Genome-wide polygenic scores for cardiovascular disease

Amit V. Khera, MD MSc
Massachusetts General Hospital
Broad Institute of MIT & Harvard
Harvard Medical School
Twitter: @amitvkhera

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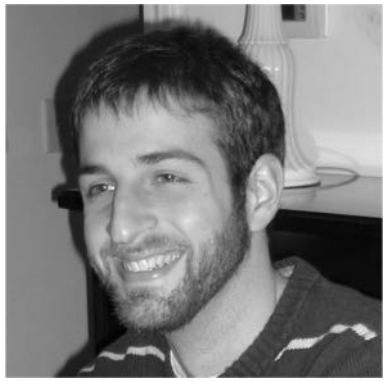
Acknowledgements

Mentorship

Sekar Kathiresan

Human genetics

Collaboration



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Harlan Krumholz
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CENTER FOR GENOMIC MEDICINE

BROAD INSTITUTE

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NIH National Human Genome Research Institute

Clinical observation

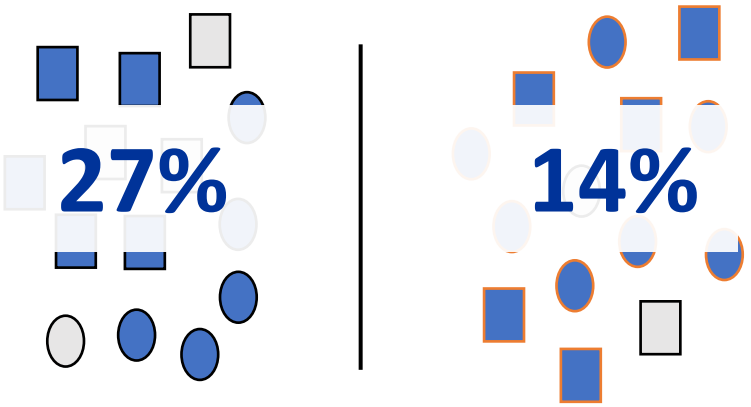
Family history of myocardial infarction linked to increased risk

YOUNG CANDIDATES FOR CORONARY HEART DISEASE

Menard M. Gertler, M.D., New York, Stanley M. Garn, Ph.D.
and
Paul D. White, M.D., Boston

JAMA (1951)

Family History



Cases
N = 100

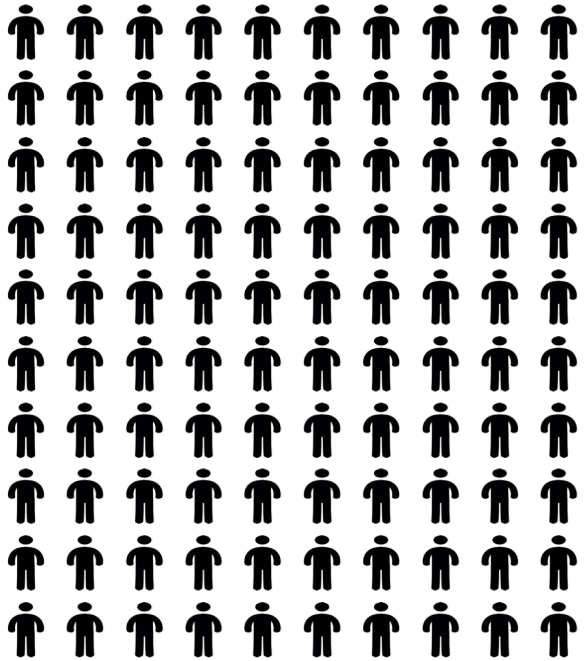
Controls
N = 146

Question: What is state of the art for genome interpretation for MI in 2019?

Khera,* Chaffin,* … Kathiresan | *Nat Genetics* | 2018
Khera,* Chaffin,* … Kathiresan | *Circulation*| 2018

2019 Genome interpretation for early-onset myocardial infarction

100 patients with myocardial infarction



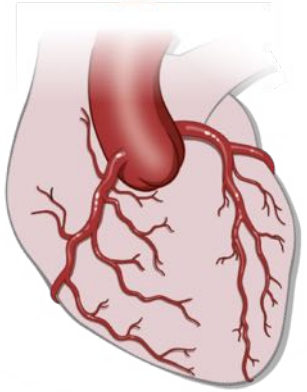
Multiethnic Study

2,081 early-onset myocardial infarction cases | 3,761 Controls

Myocardial infarction cases

Patients hospitalized with first MI at age ≤ 55 years

N = 2,081



Population controls

Multiethnic population free of coronary disease

N = 3,761

How might DNA predispose to myocardial infarction?

