biologic behavior** of cancer is **highly variable**
- Hereditary cancer is uncommon
- Our knowledge is rapidly evolving



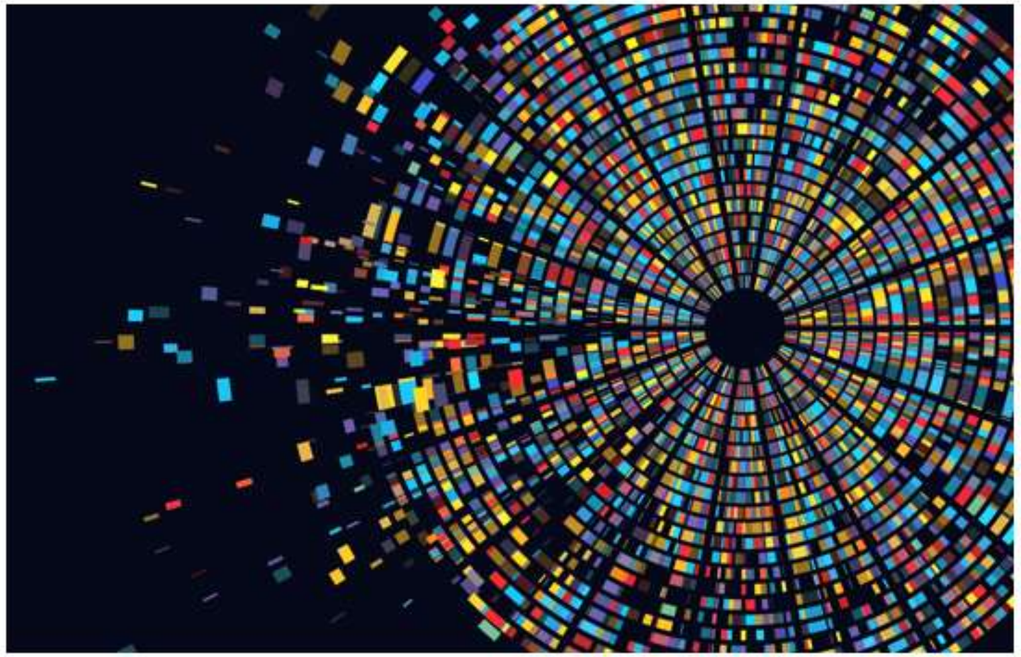
A New Way to Look at Cancer: The Genetic Signature

Two Images of a Breast Cancer



Source: https://dceg.cancer.gov/news-events/news/2021/mutational-signatures

Advances in sequencing technology and bioinformatics tools have revealed genetic patterns or mutational signatures



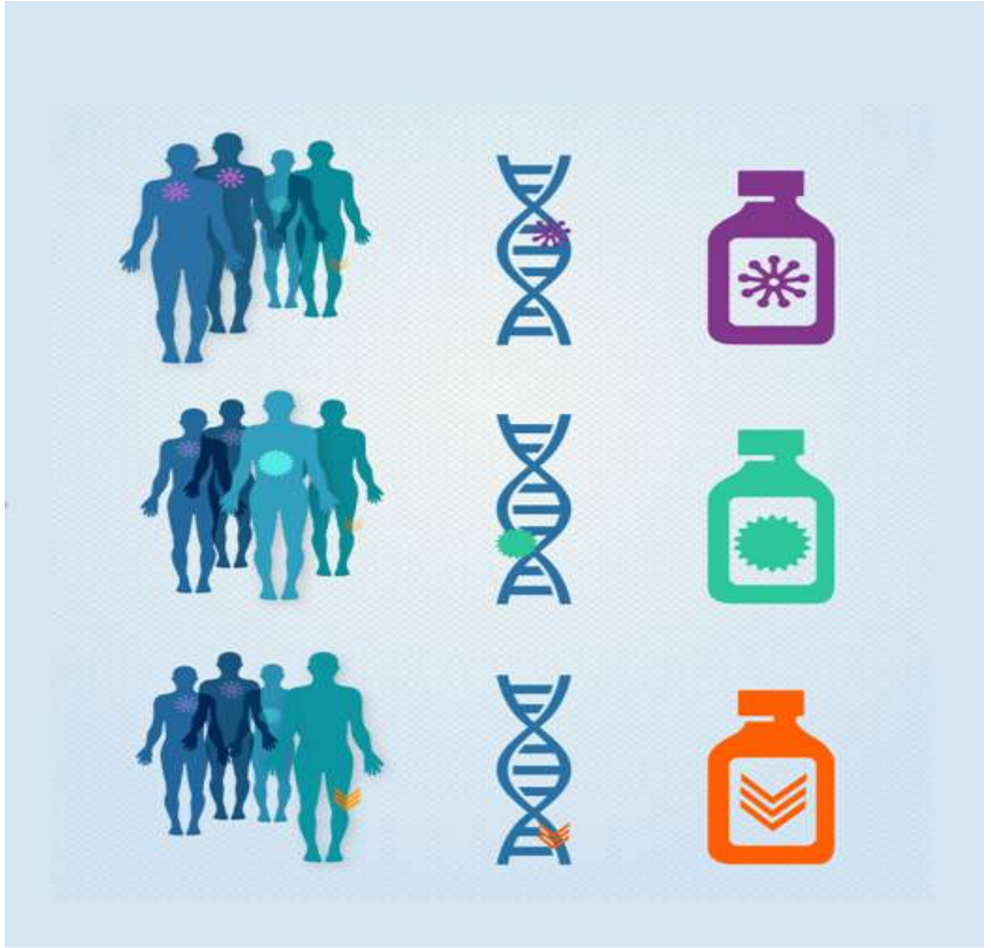
The Promise of Precision Medicine

Other Terms

Personalized Medicine or Targeted Medicine

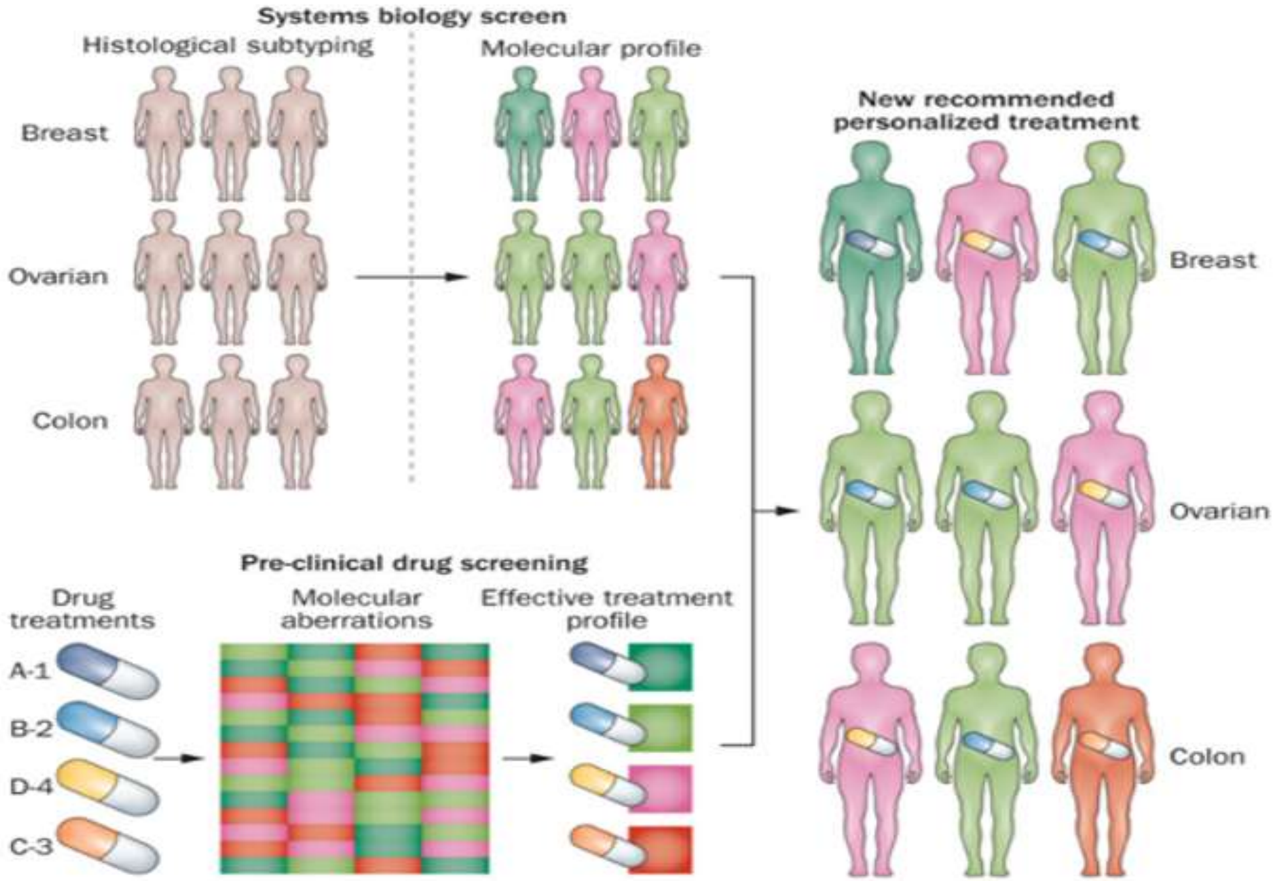
*Is a **form of medicine** that uses information about a person's own genes or proteins to prevent, diagnose or treat disease.*

*In cancer, **precision medicine** uses specific information about a person's tumor to help make a diagnosis, plan treatment, find out how well treatment is working, or make a prognosis*



Source: https://www.cancer.gov/research/areas/treatment/pmi-oncology
https://www.cancer.gov/publications/dictionaries/cancer-terms/def/precision-medicine

Cancer: Classification and Therapy “Agnostic” to Tissue of Origin



The Molecular “Footprint” of Cancer Guides Management

Source: Werner, H. et. al. Nature Reviews Clinical Oncology 11, 167-176 (2014)

Cancer – AI

Understanding Cancer

- **Clinical definition**

  Uncontrolled tissue growth that evades recognition by immune system

- **New definition**

  Fundamentally a genetic disease due to mutations in cells, with
  uncontrolled growth in surrounding tissue and development of own blood supply
  Now considered a group of diseases distinguished by uncontrolled growth

- **Organ**

  Statistics are provided by organ
  Type of uncontrolled cell growth may be similar or different within each organ

Source: Cancer Mortality at the Older Ages: An Expert Panel Discussion, November 2024, https://www.soa.org/4ad99b/globalassets/assets/files/resources/research-report/2024/older-age-mortality.pdf

Understanding Cancer (cont'd)

- Stages
  - Ranges from 1 (locally confined) to 4 (metastatic)
  - Relates to anatomical findings rather than mortality risk
  - Significance of each stage depends on type of cancer
- Grades
  - Relates to appearance of cancer cells
  - Higher grades relate to higher irregularity of the cells

