

 **Mass General Brigham**
Heart and Vascular Institute

 **HARVARD**
MEDICAL SCHOOL

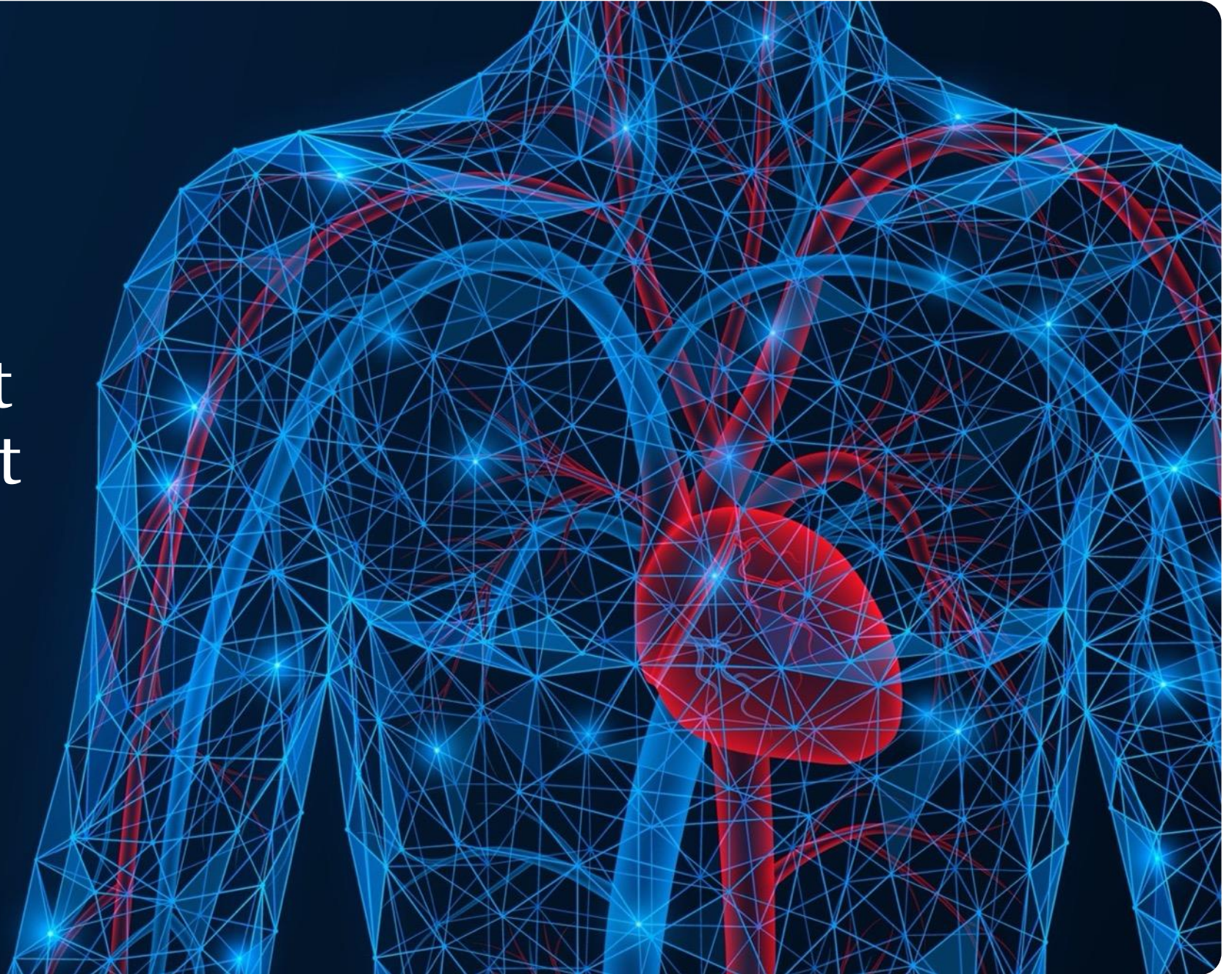
 **BROAD**
INSTITUTE

 **FAHEDLAB**

Predicting Heart Disease Before It Starts

Akl C. Fahed, MD, MPH

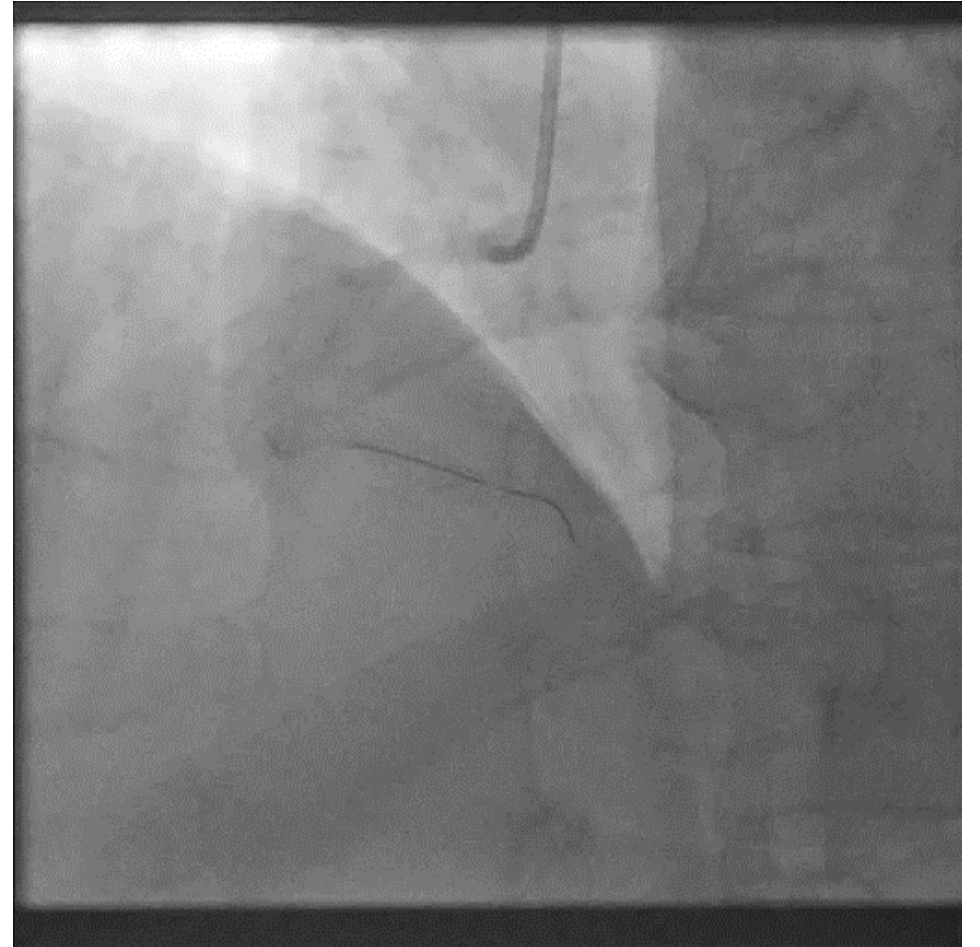
Mercy Precision Medicine Summit
Apr 30, 2026



38 year-old man, healthy lifestyle, and just had an annual physical



**Crushing
chest pain**

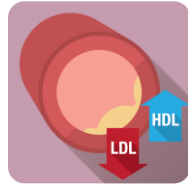


Why did this patient have a heart attack?