2 models – monogenic and polygenic

Monogenic →

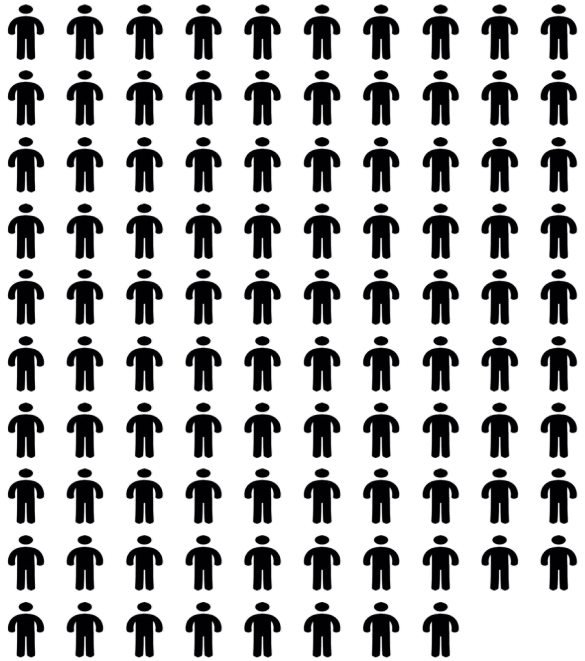
Rare driver mutation in each individual

Polygenic →→→→

Monogenic familial hypercholesterolemia mutation

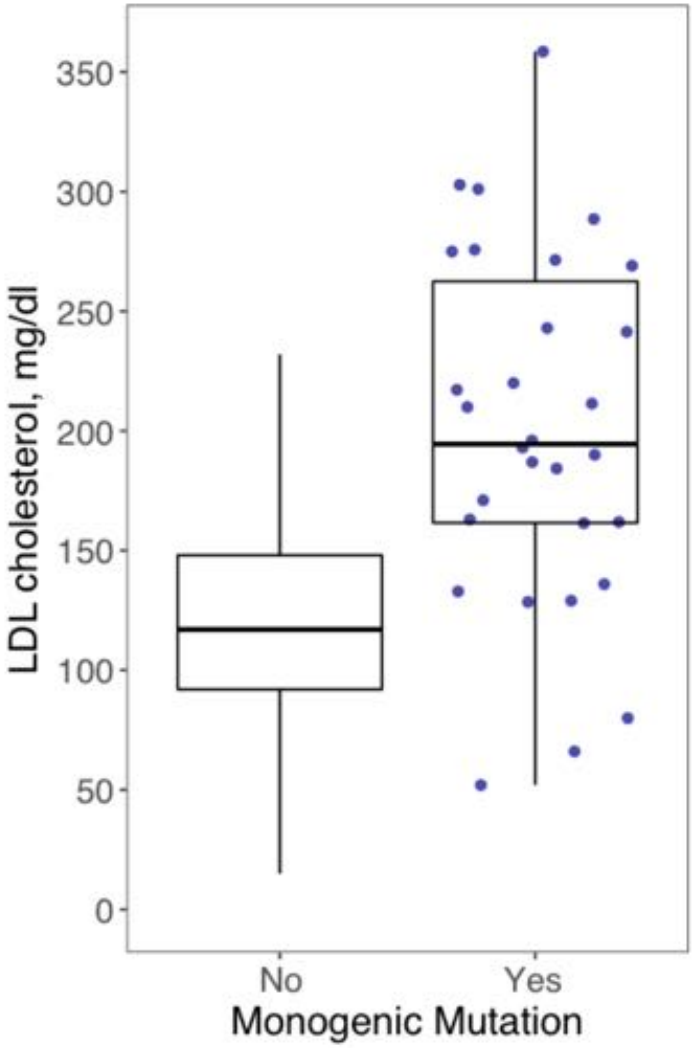
1.7% of cases -> 3.8-fold increased risk

100 patients with myocardial infarction



	↑ Risk
Monogenic	3.8-fold

Carriers of familial hypercholesterolemia mutations can be distinguished by high LDL cholesterol



Mean LDL Cholesterol

Carriers: 202 mg/dl

Non-carriers: 124 mg/dl

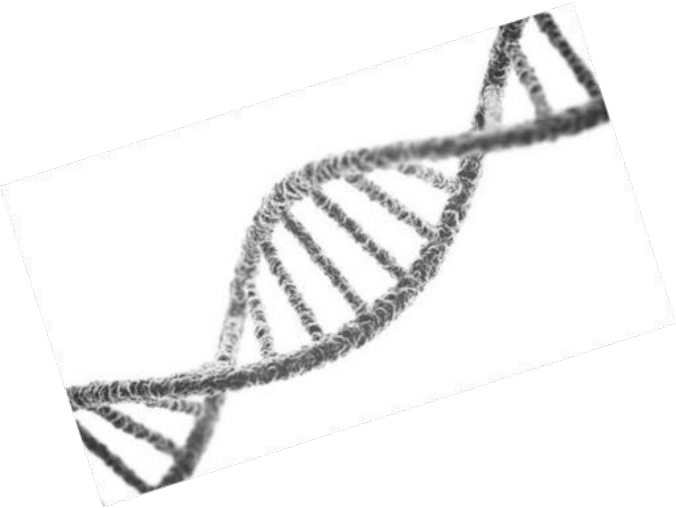
Question: Can we identify additional patients with a polygenic risk model?

Genome-wide polygenic score for myocardial infarction
6.6 million variants

Compare genomes

6.6 million variants

60K cases / 120K cont



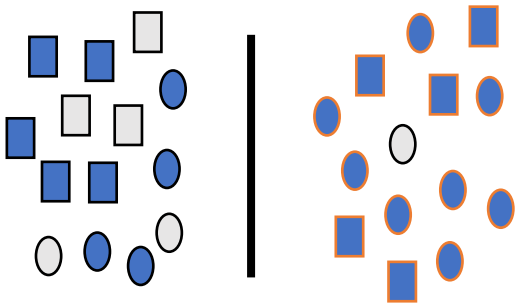
Computational algorithm

Integrate all variants into a single metric.