Understanding Cancer (cont'd)

- **Cure**

  Term rarely used today because implies permanent solution

- **Remission**

  Focus is complete remission, where all signs of cancer have disappeared

- **Actuarial and underwriting perspective**

  Tests might be positive despite no visual evidence of cancer

  Tests might be negative, which doesn't necessarily mean individual is cured

  Cancer is most likely to happen in the first two years following treatment

  If cancer doesn't recur within 10 years, risk of recurrence is low but not zero

Cancer and Life Expectancy

- Cancer affects life expectancy, however …
- If cancer is <u>completely</u> contained within an organ
  And that organ can be removed
- If acquired at older ages
  There are other competing mortality risks

Cancer and Life Expectancy

- Currently lung cancer mortality peaks at ages 80-85 and then declines

  This is based on many previous heavy smokers who quit smoking in the 1960s
  In the future, pattern of older age lung cancer deaths likely to be different

U.S. Cancer Mortality 2014-2023 (Annual percentage change)

Annual % Change in Crude Mortality Rates													
Years	Overall	Female	Male	Ages									
				1-4	5-14	15-24	25-34	35-44	45-54	55-64	65-74	75-84	85+
2014 to 2015	-0.1%												
2015 to 2016	-0.2%												
2016 to 2017	-0.6%												
2017 to 2018	-0.4%	-0.5%	-0.3%	0.0%	-2.4%	0.8%	0.9%	-3.4%	-3.3%	-1.4%	-2.4%	-2.5%	-1.4%
2018 to 2019	-0.3%	-0.3%	-0.2%	-11.1%	-7.3%	1.6%	-3.1%	-0.4%	-2.9%	-2.3%	-1.9%	-2.5%	-0.5%
2019 to 2020	0.1%	-0.1%	0.2%	9.7%	2.6%	-5.4%	-1.0%	-0.8%	-1.6%	-1.3%	-0.8%	-1.7%	-2.4%
2020 to 2021	-0.2%	0.5%	-1.0%	-7.6%	-2.6%	-0.8%	2.6%	1.2%	-3.7%	-2.9%	-1.1%	2.4%	11.5%
2021 to 2022	0.1%	0.6%	-0.3%	0.0%	7.9%	4.9%	0.6%	-0.7%	0.1%	-1.0%	-0.7%	-3.1%	-8.0%
2022 to 2023	0.3%	0.1%	0.6%	0.0%	0.0%	3.9%	-3.8%	-0.6%	-1.7%	-2.7%	-1.5%	-1.3%	5.7%

- Cancer death mortality on an overall basis improved (negative values) each year from 2014 through 2019, and then deteriorated in 3 of 4 COVID years (2020-2023)
- All overall yearly changes were less than 1%
- Results by sex and age varied over all years (2017 to 2023) in both direction and magnitude

Source: CDC Rapid Release data through March 2024

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Factors Influencing Cancer

- Lifestyle
- Diet, exercise, smoking, alcohol consumption
- Environmental
  e.g., pollution
- Genetics
- Risk mitigants
  Screenings, vaccinations

Cancer Therapeutics

- Movement towards individualized treatment
  But still not prevalent
- Each type of cancer has own treatment protocols, based on:
  Stage
  Grade
  Molecular signature of the cancer
  Other comorbidities

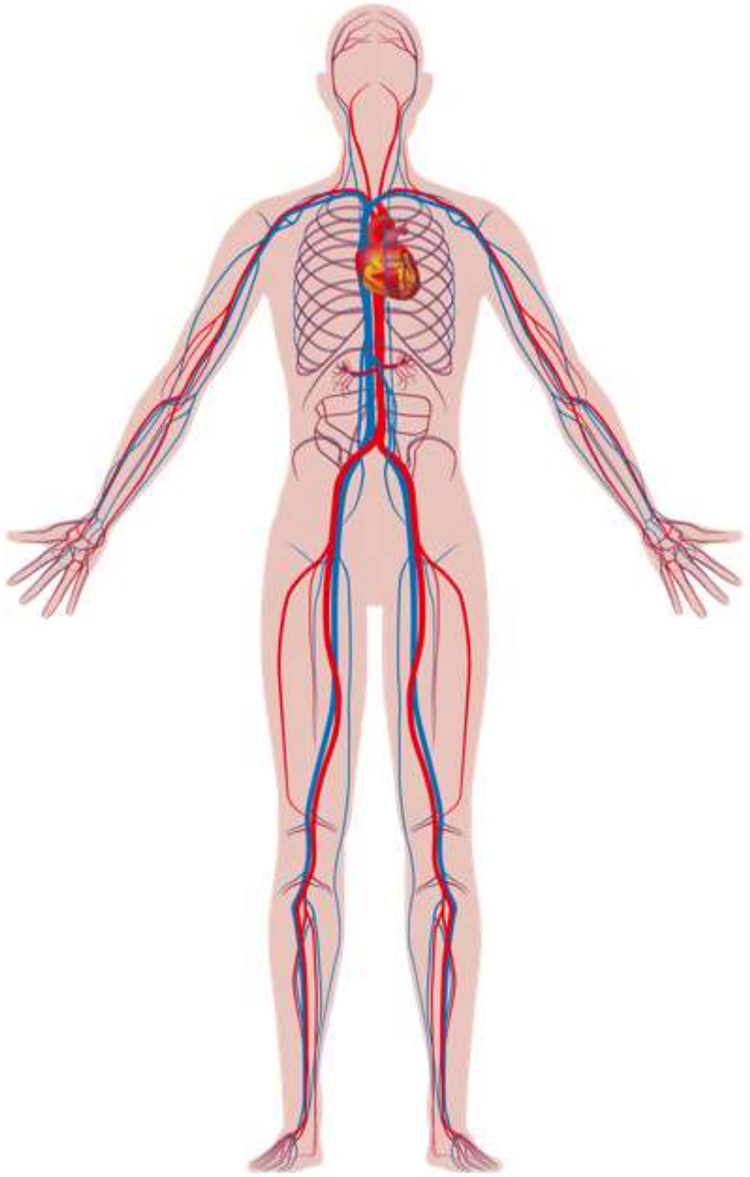
Cancer Therapeutics (cont'd)

- **Liquid biopsies**
  Fluid (generally blood) collected to identify type of cancer
  Tumor DNA or other markers, e.g., protein signatures are analyzed
  Used mainly for lung cancer now, but use will expand
- **Immunotherapy**
  Allows immune system to recognize cancer and kill it
- **InVision**
  A better way to check lymph nodes through shortwave ultraviolet light
- **AI – potential uses:**
  Quicker identification of cancer
  More accurate diagnosis and treatment protocol

Cardiovascular Disease

David Hatherell – Senior Actuary

Cardiovascular Disease is not Limited to the Heart



It includes but is not limited to:

- Coronary artery disease
- Heart valve disease
- Cerebrovascular disease
- Aortic disease
- Carotid artery disease
- Peripheral artery disease