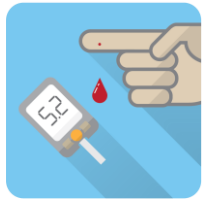
Lifestyle & Clinical Drivers



Blood pressure



Cholesterol



Blood sugar



Exercise



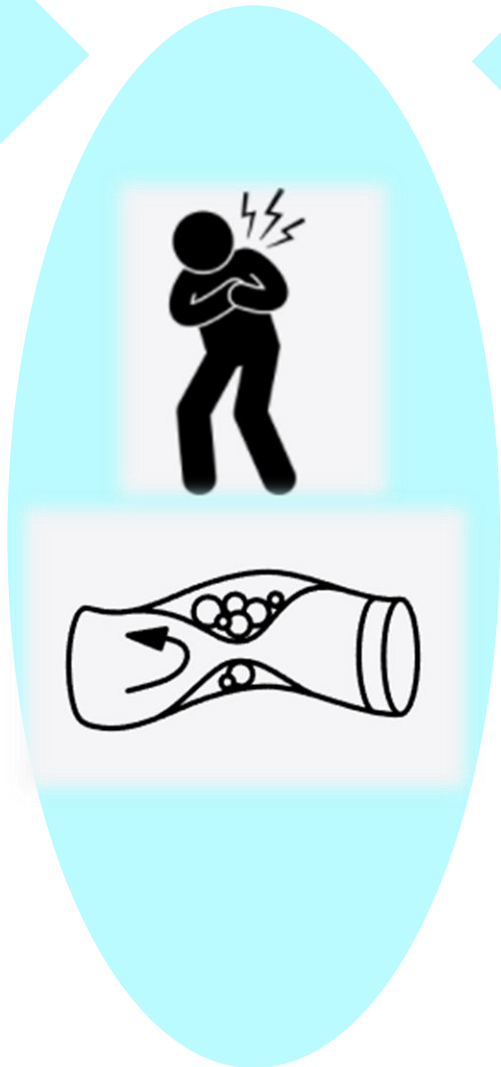
Weight



Diet



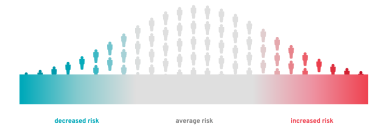
Smoking



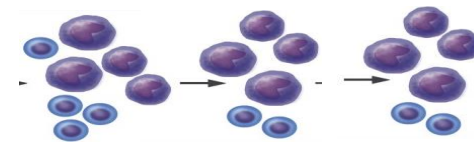
Genomic Drivers



Monogenic



Polygenic



Somatic

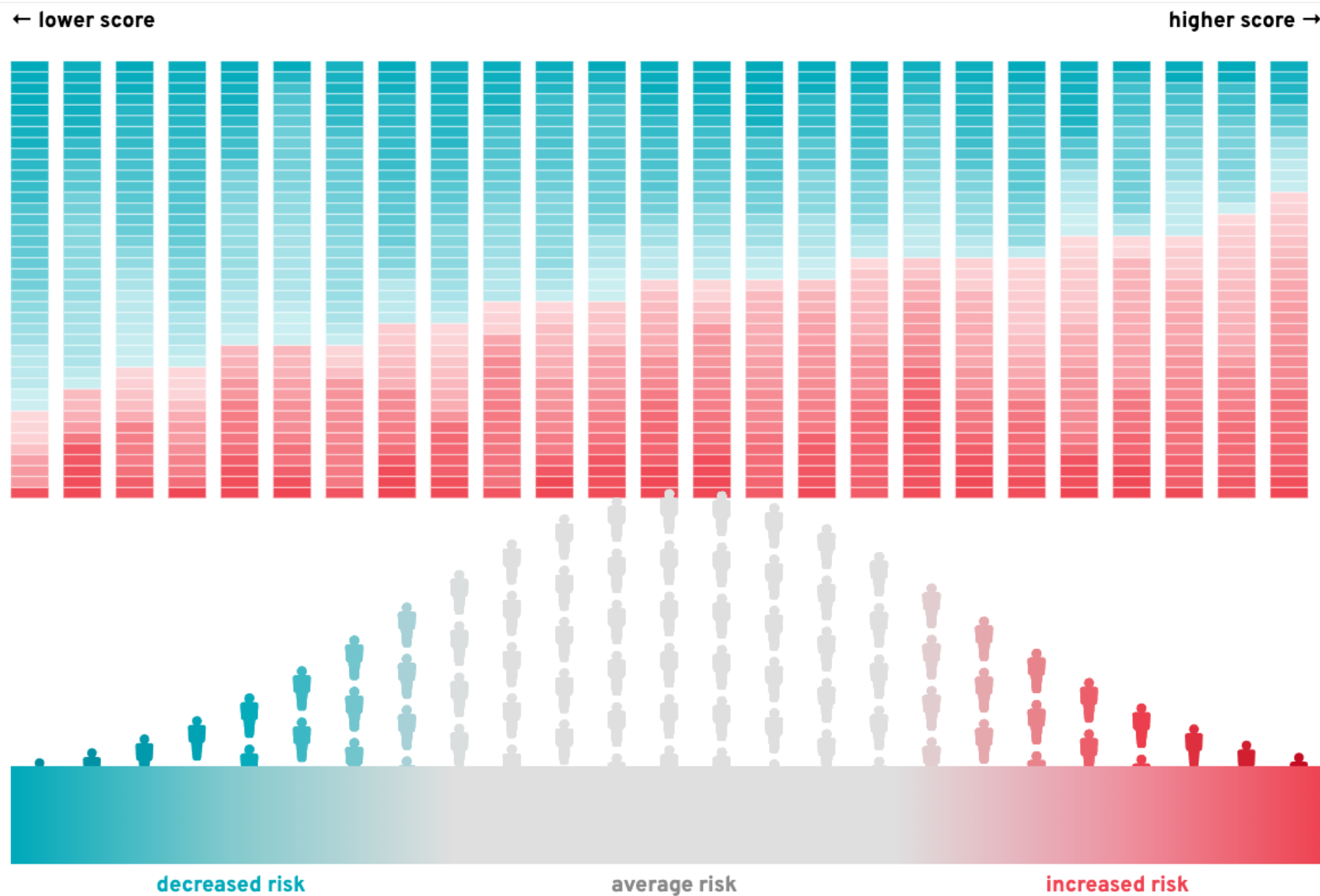
How is a polygenic score calculated?