Validation dataset

Choose best score

biobank uk

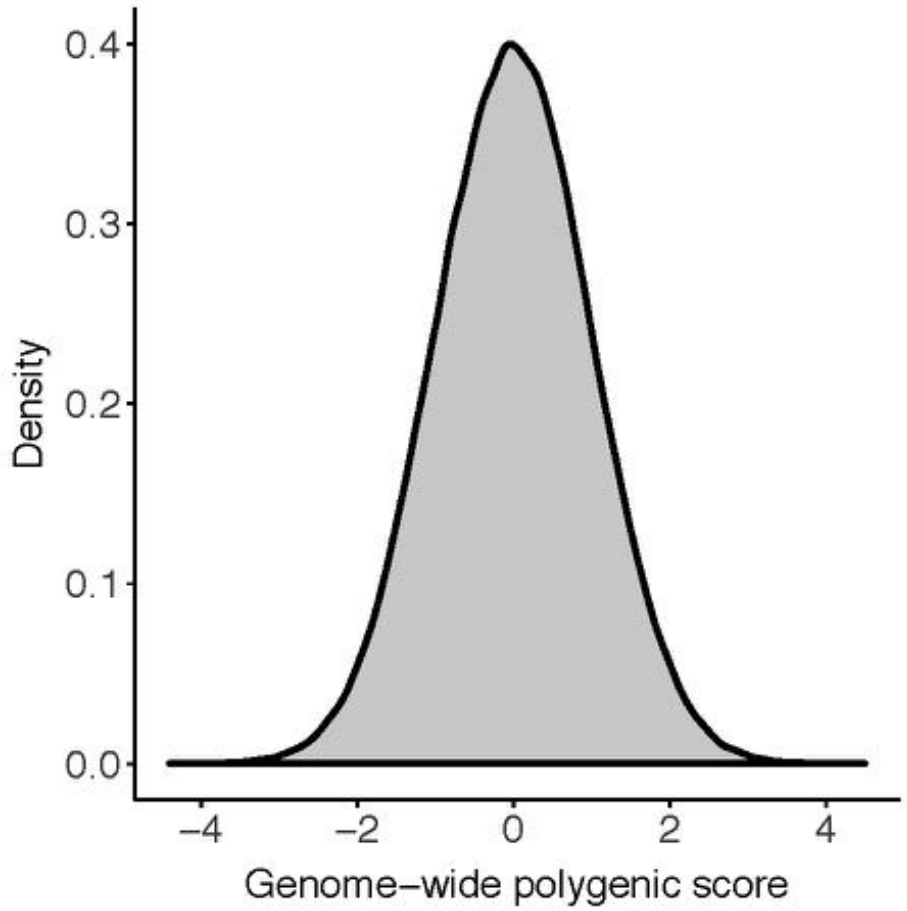


Cases
N = 4K

Controls
N = 120K

Test genome-wide polygenic score in 300,000 additional people

Normally distributed in population



Test genome-wide polygenic score in 300,000 additional people

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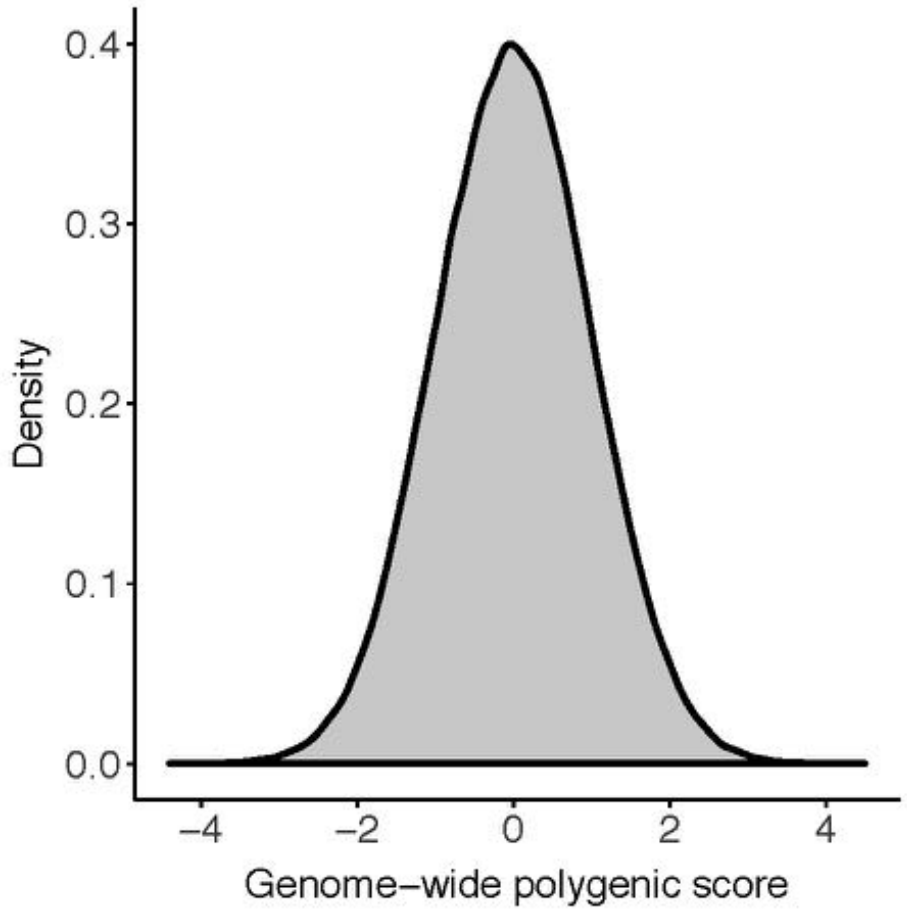
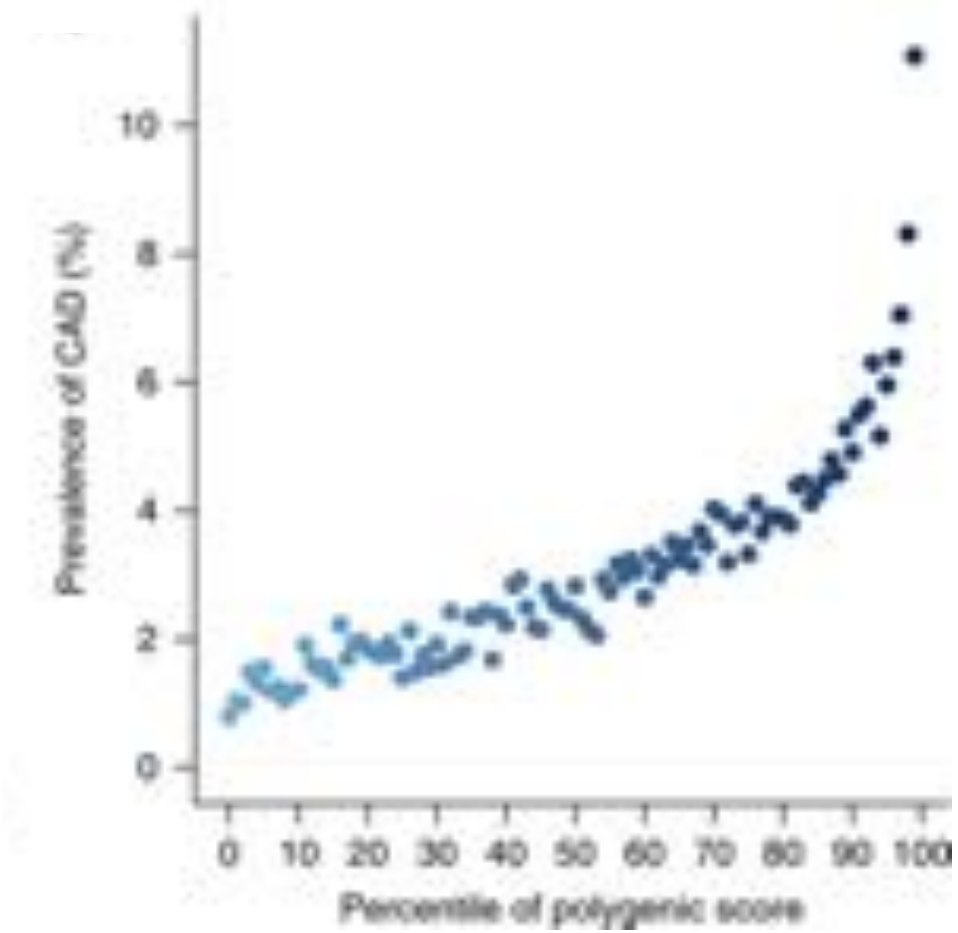
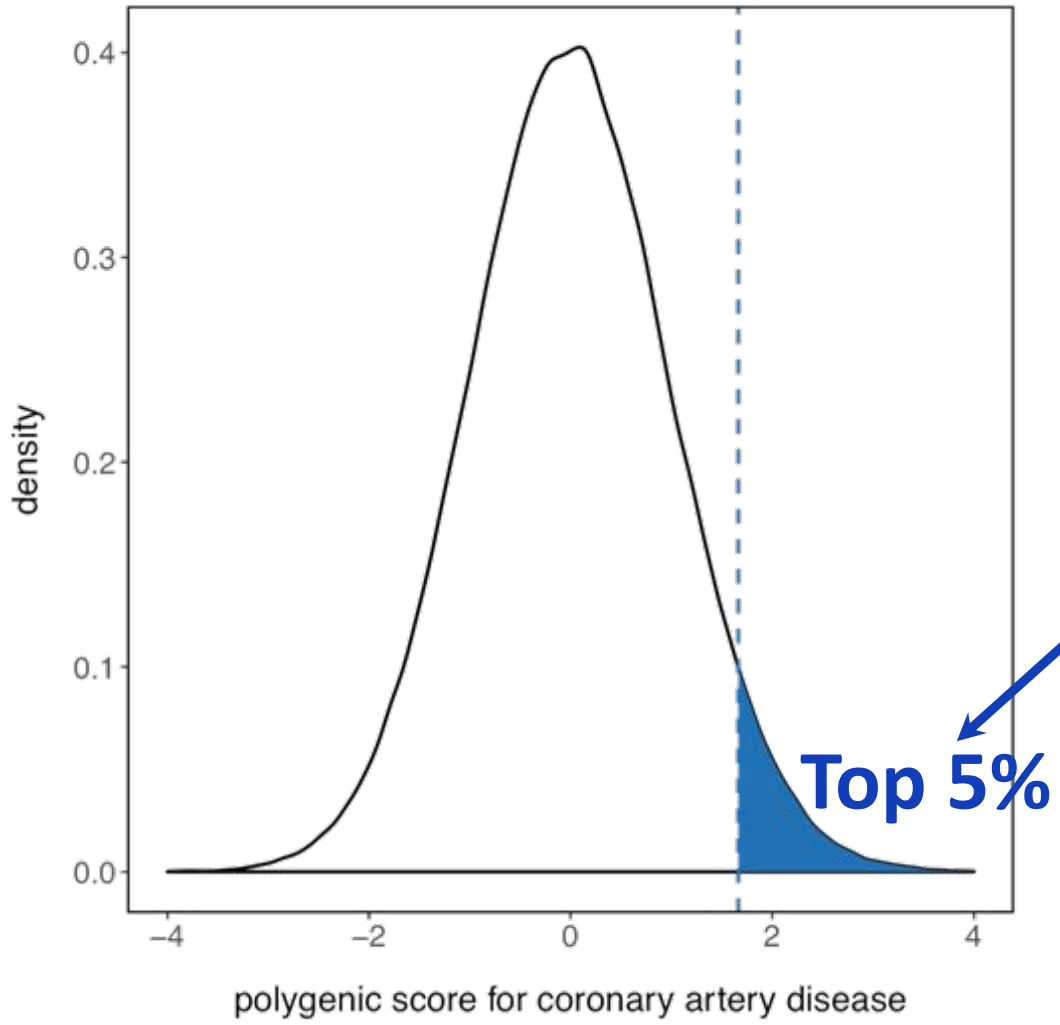