Some Cardiovascular Disease Risk Factors

Diabetes

Hyperlipidemia

Smoking

High Blood Pressure

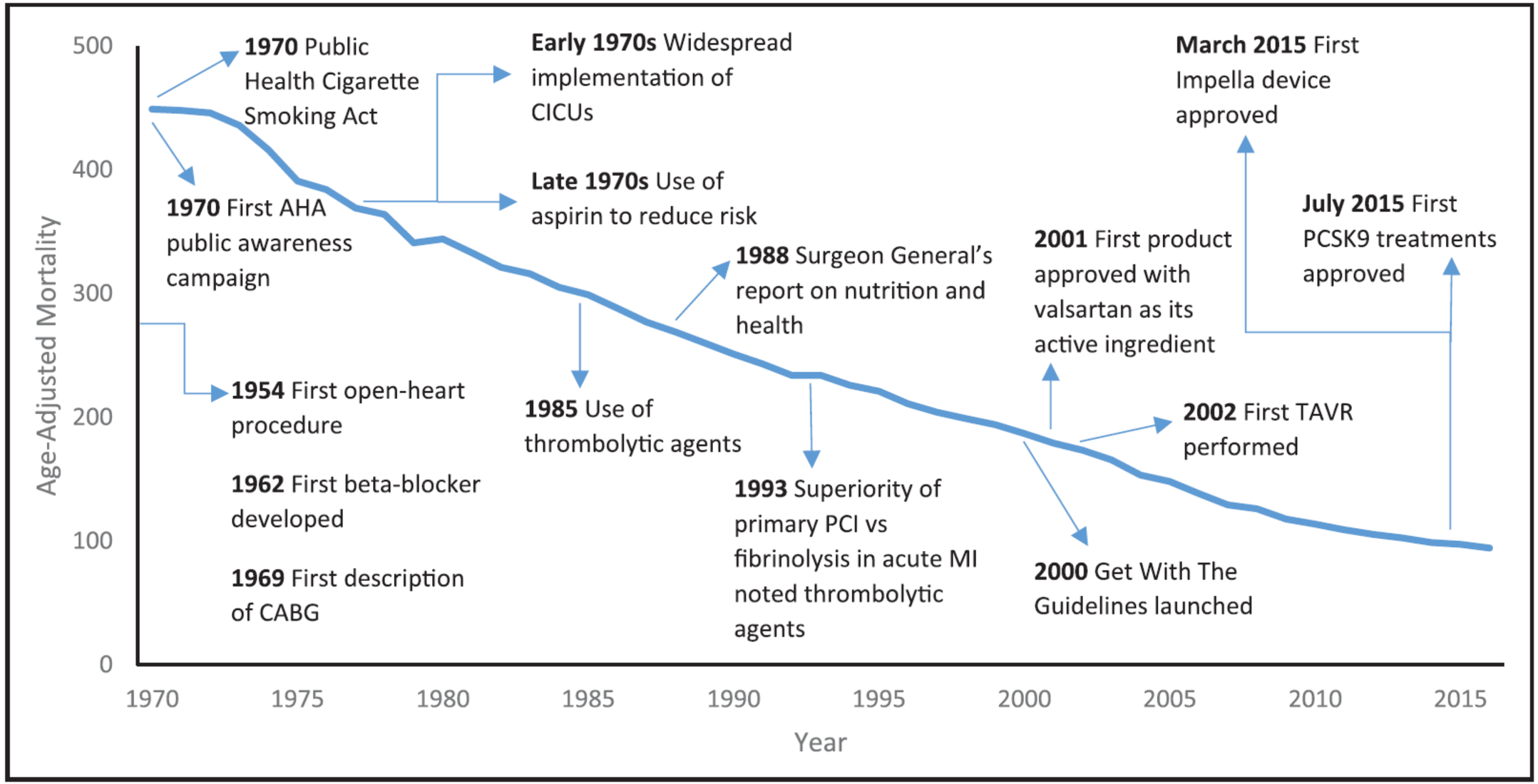
Obesity

Physical Inactivity

Diet

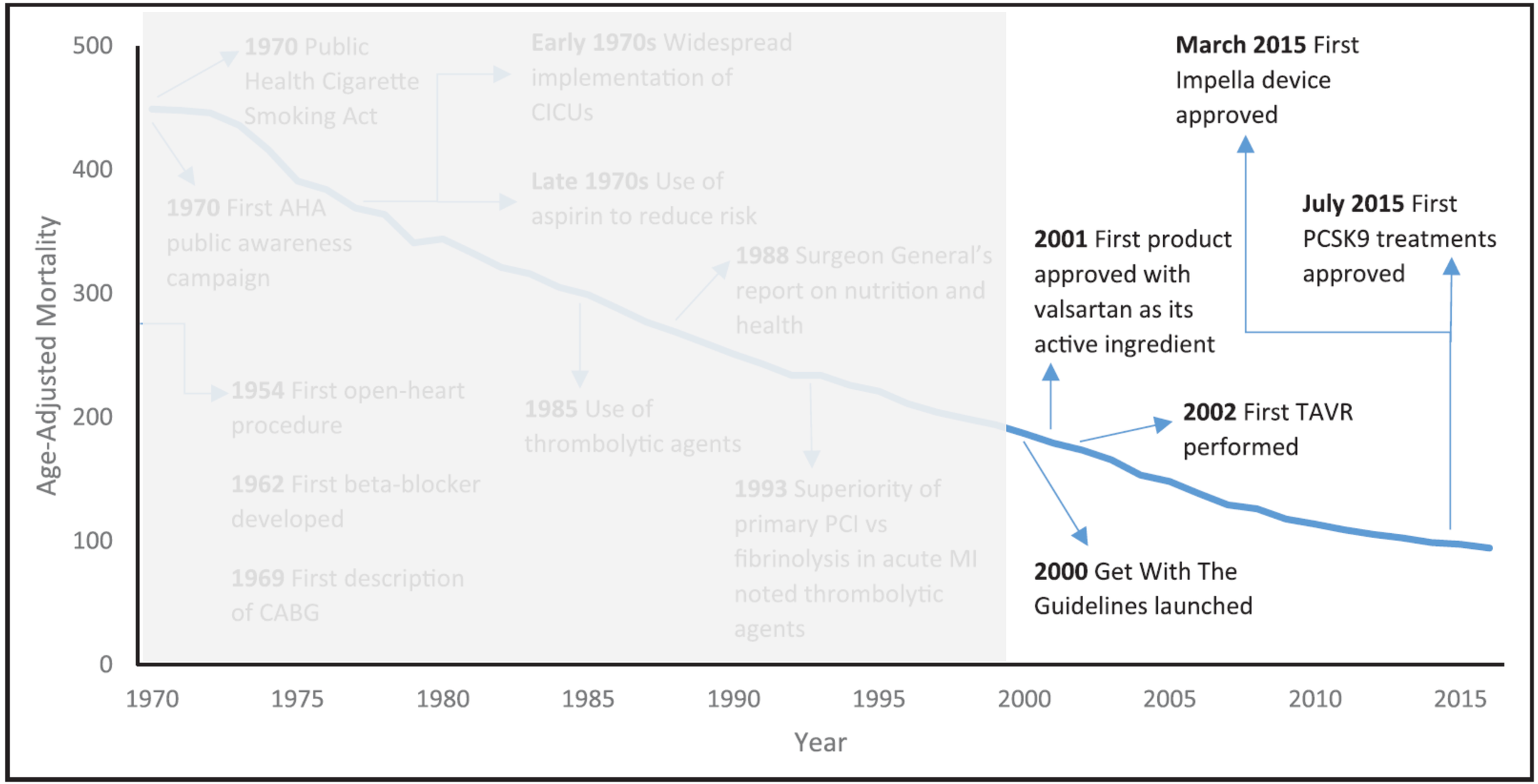
Source: https://stanfordhealthcare.org/medical-conditions/blood-heart-circulation/vascular-disease/causes/risk-factors.html

Cardiovascular Treatments Over Time



McClellan, M., Brown, N., Califf, R. M., & Warner, J. J. (2019). Call to action: Urgent challenges in cardiovascular disease: A presidential advisory from the American Heart Association. Circulation, 139(9), e44–e54. https://doi.org/10.1161/CIR.0000000000000652

Cardiovascular Treatments Over Time



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Cardiovascular Disease – Data Considerations

Data Considerations

- Data coding
- Known influences (smoker cessation)
- Additional considerations

Data Coding and Comorbidities

Deaths removed from a specific cause may create artificial mortality improvements for that cause

We may only have primary cause of death

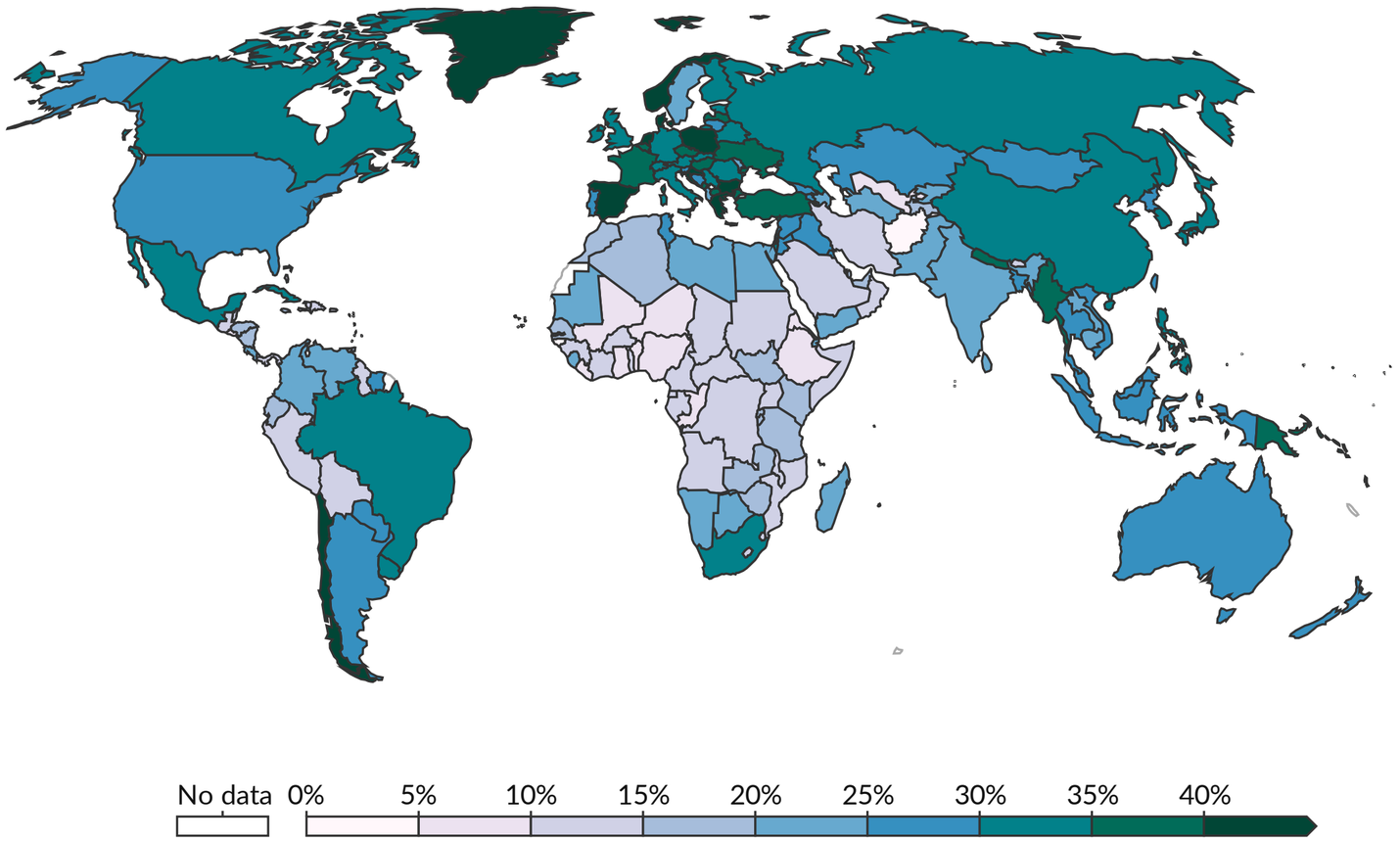
Known Influences – Smoker Cessation

- Observe population mortality improvements by looking at changes in mortality rates
- Recent periods have lower smoker proportions
  - Smoker cessation
  - People did not start smoking
- Lag effects exist

Known Influences – Smoker Cessation

Prevalence of daily smoking in populations, 1990

Shown is the sharer of people aged 15 years and older that smoke tobacco daily. This rate is age-standardized, which assumes a constant age structure of the population over time and between countries.