Step 1: Compare variants in people with vs. without the disease



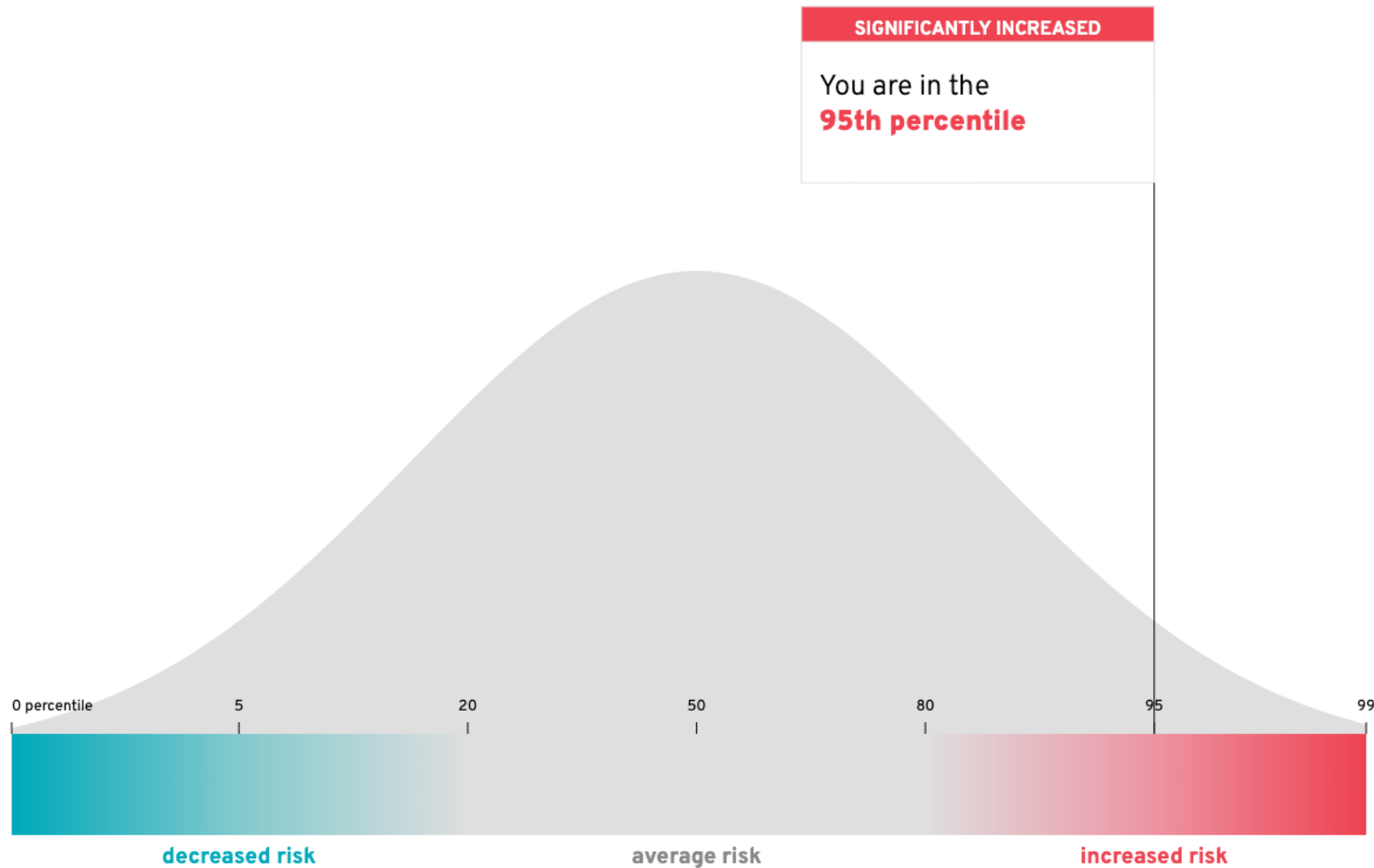
How is a polygenic score calculated?

Step 2: Add up risk- increasing and decreasing variants in an individual



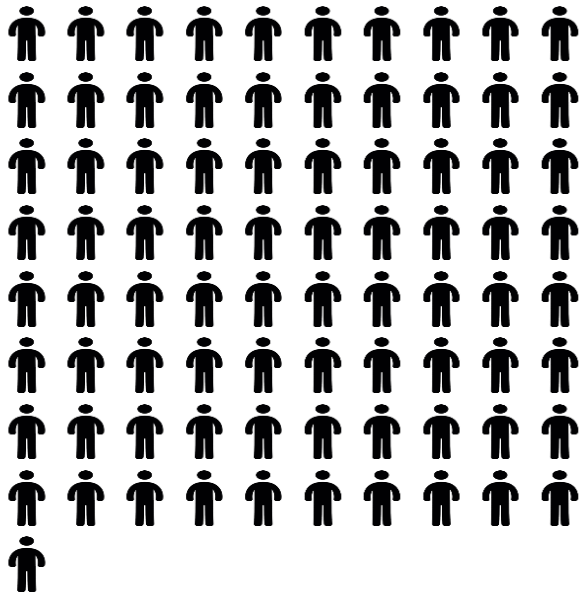
How is a polygenic score calculated?

Step 3: Report as percentile on a population distribution with associated risk



For every 100 people with heart attack at a young age 2 have monogenic vs. 20 have polygenic drivers

**100 people with
early heart attack**



Monogenic

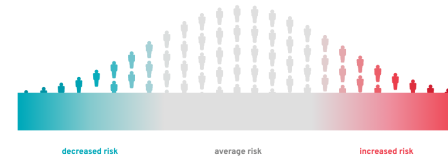


↑ Risk

3.8-fold



High polygenic



3.7-fold

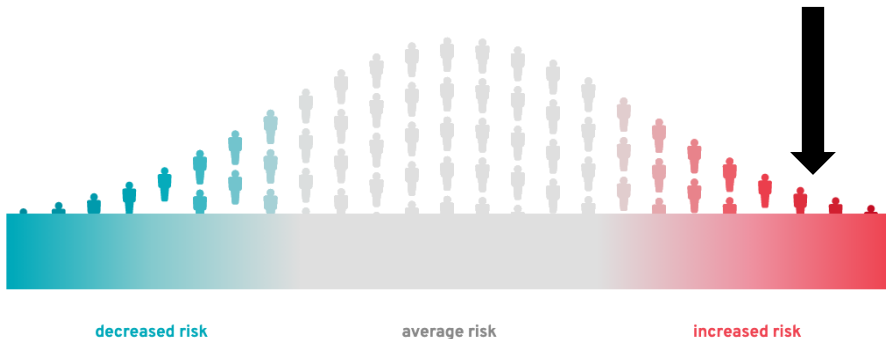
Monogenic and polygenic risk are additive