Significant gradient in risk



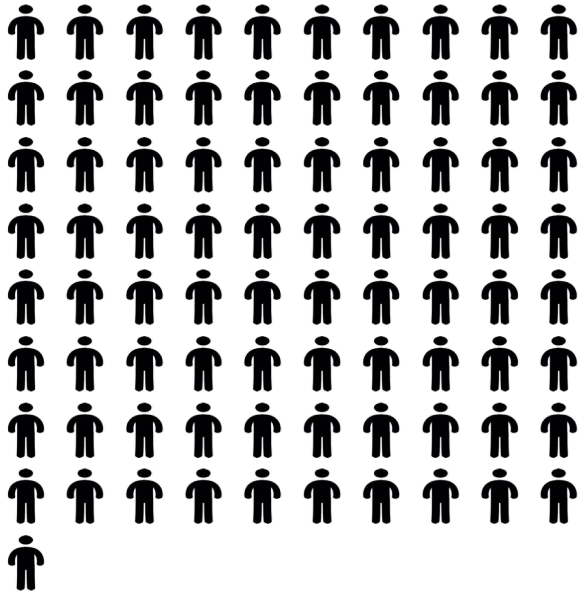
Top 5% of population has polygenic risk equivalent to risk of a monogenic FH mutation in external dataset



Greater than 3-fold risk

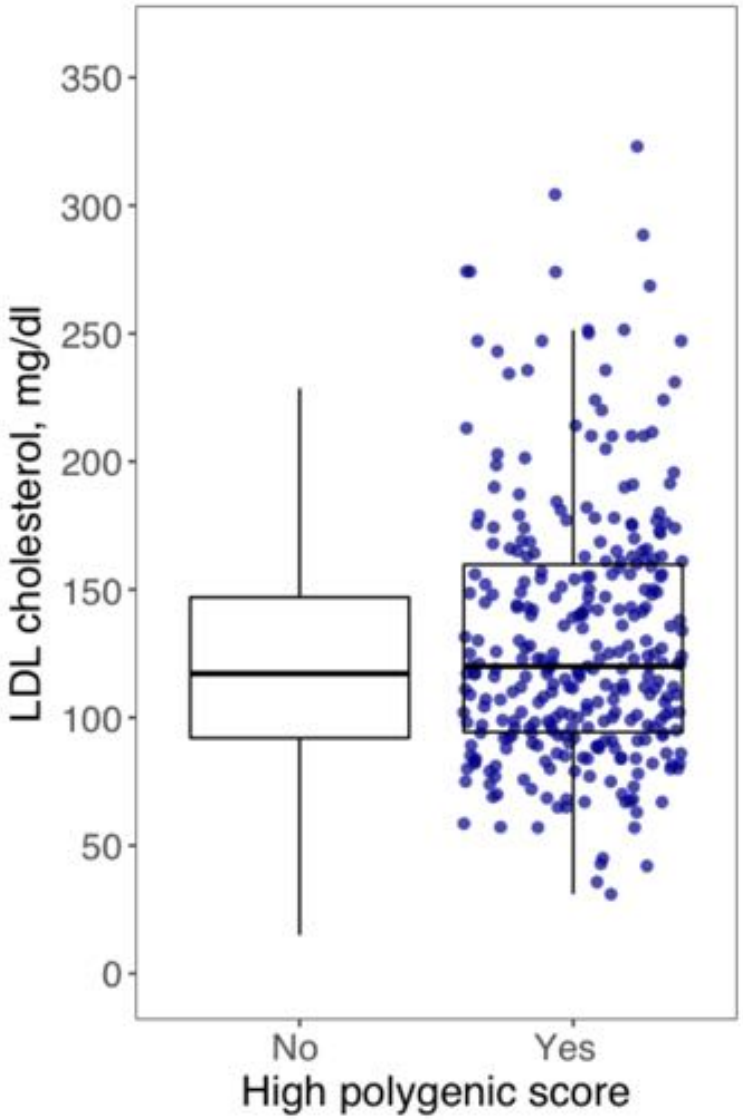
High polygenic score identified in 17% of patients and confers a 3.7-fold increased risk

100 patients with myocardial infarction



	↑ Risk
Monogenic	3.8-fold
High polygenic	3.7-fold

High polygenic score individuals can NOT be distinguished by high LDL cholesterol