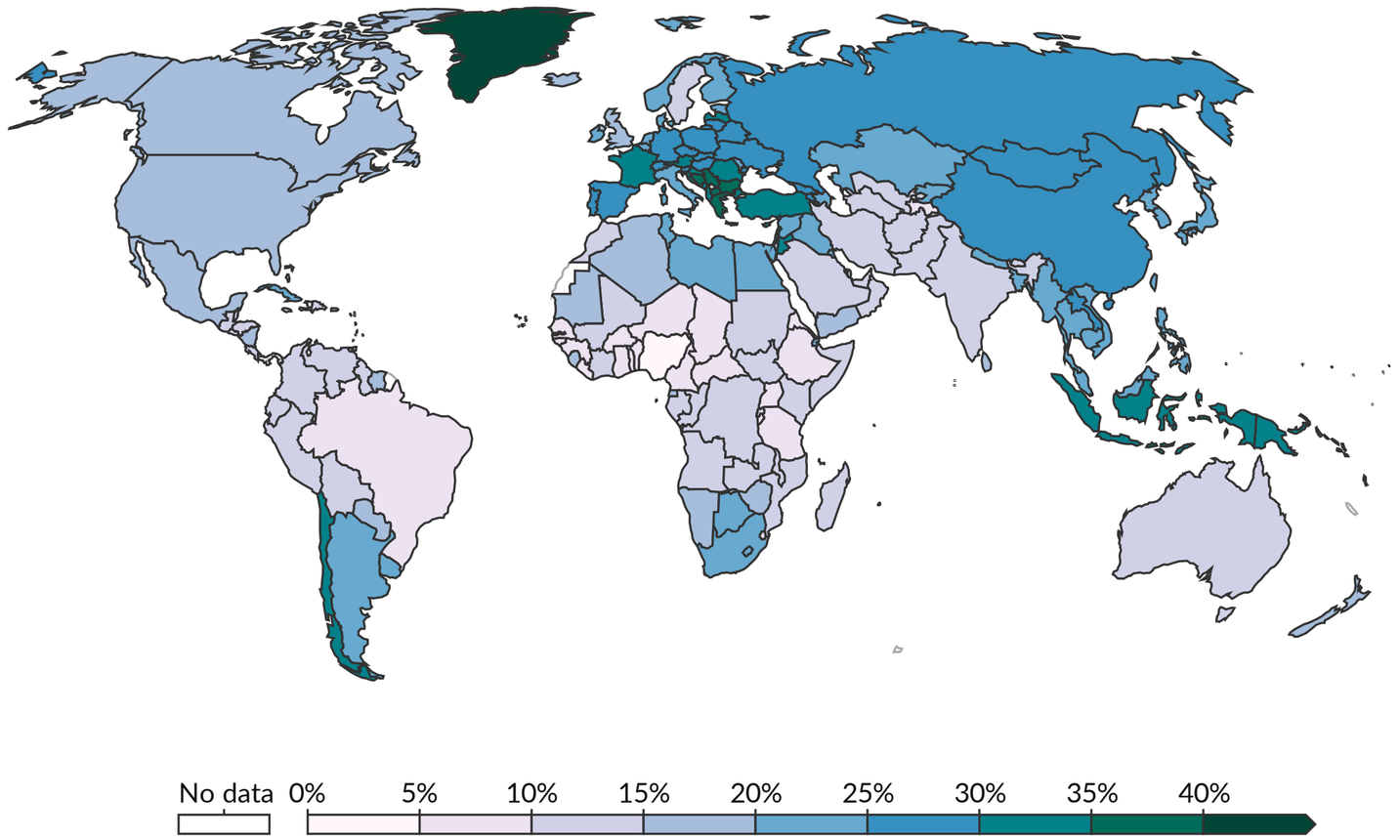


Source: IHME, Global Burden of Disease, OurWorldInData.org/smoking

Known Influences – Smoker Cessation

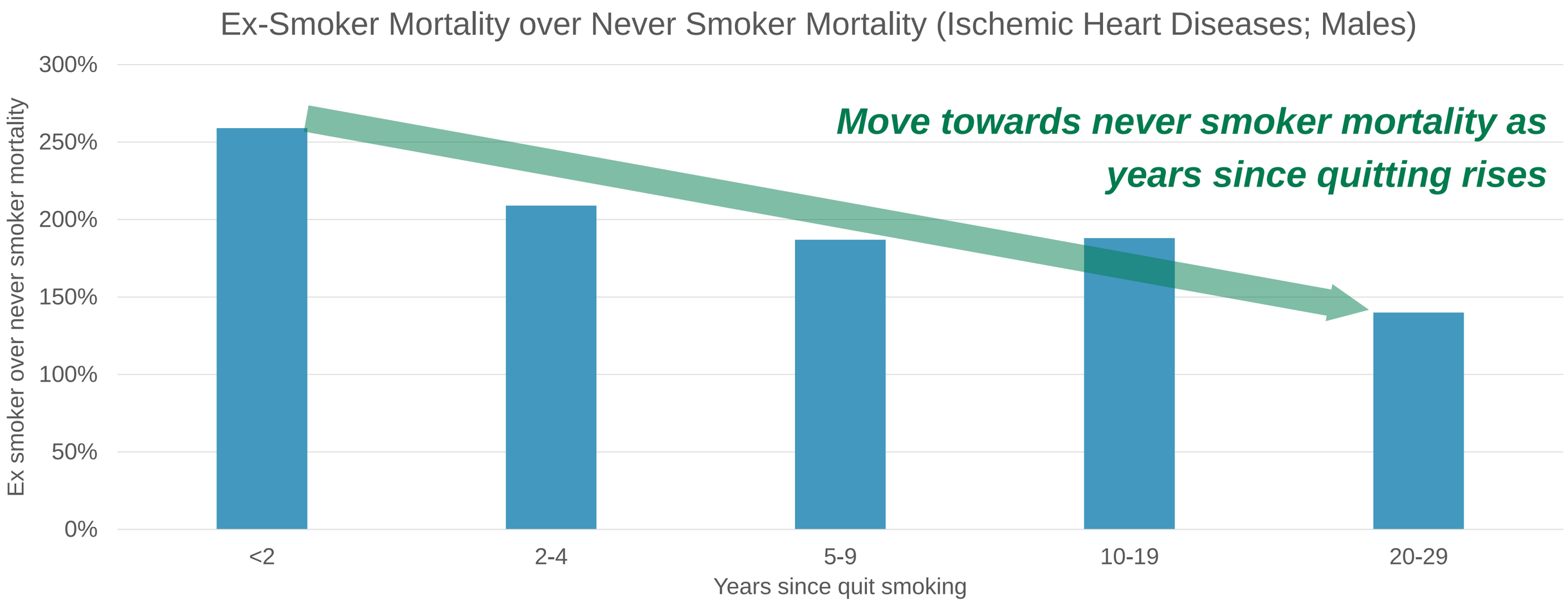
Prevalence of daily smoking in populations, 2021

Shown is the sharer of people aged 15 years and older that smoke tobacco daily. This rate is age-standardized, which assumes a constant age structure of the population over time and between countries.



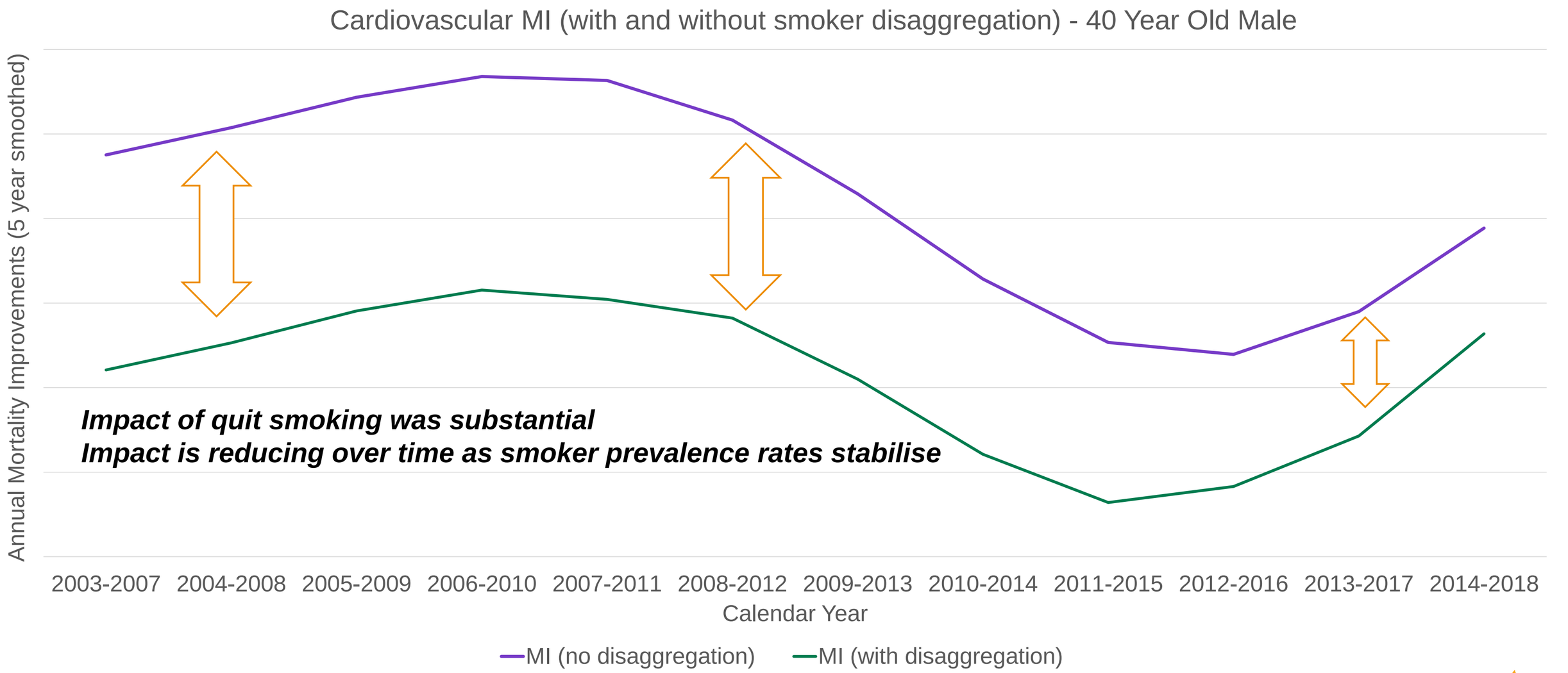
Source: IHME, Global Burden of Disease, OurWorldInData.org/smoking

The Effect of Smoking on Ischemic Heart Disease



Source: [nejmsa1211127_appendix.pdf]

Impact of Smoker Disaggregation Over Time



Additional Data Considerations

Climate change

Migration

Excess deaths

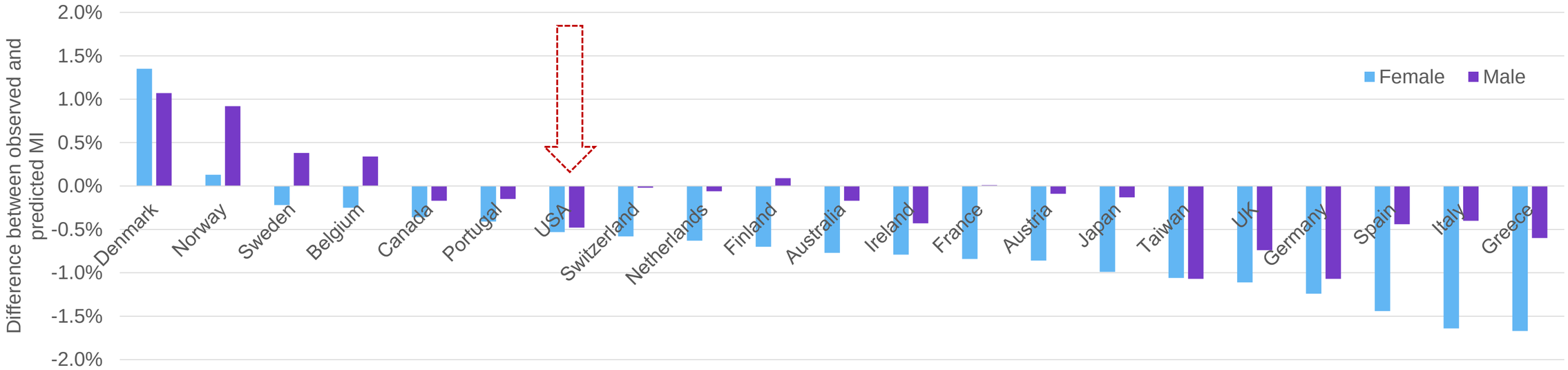
Uncertainty

We can find additional insights with access to timely data, but mortality uncertainty remains…