“Double whammy” genetic risk

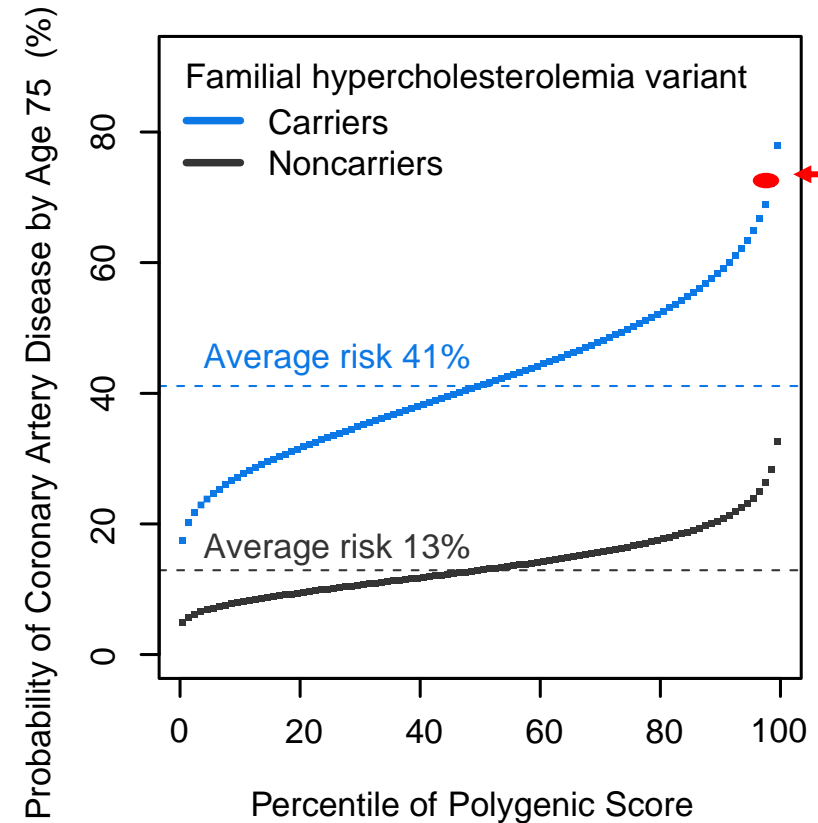
Pathogenic variant in *LDLR*



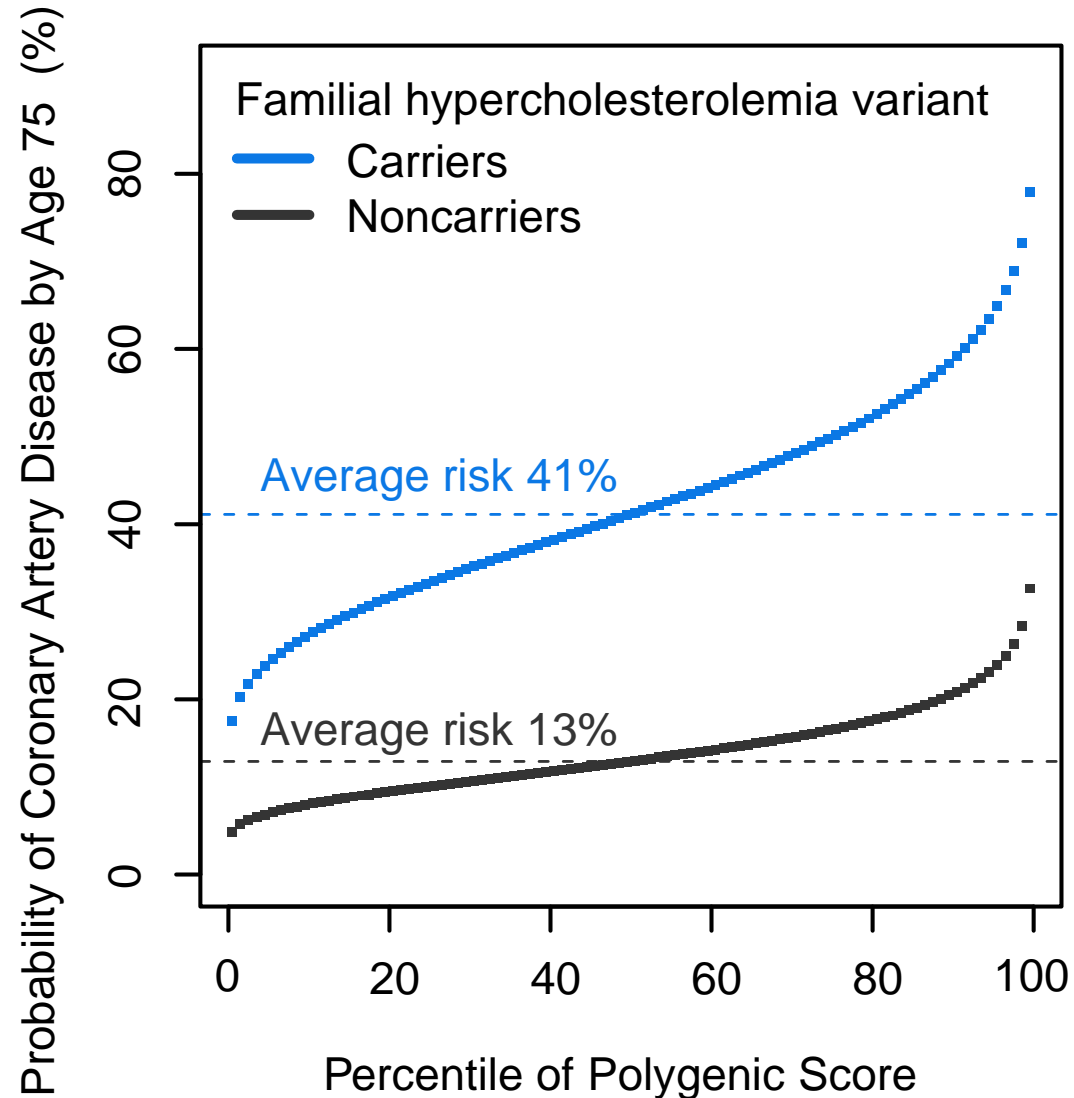
High polygenic score



200 possible genomic risk profiles



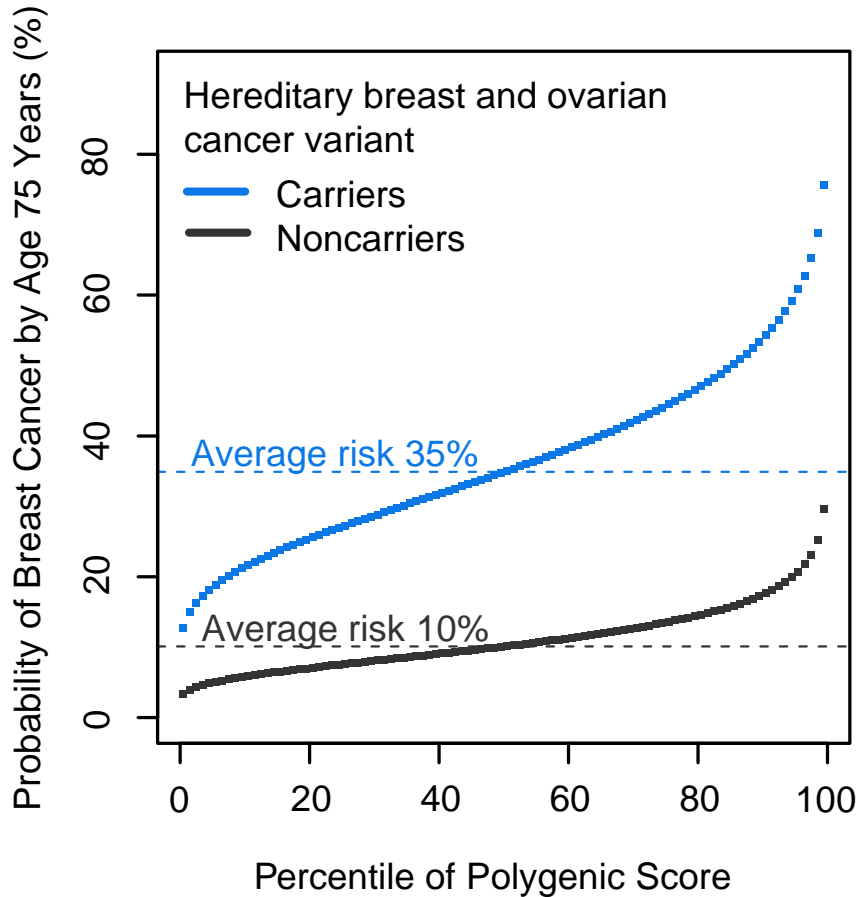
Substantial gradient of risk by both monogenic and polygenic state