Mean LDL Cholesterol

Carriers: 132 mg/dl

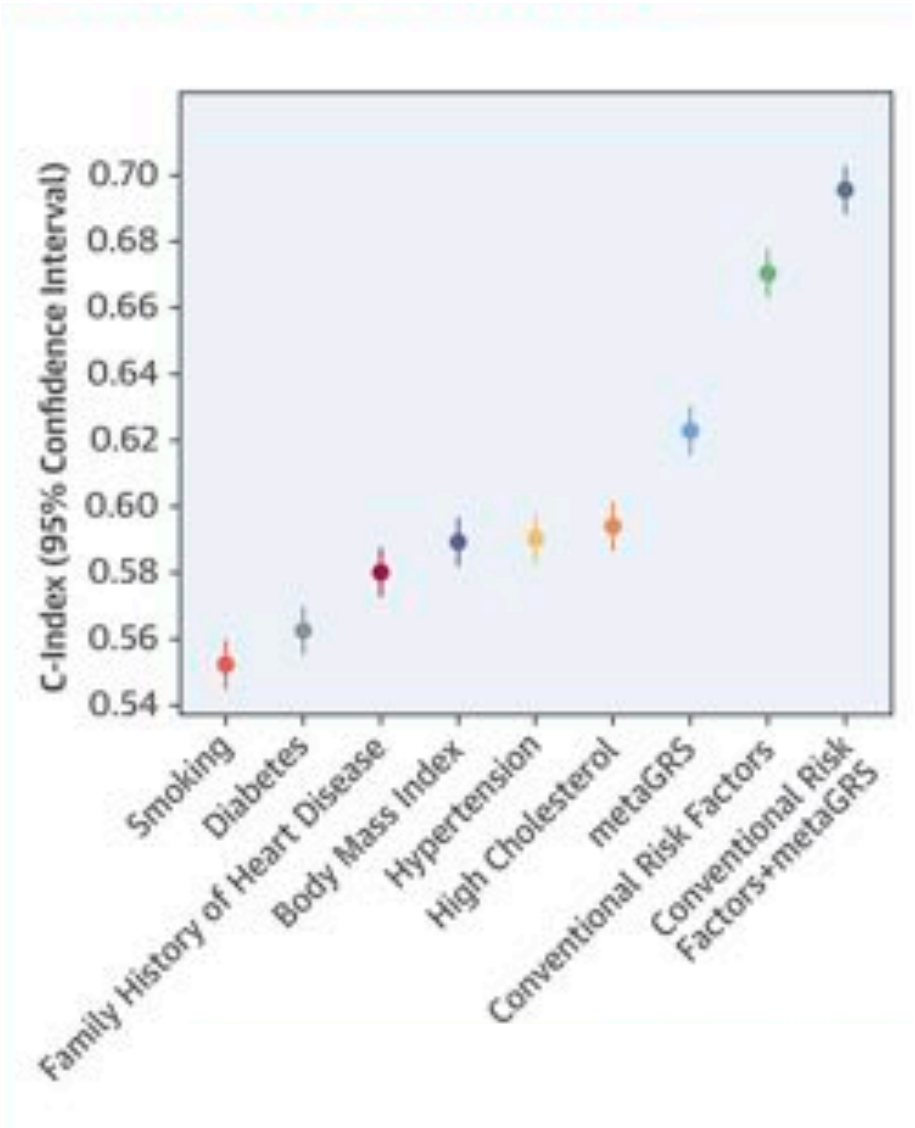
Non-carriers: 124 mg/dl

Traditional risk factors used in clinical practice are inadequate to pinpoint at-risk patients

	Remainder of population	Top 5% of polygenic score
Family history	**35%**	**44%**
Hypertension	28%	32%
Type 2 diabetes	2%	2.7%
Hypercholesterolemia	13%	20%
Current smoking	9.2%	9.5%
Body mass index	27.3	27.7
Systolic blood pressure	140	141

Some traditional risk factors are slightly elevated, but not enough to be useful

Genome-wide polygenic score complementary to existing risk stratification approaches

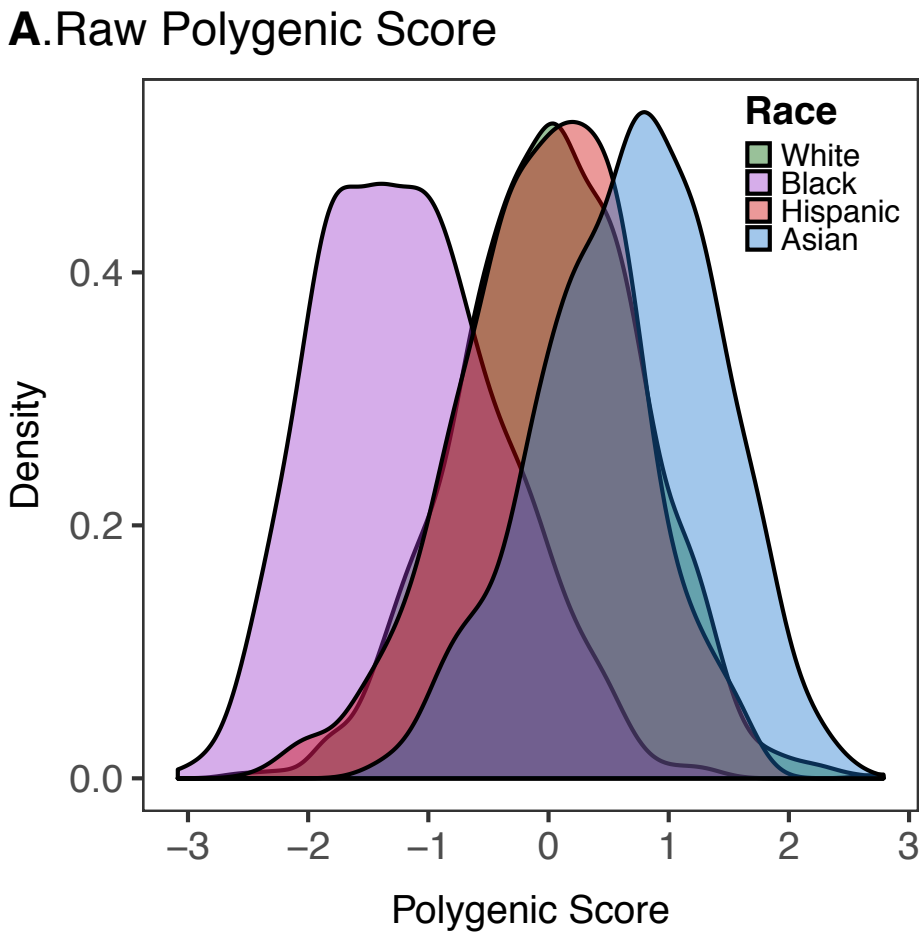


- **Stronger association than any single risk factor**
- **Largely independent of traditional risk factors**
- **Quantifiable at time of birth**
- **Varying trajectories of coronary risk**