Cardiovascular Disease – Mortality Trends

Recent Slowdown in Mortality Improvements

Multi-country analysis that uses stochastic mortality models to predict mortality improvement rates for 2011-2017 based on historical data (1965-2010)



Potential drivers:

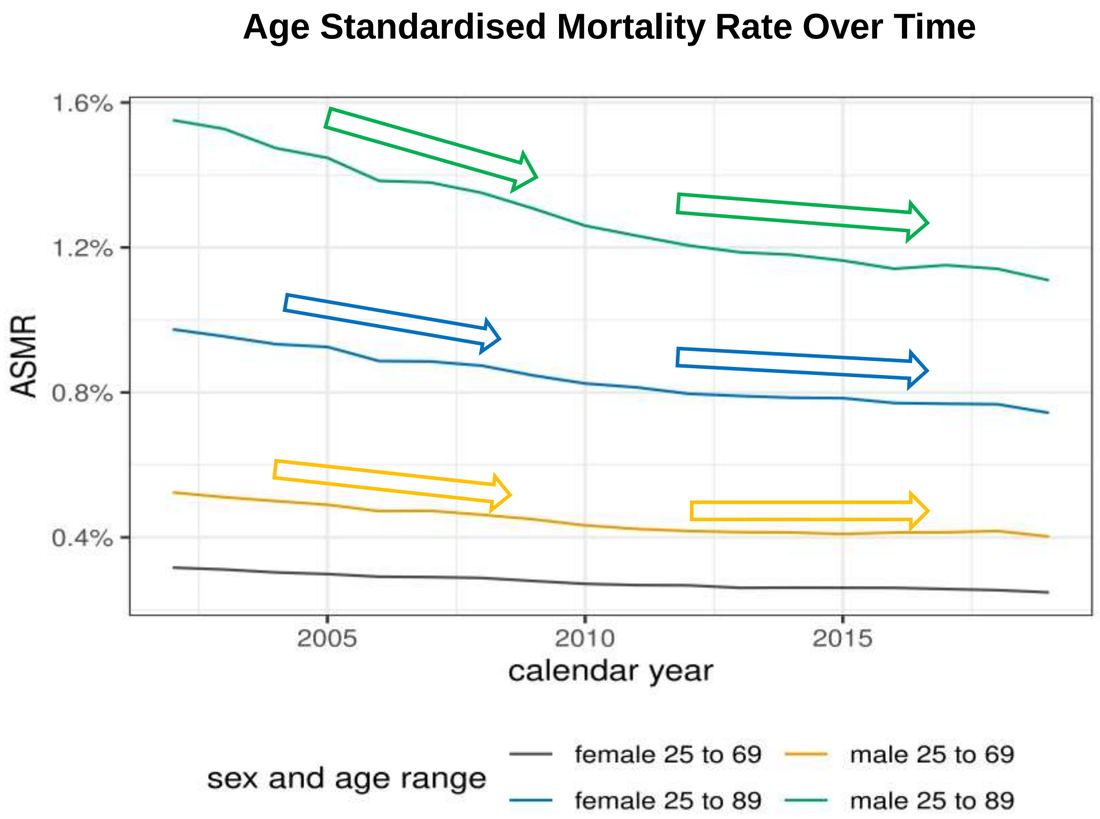
Austerity, winter deaths, worsening trends in diabetes and obesity, **stabilizing smoking prevalence rates** and **cholesterol levels** (→ decreasing improvements from circulatory diseases), rising mortality rates related to **dementia** and **alzheimer diseases** (→ coding practices?).

Source: Djeundje, V.B., Haberman, S., Bajekal, M. et al. The slowdown in mortality improvement rates 2011–2017: a multi-country analysis. Eur. Actuar. J. (2022). https://doi.org/10.1007/s13385-022-00318-0

Trends: How We Look at Mortality Improvements

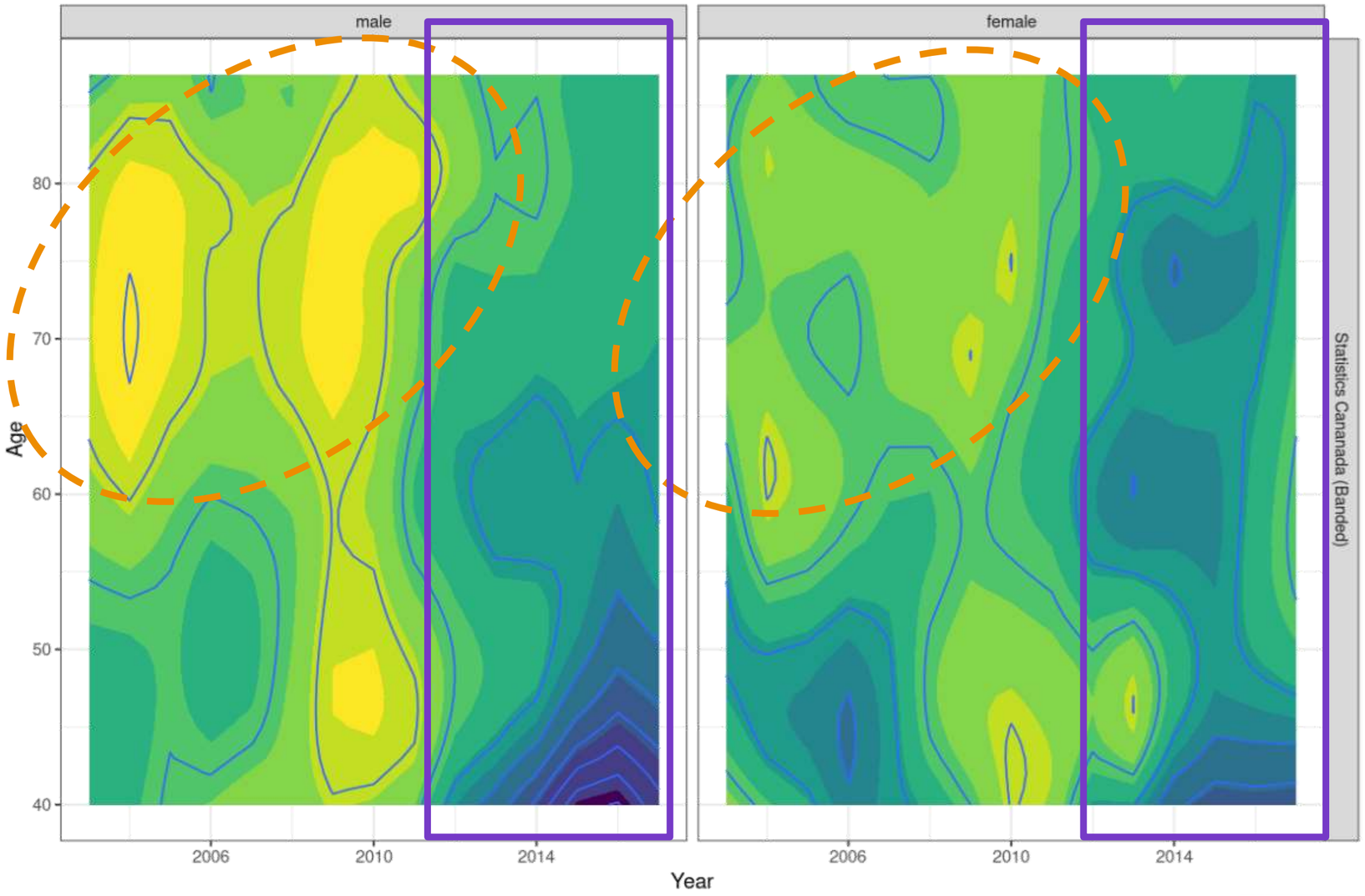
- Age standardized mortality rates (ASMR or SMR)
- Heat maps
- Contribution to mortality improvements
  - Cause
  - Socio-economic group

Trends: Historic Mortality



- Higher mortality improvement rates prior to 2012.
- Historic mortality improvements from:
  - Smoker cessation
  - Cardiovascular related medical improvements

All-Cause Mortality Improvement Heatmap

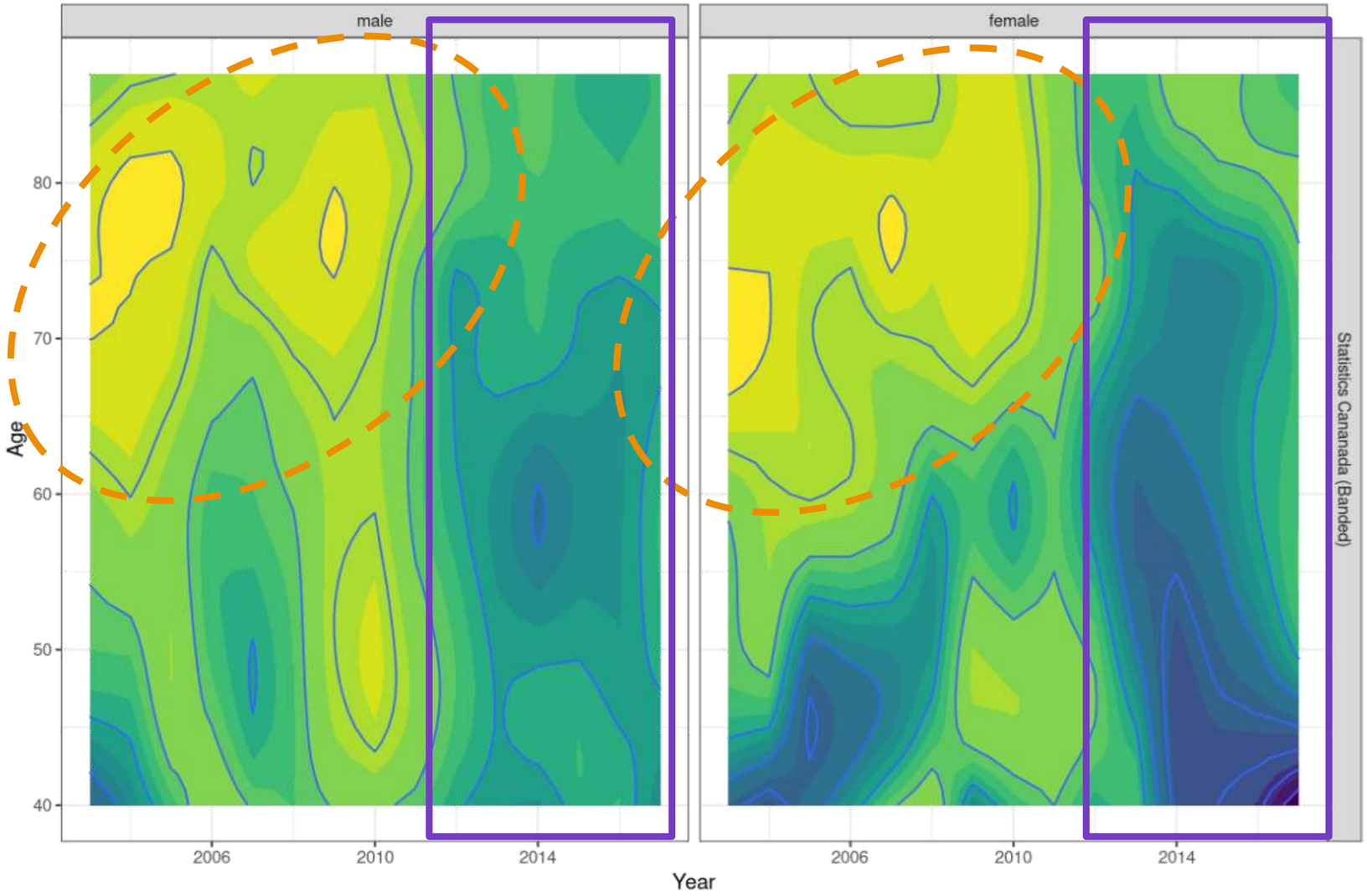


Higher mortality improvements (yellow) at older ages prior to 2012.