Probability of disease by age 75 years ranges from 5% to 78%

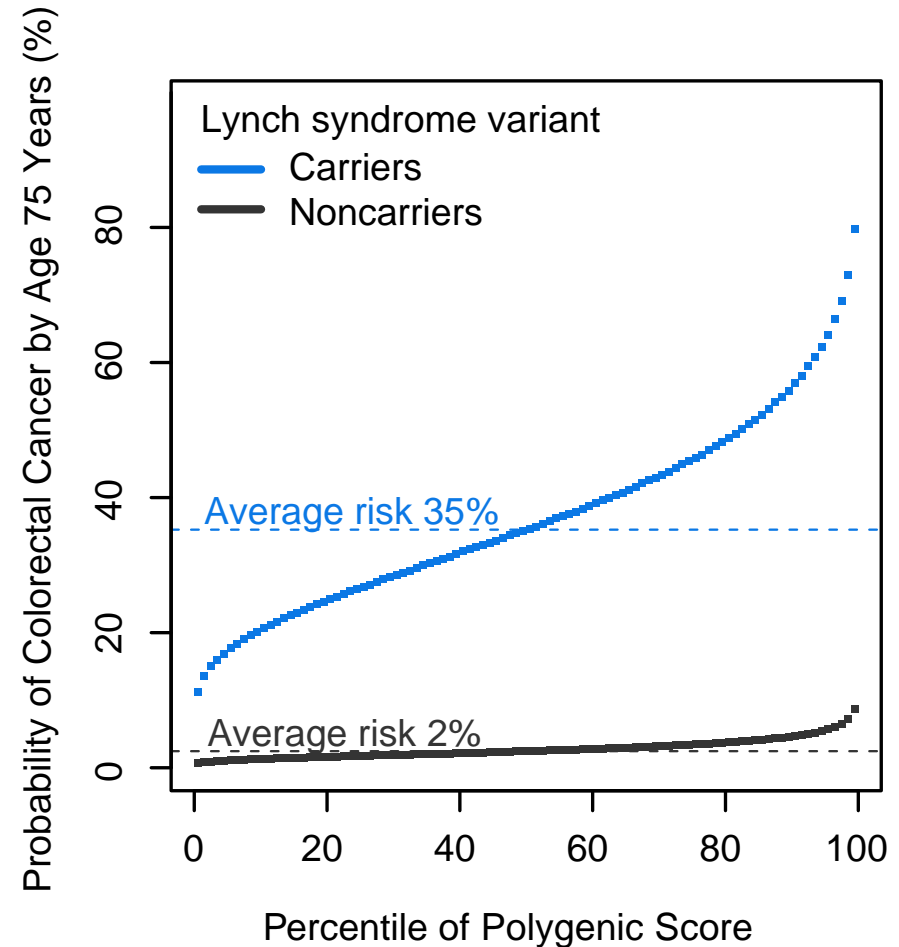
Similar findings for breast cancer and colorectal cancer

Hereditary breast and ovarian cancer



13-76%

Colorectal cancer



11-80%

One of the top discoveries in genomic medicine in 2020

YEAR IN REVIEW

Genomic Medicine Year in Review: 2020

Teri A. Manolio,^{1,*} Carol J. Bult,² Rex L. Chisholm,³ Patricia A. Deverka,⁴ Geoffrey S. Ginsburg,⁵ Madison Goldrich,¹ Gail P. Jarvik,⁶ George A. Mensah,⁷ Mary V. Relling,⁸ Dan M. Roden,⁹ Robb Rowley,¹ Cecelia Tamburo,¹ Marc S. Williams,¹⁰ and Eric D. Green¹

Is Anything Truly Monogenic?

Fahed, A.C., et al. (2020). Polygenic Background Modifies Penetrance of Monogenic Variants for Tier 1 Genomic Conditions. *Nat. Commun.* 11, 3635

Genomic variation influencing disease risk is commonly divided into monogenic variants of large effect and polygenic variants of small effect, but the interplay between monogenic and polygenic risk has not been widely examined. Data from over 80,000 individuals from the UK BioBank and Color Genomics laboratory carrying monogenic risk variants for HBOC, Lynch syndrome, and FH were analyzed to show that polygenic background significantly influences the risk of developing disease by age 75. Odds ratios for coronary disease, for example, in monogenic carriers of FH variants



Angelina Jolie had a preventive mastectomy after doctors told her she had an 87 per cent risk of breast cancer

JASON MERRITT/GETTY IMAGES

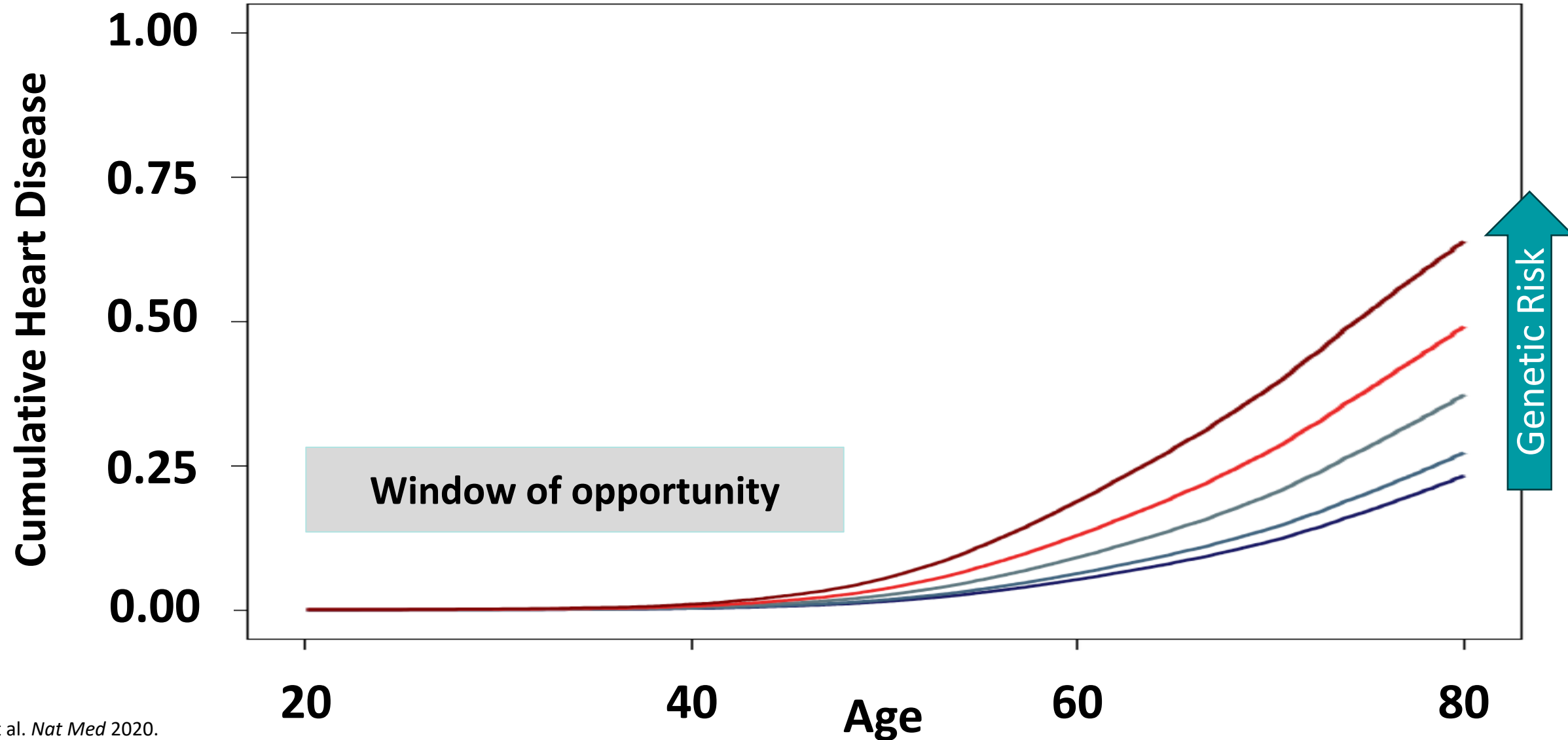
‘Jolie gene’ BRCA1 is not a cancer certainty

Kat Lay, Health Correspondent

Friday September 11 2020, 12.01am, The Times

Polygenic Risk Score is the “first risk factor”