Inouye et al.| *J Am Coll Card* | 2018

High polygenic score increases risk in all races but performance best in whites

Adjustment for ancestry can standardize score distribution



High polygenic score increases risk in all races but performance best in whites

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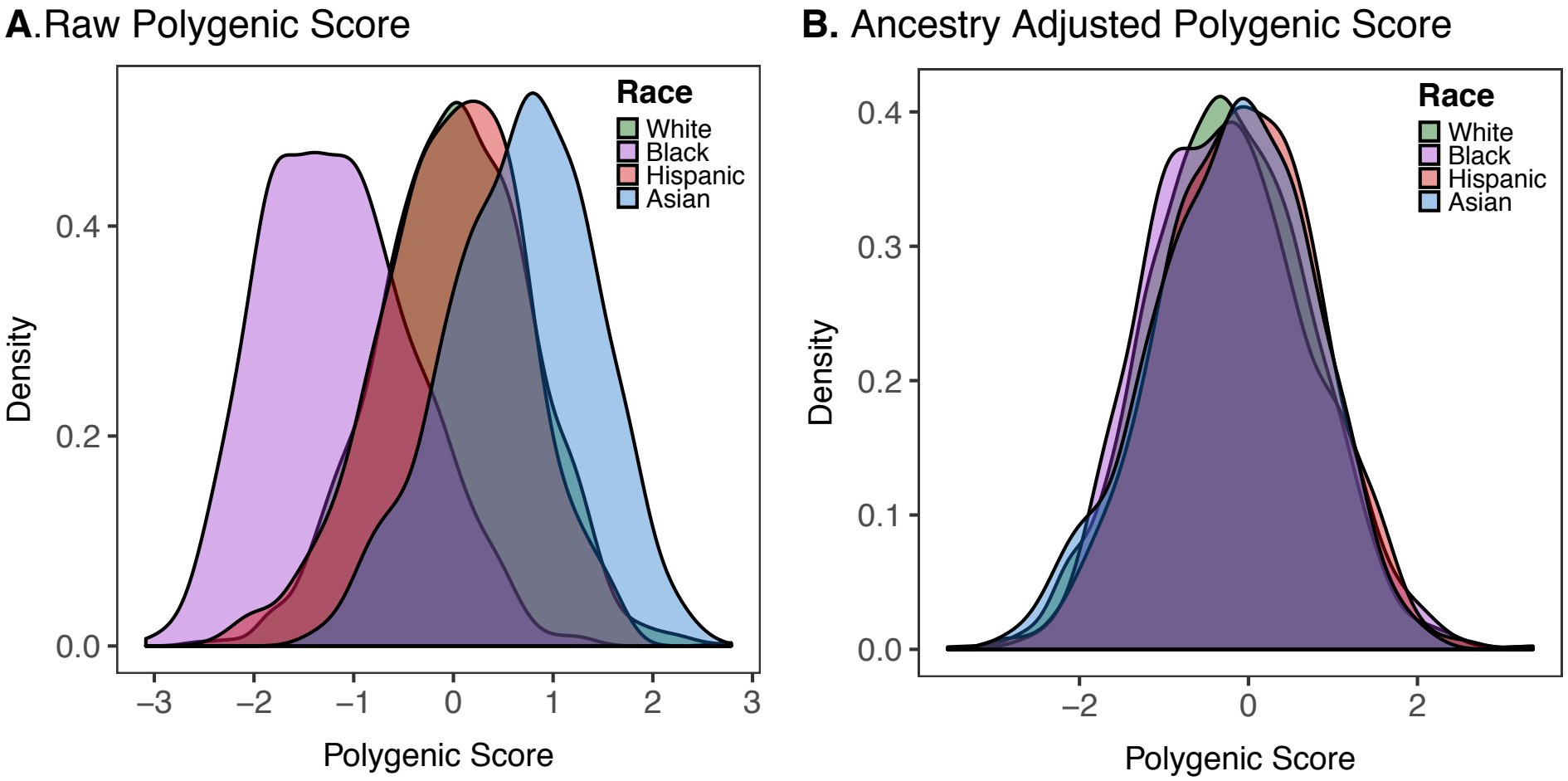
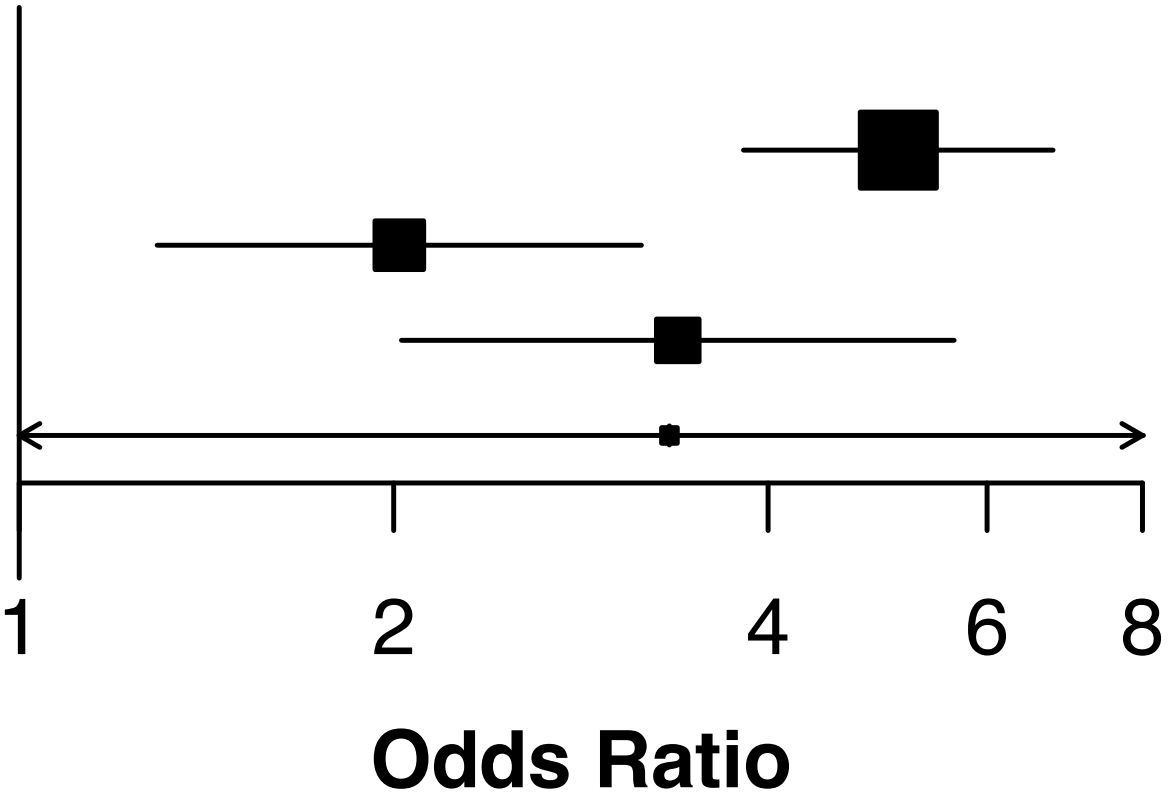