Improvements have since reduced.

5x5 smoothing applied

Cardiovascular Mortality Improvement Heatmap

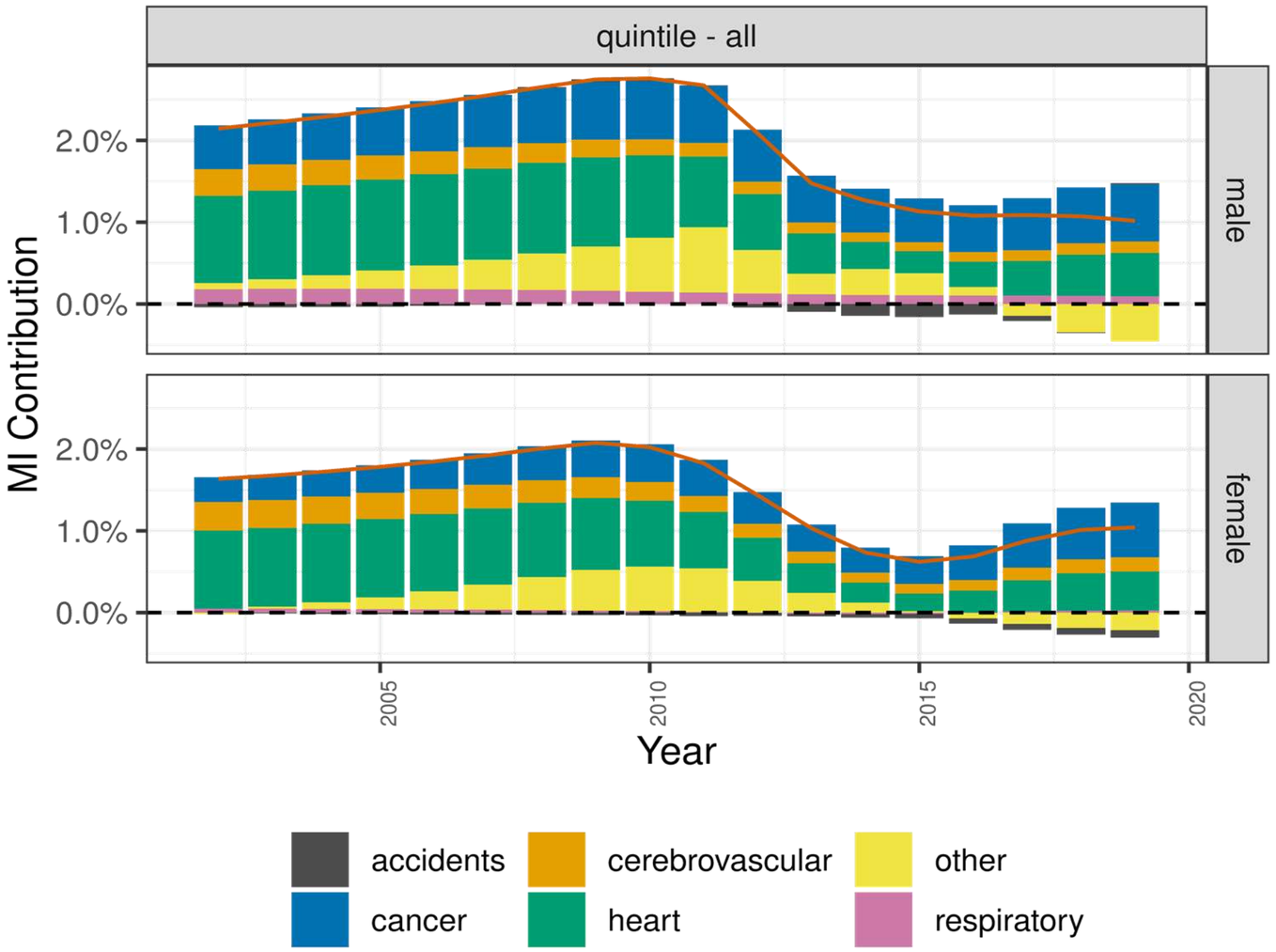


Higher cardiovascular mortality improvements (yellow) at older ages prior to 2012.

Improvements have since reduced.

5x5 smoothing applied

Contribution to Mortality Improvements



Similar trends seen for males and females.

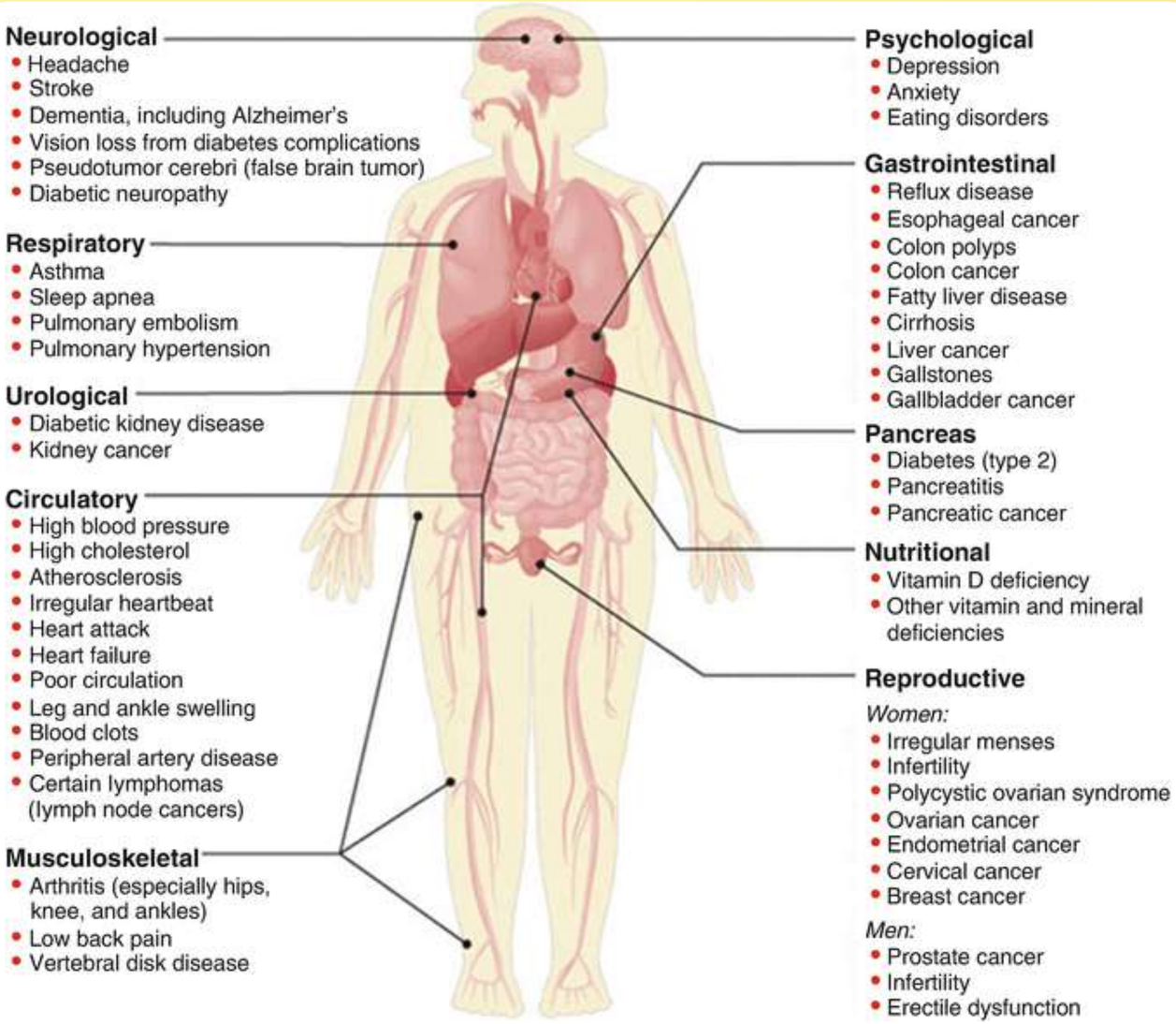
Higher contributions to mortality improvements from heart prior to 2013 which have dropped in recent periods.