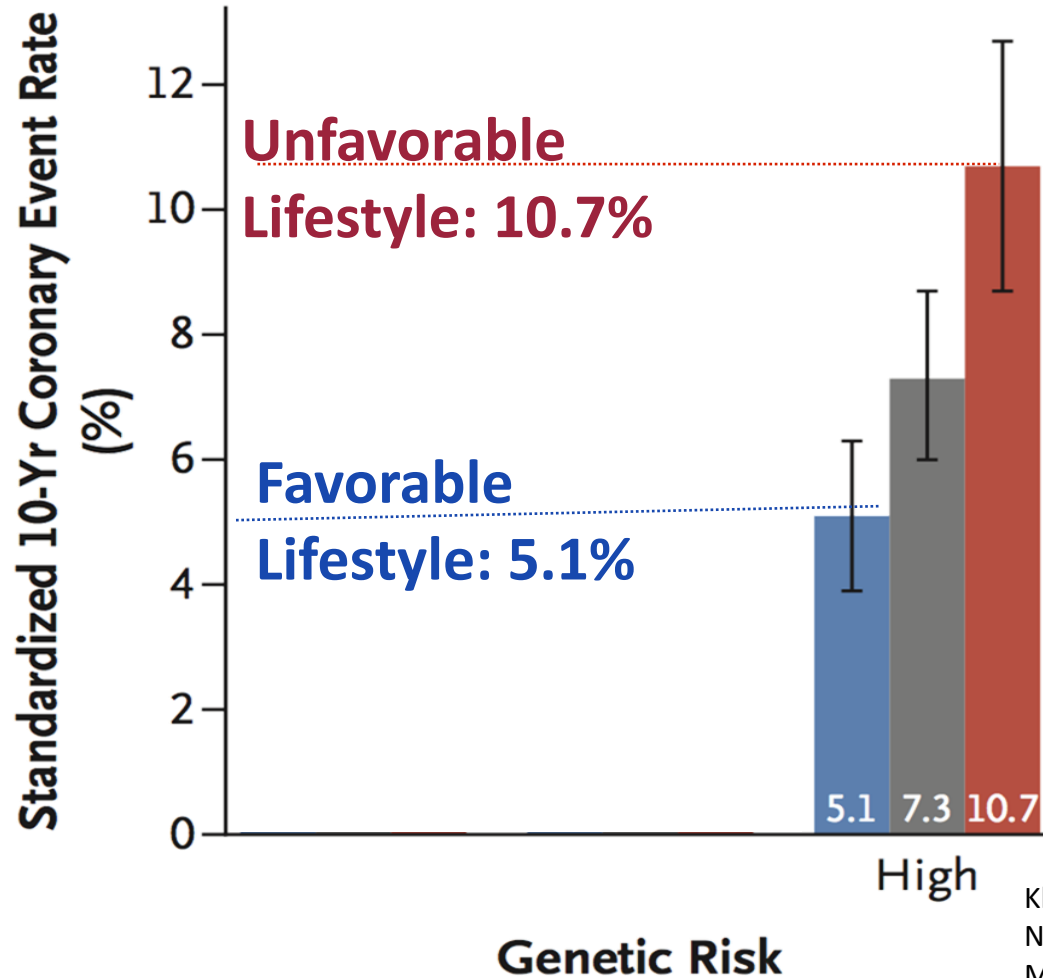
It can be used to predict heart disease before it starts



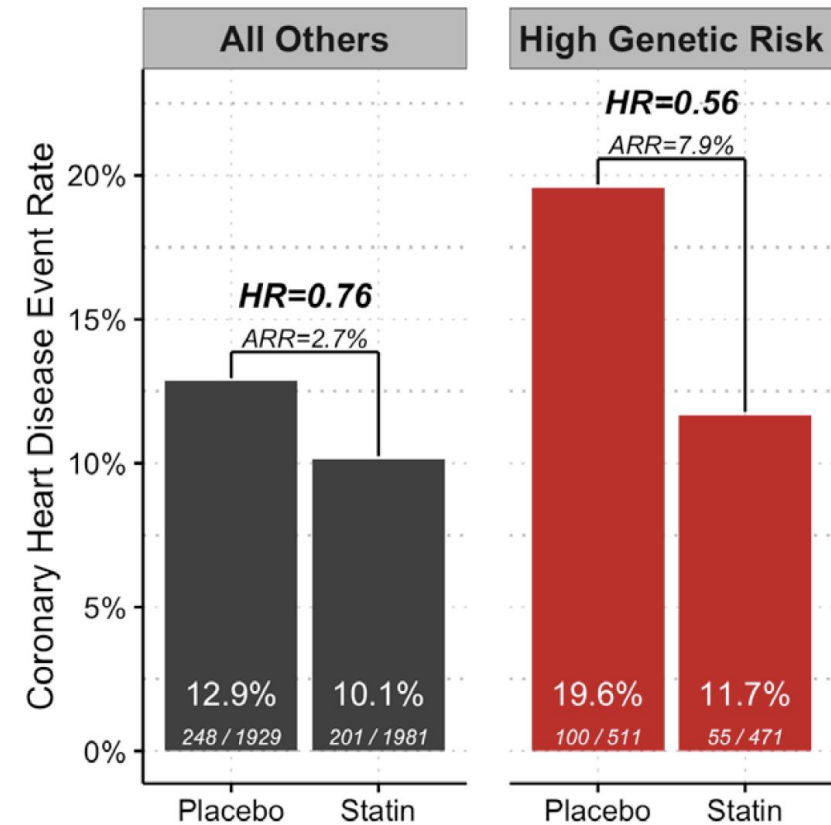
DNA is not destiny!

We can reduce your risk if we know

Favorable lifestyle linked to 50% lower risk



Even more benefit from cholesterol lowering medicine



Khara AV et al. *NEJM* 2016
Natarajan P et al. *Circulation* 2017
Marston N et al. *Circulation* 2019

The Four Biomarkers for Heart Disease

Single measurement strongly predicts risk



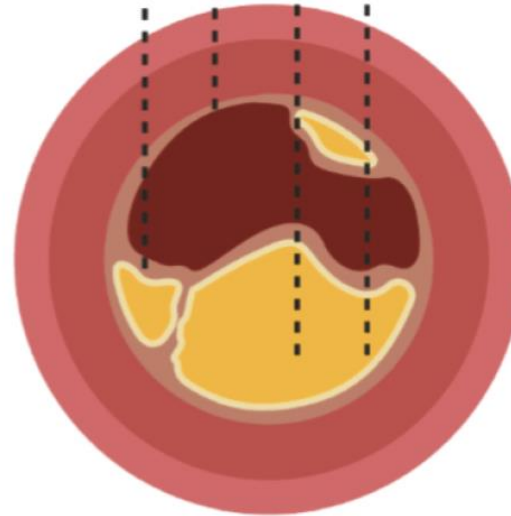
CAD PRS: Sets a baseline inherited risk through a weighted summation of variants related to CAD pathogenesis such as lipids, inflammation, endothelial dysfunction and others.

Biomarker: ≥ 80 th percentile of CAD PRS



Hs-CRP: A key marker of systemic inflammation that promotes plaque growth, instability, and rupture.

Biomarker: hs-CRP ≥ 2 mg/L



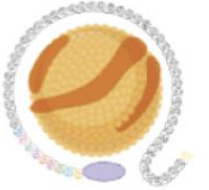
LDL-C: Drives atheroma via subendothelial deposition and oxidation.