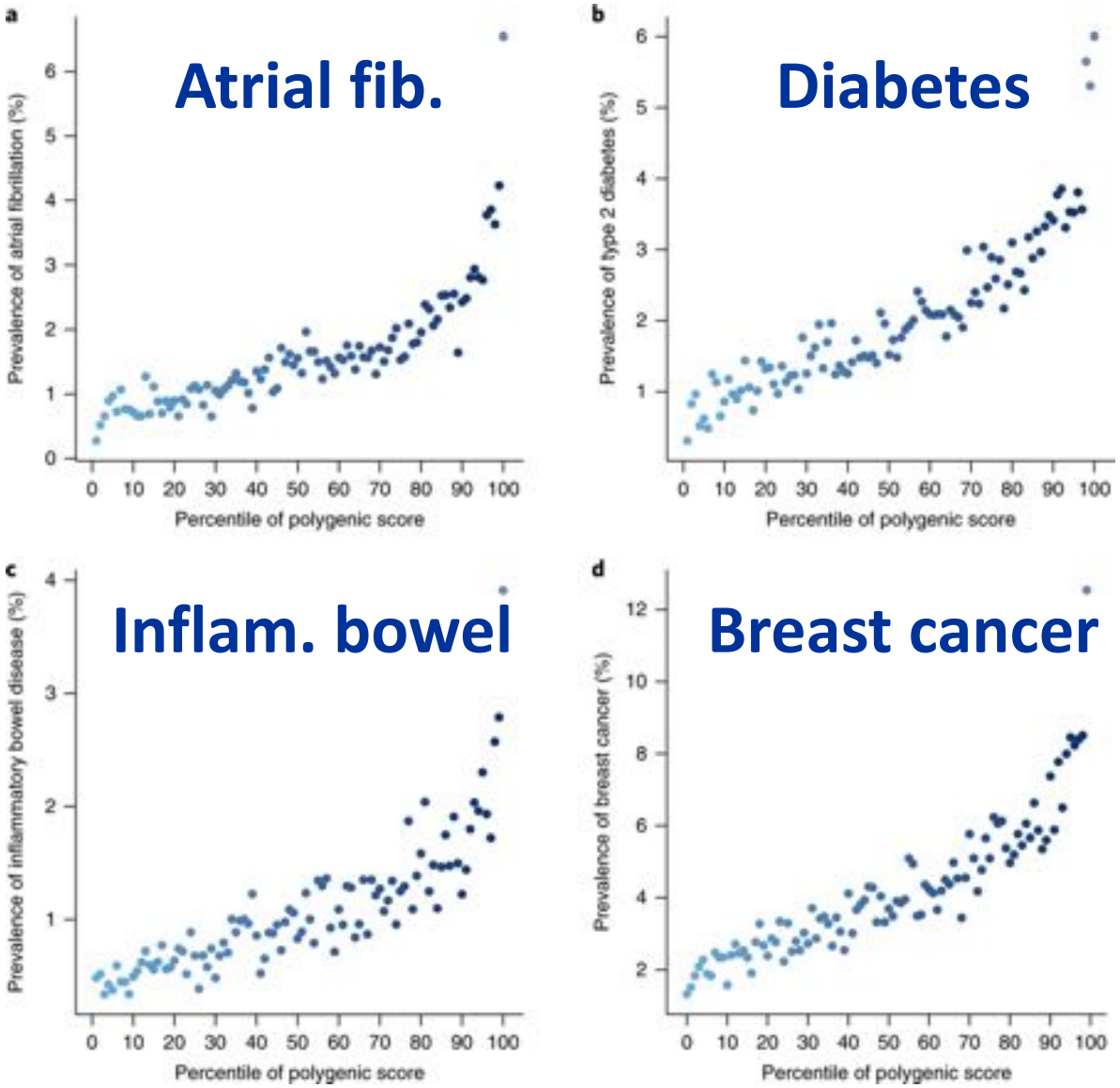
High polygenic score increases risk in all races but performance best in whites

… but differential clinical performance remains

Race	N (%) MI Patients	OR
White	(285 / 1537) 19%	5.09
Black	(35 / 336) 10%	2.02
Hispanic	(32 / 168) 19%	3.38
Asian	(7 / 40) 18%	3.33



Approach works for other common diseases . . . including those without monogenic risk factors



	% of population at >3-fold risk
Heart attack	8.0%
Atrial fibrillation	6.1%
Diabetes	3.5%
Inflam. bowel	3.2%
Breast cancer	1.5%

Khera, et al. *Nat Gen* 2018

Genome-wide polygenic score for myocardial infarction identifies 10x than monogenic mutations

	Monogenic	Polygenic
Prevalence	1.7%	**17%**
Odd ratio for MI	3.8x	**3.7x**
Mode of detection	↑ LDL-cholesterol	**Currently undiagnosed**
Intervention	Statin, ezetimibe PCSK9i	?

Question: Is DNA destiny? To what extent can a healthy lifestyle offset high polygenic risk