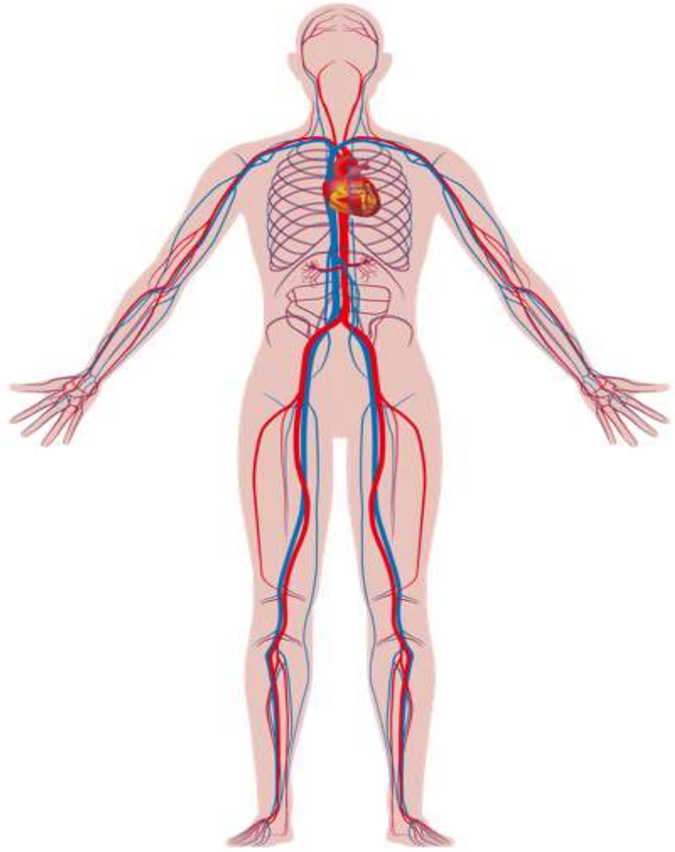
Future Considerations

- Transcatheter aortic valve replacement (TAVR)
- Technological advancements

Cardiovascular Disease – Additional Considerations

Related Conditions – Causes of Death Linked to Obesity





For comparison

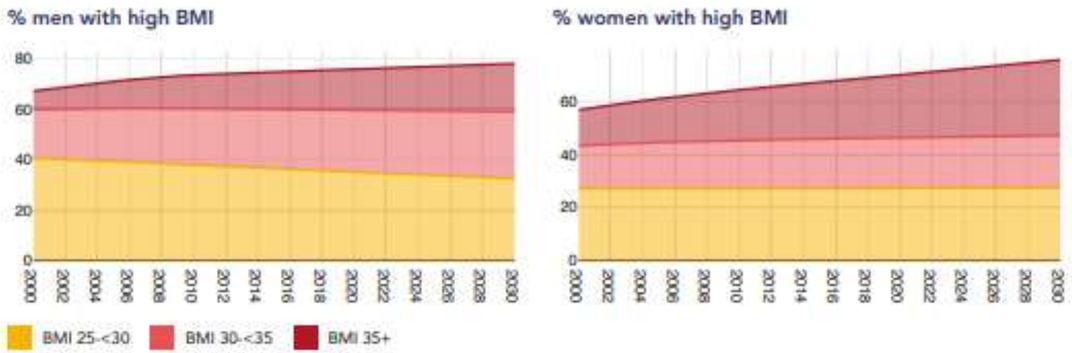
Source: https://link.springer.com/chapter/10.1007/978-3-319-42536-8_5

Future Considerations – Obesity

United States

Overweight and obesity prevalence over time

Projected proportion of adults living with high Body Mass Index (25kg/m^2 and above)



Adult population living with high BMI estimated in 2010, 2015 and projected to 2030 (in thousands)

	Men			Women		
BMI (kg/m^2)	2010	2015	2030	2010	2015	2030
25-<30	42,310	43,770	44,730	31,280	33,090	38,020
30-<35	25,350	28,220	36,580	21,060	22,860	27,130
35+	14,840	17,740	26,230	22,020	26,050	39,440
All high BMI	**82,500**	**89,730**	**107,540**	**74,360**	**82,010**	**104,590**

Totals may not add up due to rounding

75%
Adults with high BMI in 2025

44%
Adults living with obesity in 2025

212.13m
Adults with high BMI in 2030

116,634
Premature NCD deaths due to high BMI, 2021

Source: https://data.worldobesity.org/publications/world-obesity-atlas-2025-v6.pdf

New Weight Loss Drugs – Loraine

Ozempic Use – In the News…

"Will the Ozempic Era Change How We Think About Being Fat and Being Thin?"

The New Yorker, March 20, 2023

Pathogenesis of Obesity is Multifactorial

Labelling obesity as a "lifestyle choice" leads to stigmatization

- **Complex interaction of genetic and environmental factors**
  - Demographic, social, economic factors
  - Fetal, Childhood factors
  - Adults: aging, pregnancy, menopause
  - Lifestyle
    - Diet, physical activity, sleep
  - Medications
    - Antidepressants, some diabetes medications
  - Medical conditions
    - Thyroid disease, other endocrine conditions
  - Other

Multiple Comorbidities

Drug Therapy for Weight Loss

- Use with "thorough and compassionate counseling around healthy eating, physical activity, and health-seeking behavior…"
- Underlying comorbidities: Chronic disease management
- Consider: Access/insurance issues, adverse effect profile, cost
- Consider Durability of Effect if medication is stopped

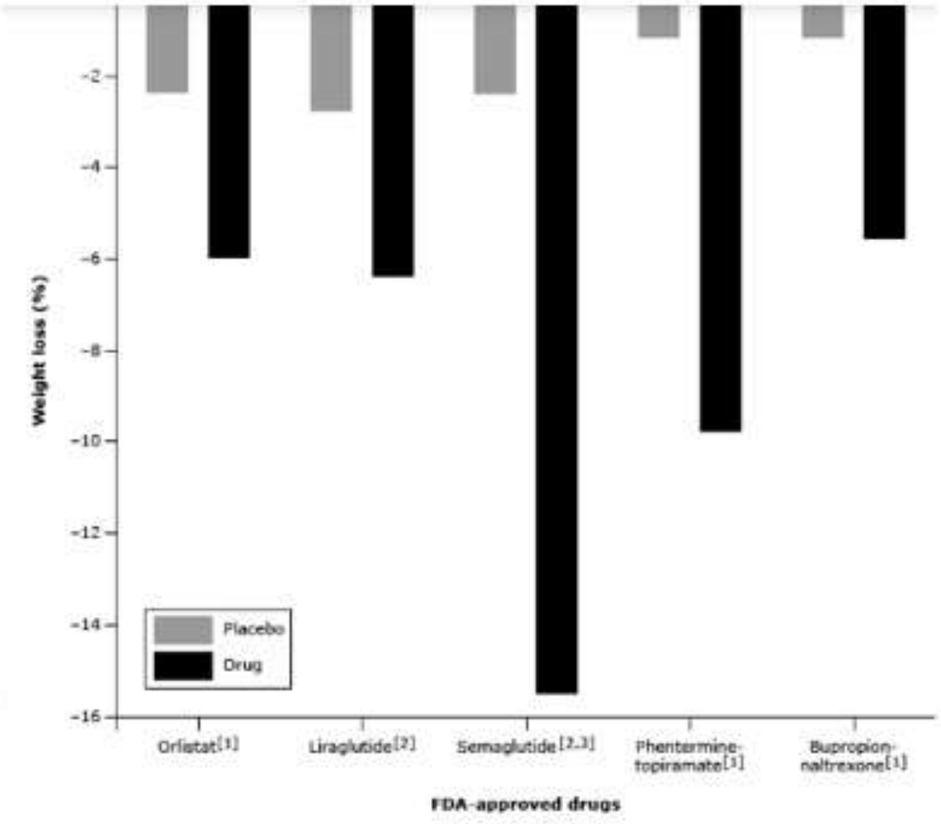
Source: UpToDate accessed September 21, 2023

Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RA's)

What is a GLP-1 Receptor Agonist?

- First Line pharmacotherapy for obesity: FDA approved- semaglutide* and liraglutide
  (*dose once weekly, greater efficacy)
- Highly effective for T2DM treatment (original indication 2005)
  GLP-1 a hormone produced in small intestine, released after eating
- Receptors in many tissues: pancreas, stomach, kidneys, heart, lungs, skin, hypothalamus, immune cells
  GLP-1 RA Action:
  - Stimulates insulin secretion from pancreas,
  - Inhibits glucagon release and gastric emptying
  - Satiety
- Reduction in A1C, weight, major CV events
- Additional Indications being explored

Weight Loss Outcomes with FDA-Approved Medications



Weight loss reflects results at 52 weeks, except for semaglutide and liraglutide, which reflect weight loss at 68 weeks.

Source: FDA; US Food and Drug Administration.

Weight Loss at:

- 52 weeks
- At 68 weeks, mean weight change
- Semaglutide -15.8%
- Liraglutide -6.4%

Courtesy of George A Bray, MD.

Data from:

1. *Khera R, Murad MH, Chandar AK, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: A systematic review and meta-analysis. JAMA 2016; 315:2424.*
2. *Rubino DM, Greenway FL, Khalid U, et al. 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. JAMA 2022; 327:138.*
3. *Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 2021; 384:989.*

Graphic 115096 Version 5.0

Semaglutide Adverse Effects

Gastrointestinal: most common, dose-dependent

- Abdominal pain, constipation, diarrhea, nausea, vomiting, decreased appetite, dyspepsia

Muscle Wasting

Acute kidney injury

Gallbladder disease

- Cholelithiasis, cholecystitis

Hypersensitivity reactions

Psychiatric effects- data is evolving

Medullary thyroid carcinoma (animal studies)

- Contraindications: personal or family history MTC or MEN2

GLP-1 Ras for Weight Loss: Insurance Implications

Consider: Mortality Impact of Obesity and Comorbidities

Favorable Features:

- Significant weight loss sustained during treatment
- Comorbidities associated with obesity- reduced blood glucose, BP, improved serum lipids , musculoskeletal issues etc.
- Potential decrease major CV events
- Psychologic impact- favorable
- May increase ability to engage in physical activity

Unfavorable Features

- Only effective while it is being used
- Cost
- Adverse effects e.g., GI symptoms, fatigue, headaches; potential psychiatric
- Administration: Injectable
- Limited data regarding long term adverse effects
- Risks associated with specific conditions (MTC, MEN2A)

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Connectivity – A Tapestry of Comorbidities

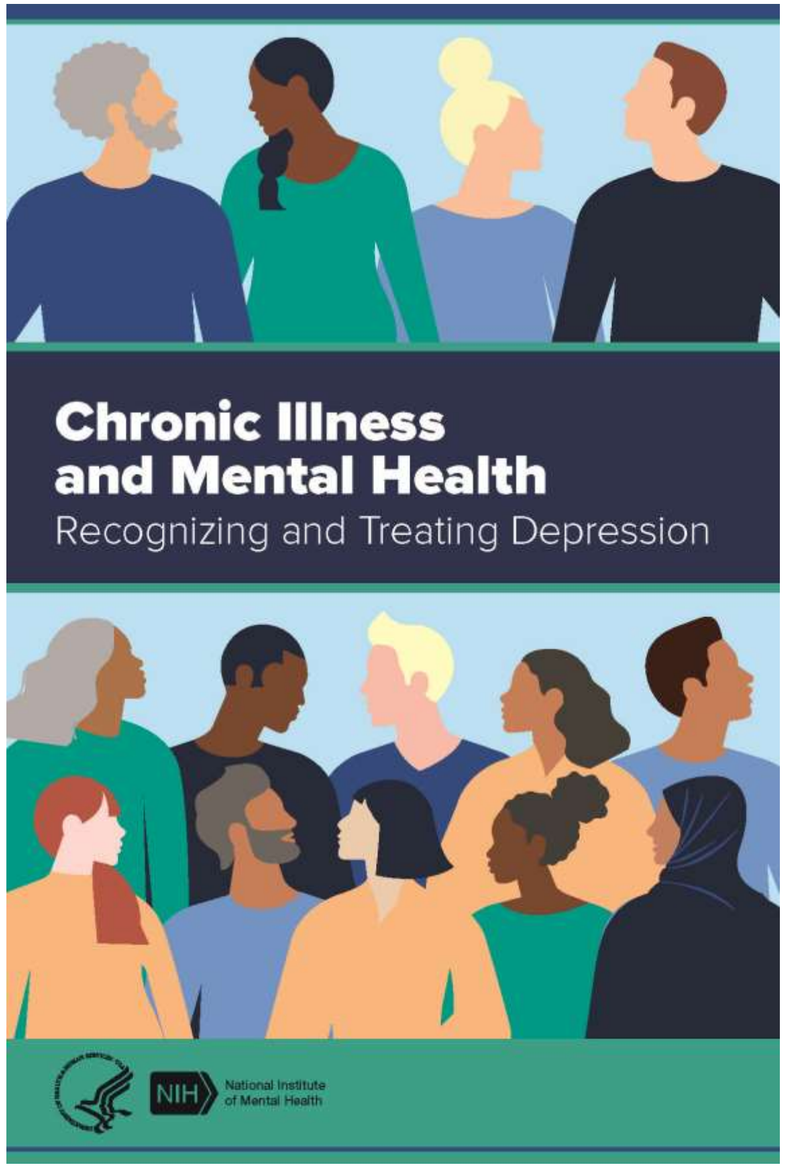
Which is most likely to decrease population mortality?