Biomarker: LDL-C ≥ 130 mg/dL

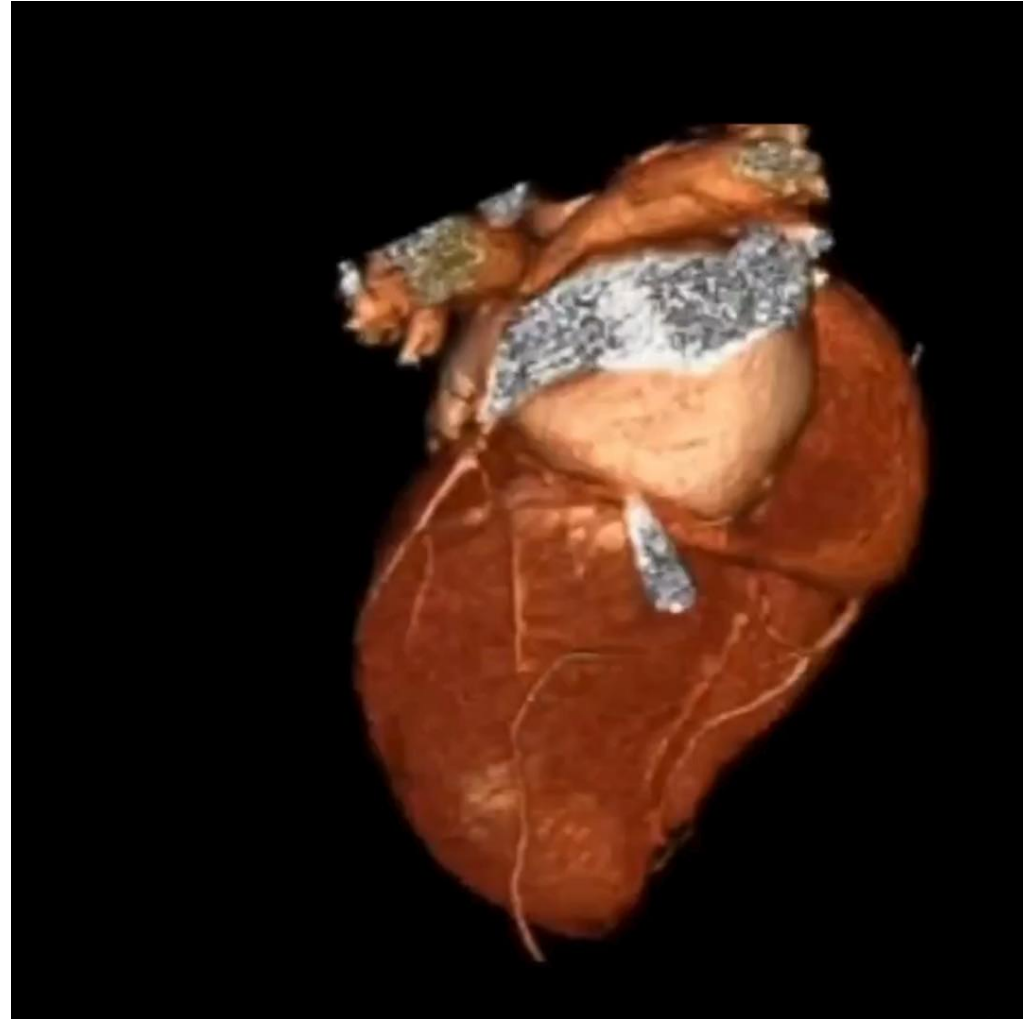


Lp(a): A highly heritable cholesterol particle that promotes vascular inflammation, atherogenesis, calcification, and thrombosis.

Biomarker: Lp(a) ≥ 50 mg/dL



We have technology to screen for coronary plaque, the precursor to heart attack



People with high CAD PRS accumulate plaque faster It's like someone who continues to smoke