A. New Weight Loss Drugs

B. New Treatments for Cancer

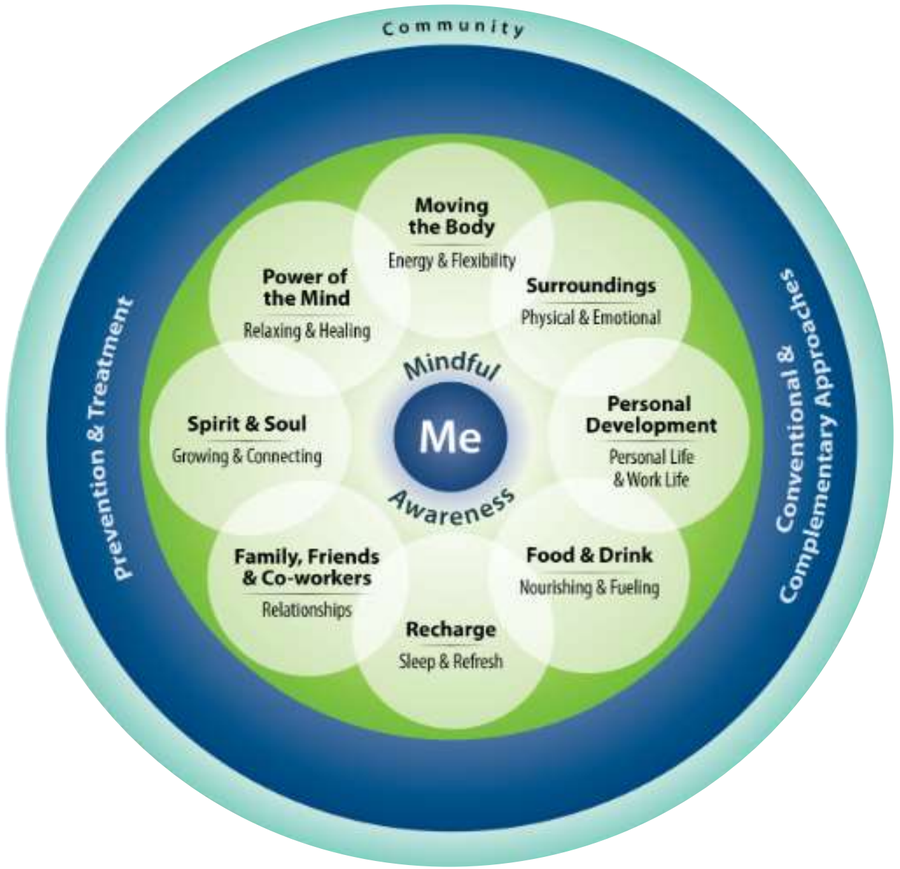
C. New Treatments for Cardiovascular Disease

A Tapestry of Comorbidities



- Obesity
- Cardiovascular disease
- Diabetes
- Cancer
- Musculoskeletal
- Pain
- Sleep disorders

The Biopsychosocial Model: Whole Health

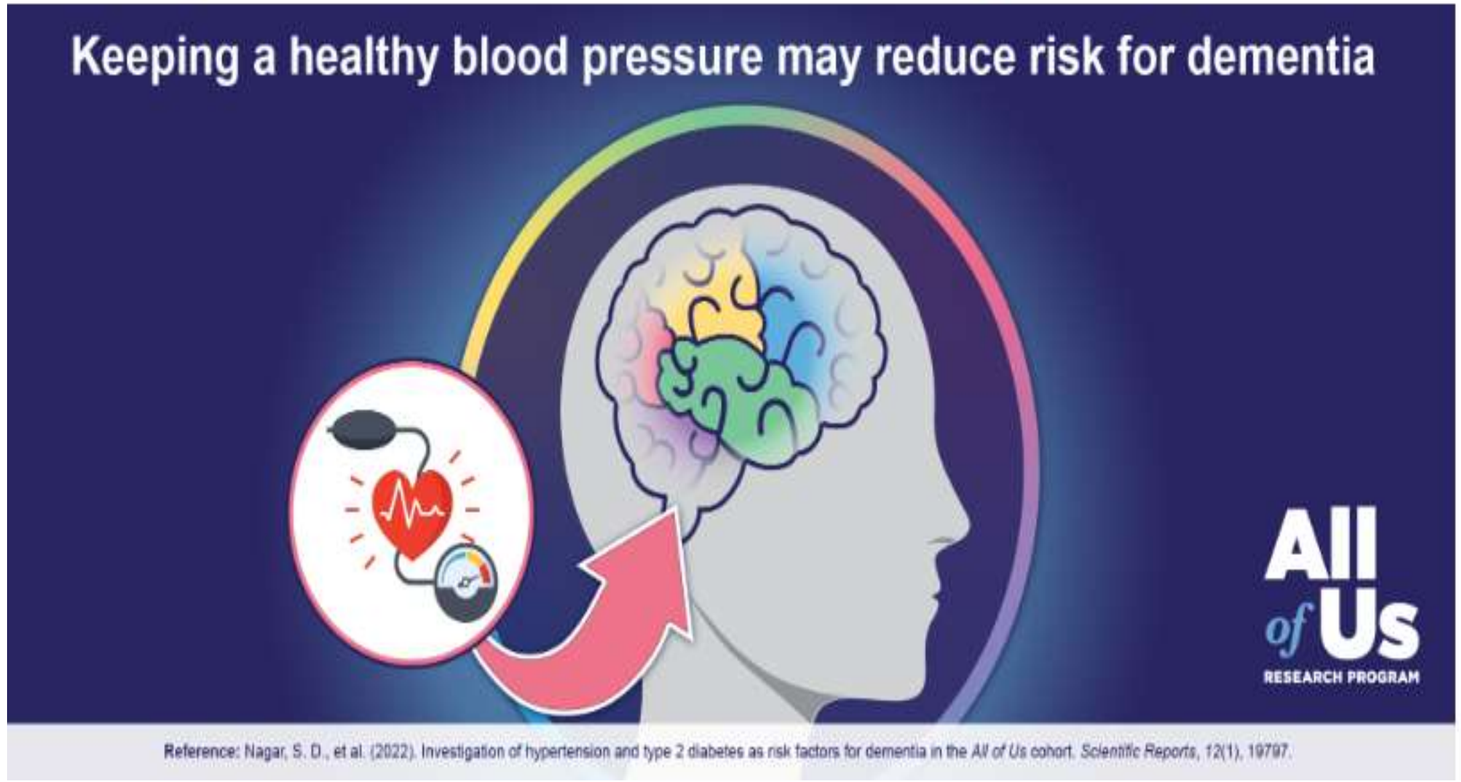


Source: https://www.va.gov/wholehealthlibrary

The Origins of Dementia are Multifactorial, and Occur Over Years

March 22, 2023

Learning More About Dementia Risk Through *All of Us*



- Hypertension
- Obesity
- Depression
- Diabetes
- Physical Inactivity
- Smoking
- Hyperlipidemia
- Isolation
- Alcohol overuse

Source: https://allofus.nih.gov/article/learning-more-about-dementia-risk-through-all-us

Which is most likely to decrease population mortality?

There may be more than one answer…

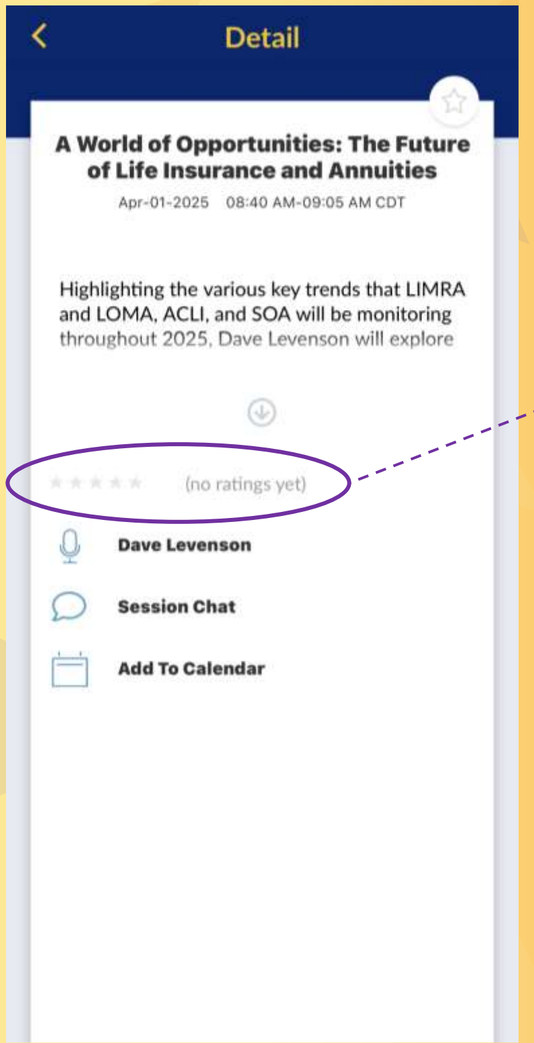
A. New Weight Loss Drugs

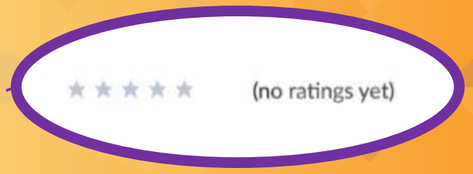
B. New Treatments for Cancer

C. New Treatments for Cardiovascular Disease

Open Discussion – All

Please Provide Your Feedback on the Conference App





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Thank You


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