Patient with **High CAD PRS**

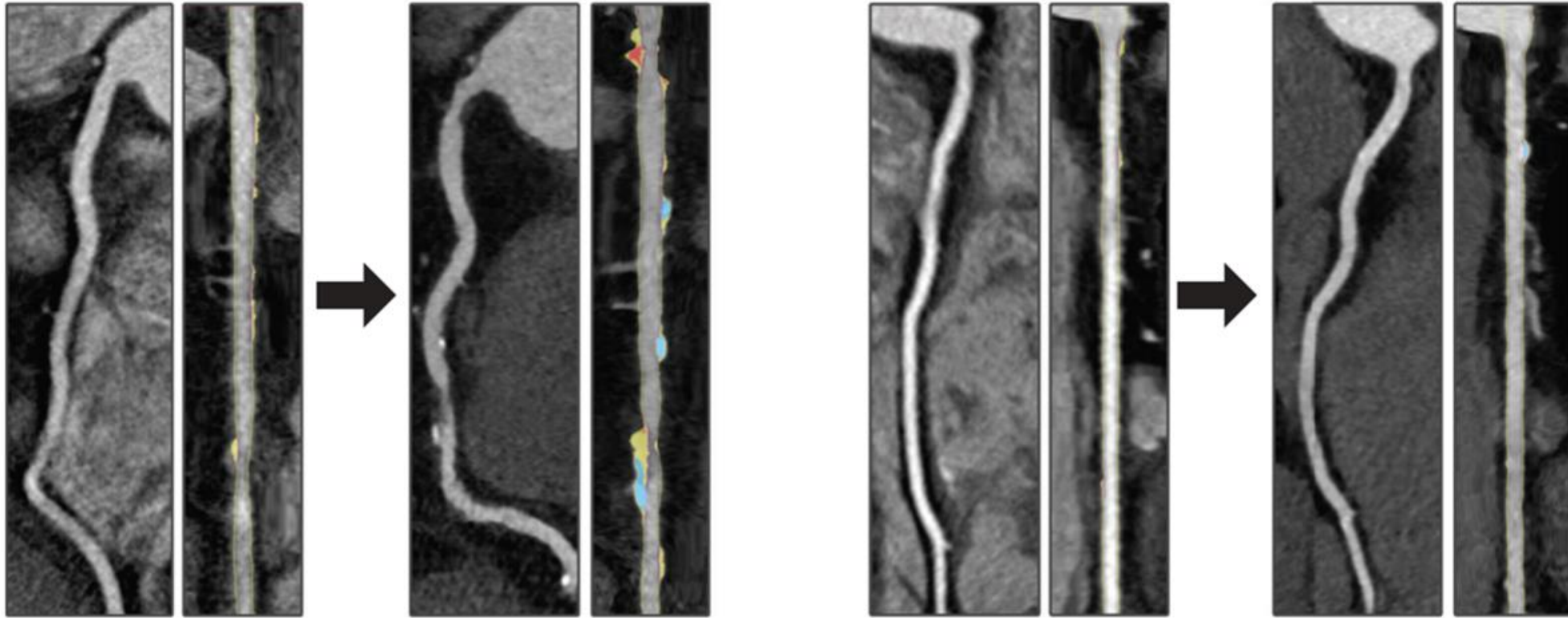
Patient with **Low CAD PRS**

Baseline

10 years later

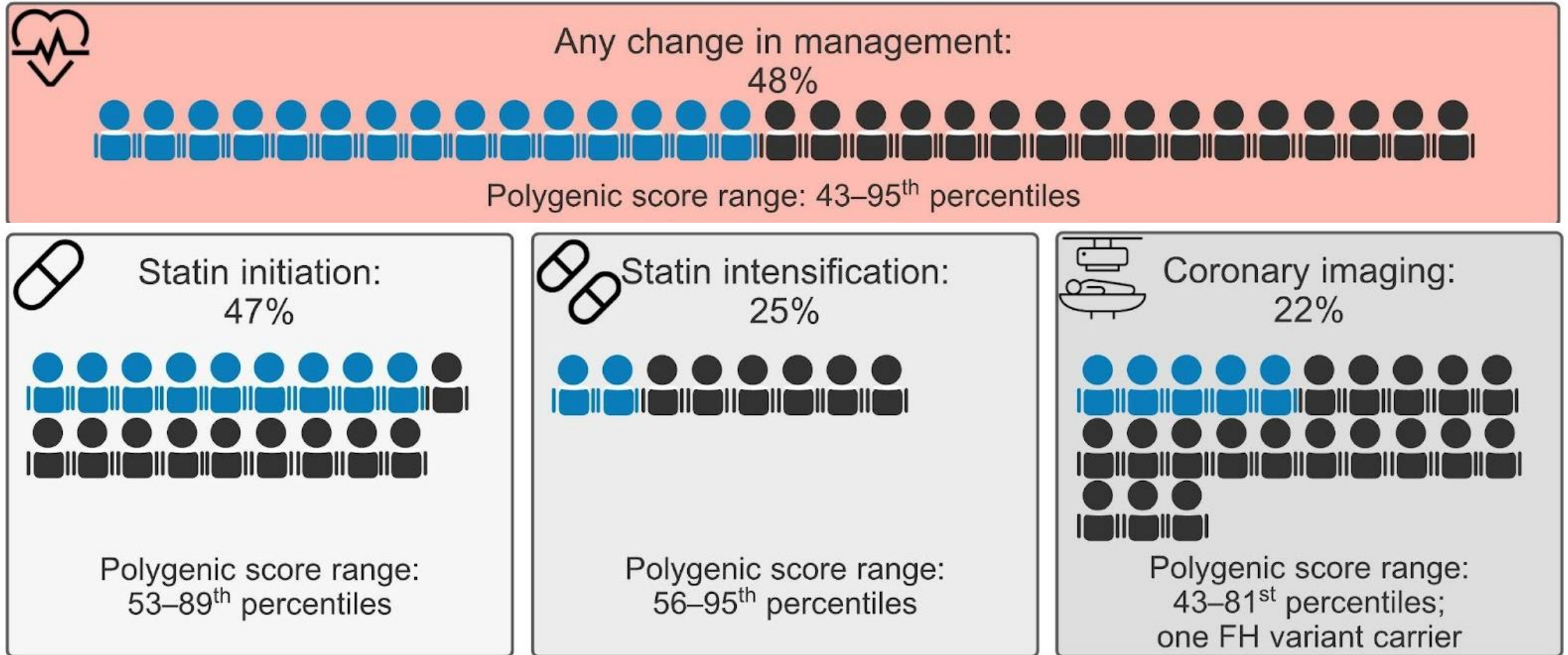
Baseline

10 years later



Plaque composition
Low-density plaque Non-calcified plaque Calcified plaque

2019: First preventive genomics clinic at Mass General Hospital



2026: Polygenic risk of many diseases from a single sample



Personalized Medicine
Laboratory for Molecular Medicine
65 Landsdowne St, Cambridge, MA 02139
Phone: (617) 768-8500 / Fax: (617) 768-8513

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MRN: 9999999999

LMM Accession ID: **PM-12-N12874**

POLYGENIC RISK SUMMARY

Atrial Fibrillation	Below Average	Average	Above Average	High
Coronary Artery Disease	Below Average	Average	Above Average	High
Diabetes Mellitus, Type 2	Below Average	Average	Above Average	High
Elevated lipoprotein(a)	Below Average	Average	Above Average	High
Hypercholesterolemia	Below Average	Average	Above Average	High
Hypertension	Below Average	Average	Above Average	High
Thoracic Aortic Aneurysm	Below Average	Average	High	
Venous Thromboembolism	Below Average	Average	High	

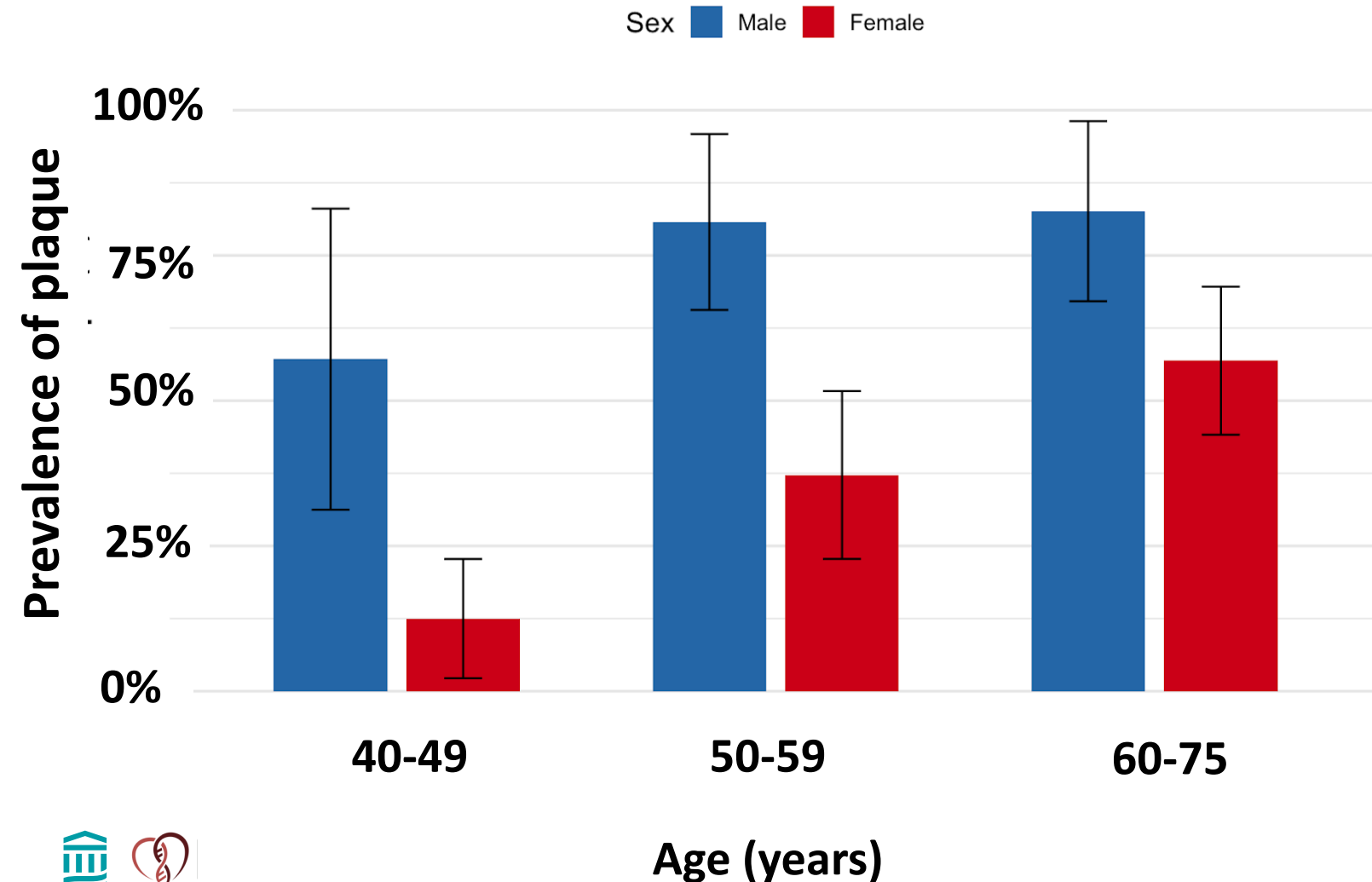


2026: PROACT clinical trials to identify and treat people “flying under the radar”



1 in 2 people have coronary plaque!

**76% of males
39% of females**



2026: PROACT clinical trials to identify and treat people “flying under the radar”



46-year-old man

- No clinical risk factors
- CAD PRS: 98th percentile
- CAC = 0
- Non-calcified mid LAD plaque



Science is a team effort!

Postdocs

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Roukoz Abou-Karam

Kelvin Supriami

Injeong Shim

Fouad Bitar

Graduate students

Xingyu Chen

Jose Roberto Ayala

Raysha Farah

Shengxin Liang

Undergrad students

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