Khera,* Emdin,* … Kathiresan | *New Eng J Med* | 2017

Healthy lifestyle score (AHA criteria)
4 key factors

No Current Smoking

BMI < 30 kg/m^2

Regular Exercise

Healthy Diet

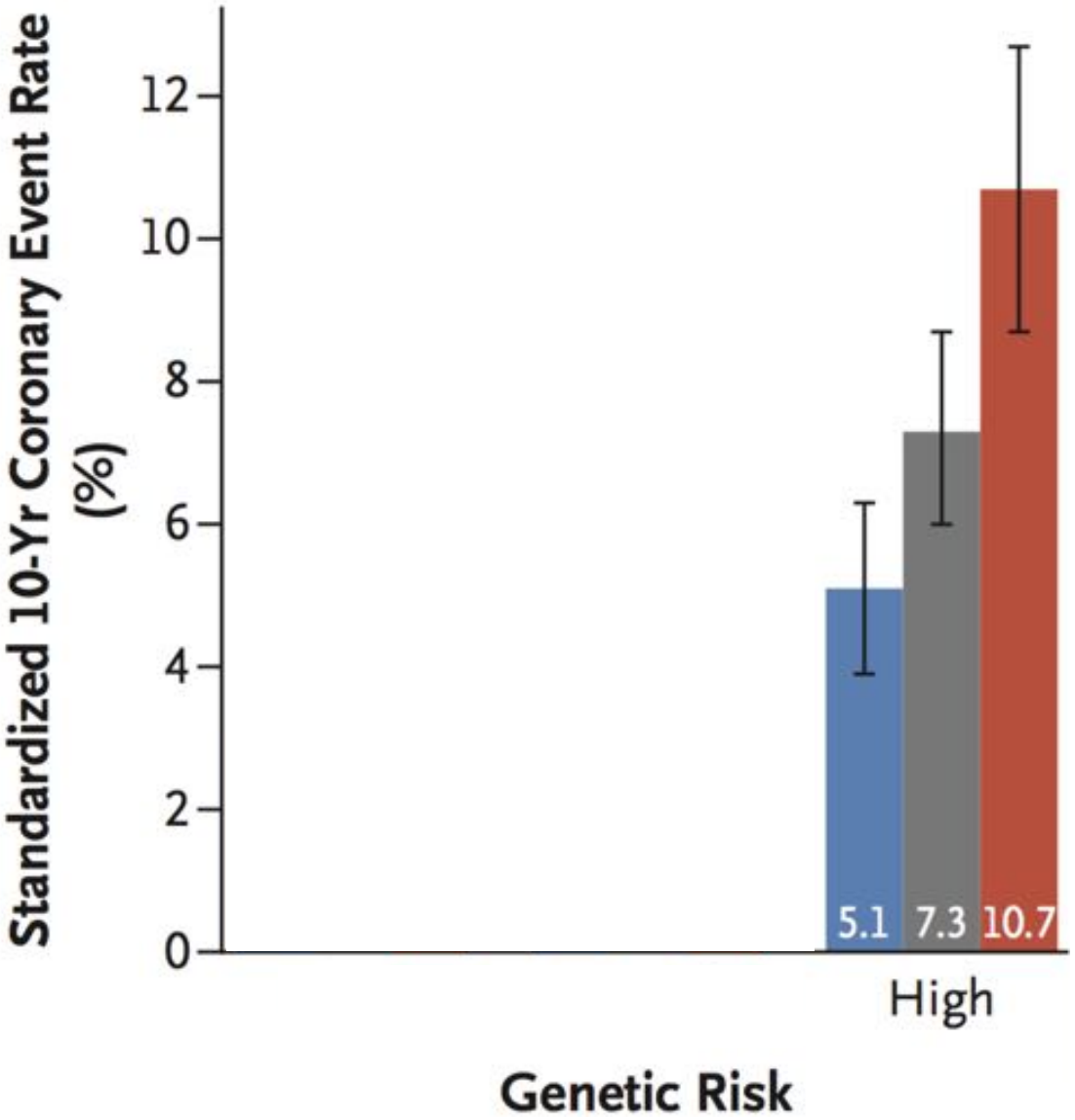
Favorable Lifestyle
3-4 Healthy Lifestyle Factors

Intermediate Lifestyle
2 Healthy Lifestyle Factors

Unfavorable Lifestyle
0-1 Healthy Lifestyle Factor

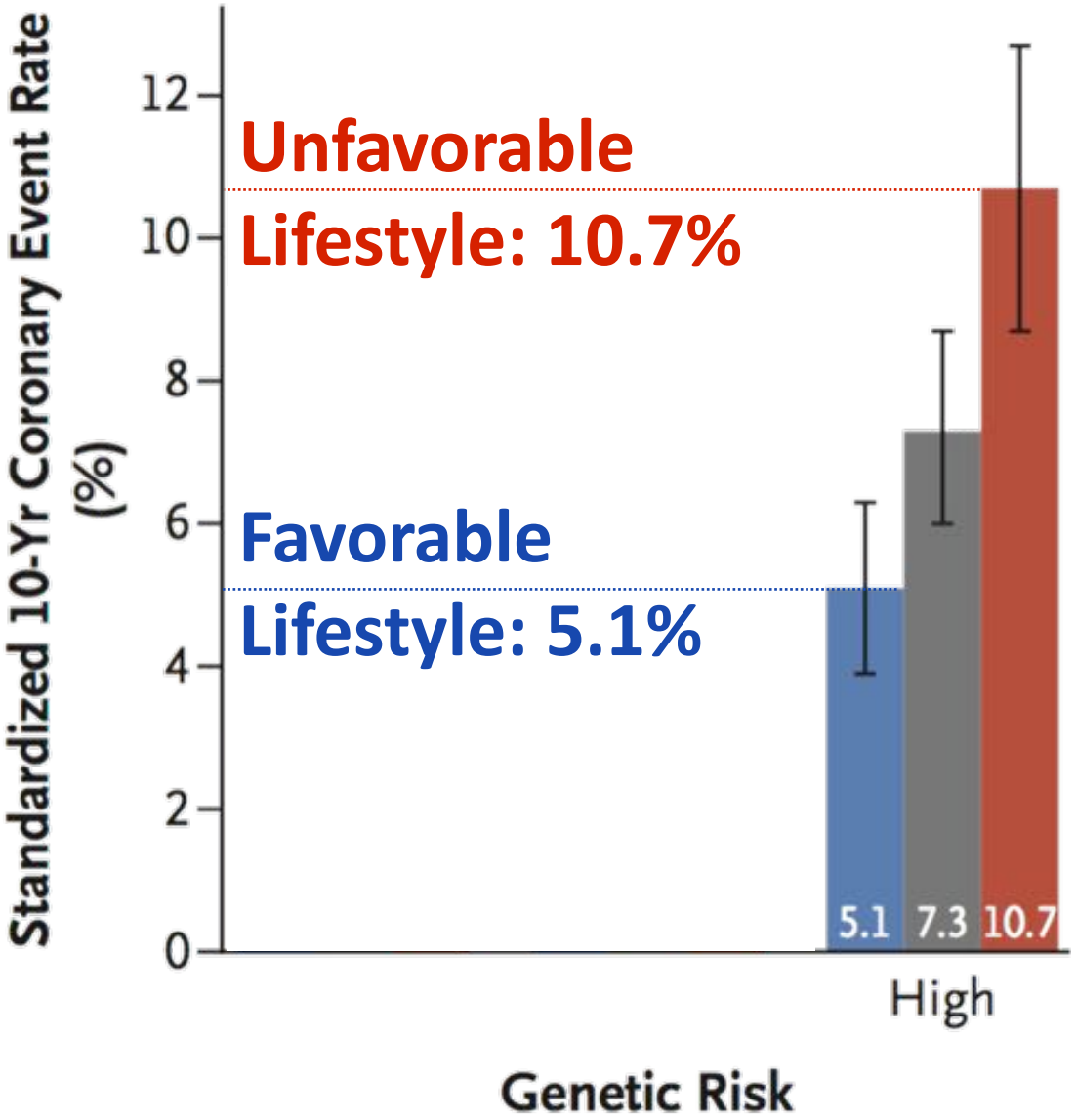
Among high polygenic risk individuals

Favorable lifestyle linked to 50% lower event rate



Among high polygenic risk individuals

Favorable lifestyle linked to 50% lower event rate



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Mode of detection	↑ LDL-cholesterol	**Currently undiagnosed**
Intervention	Statin, ezetimibe PCSK9i	Lifestyle Medication

Genome-wide polygenic score for myocardial infarction
Opportunity to deliver on 'genomic medicine'

Charting a course for genomic medicine from base pairs to bedside

Eric D. Green[1], Mark S. Guyer[1] & National Human Genome Research Institute*

IDENTIFY high-risk individuals → **DISCLOSE** risk to participants → **INTERVENE** to decrease risk of disease

Genome-wide polygenic score for myocardial infarction
Opportunity to deliver on 'genomic medicine'

color

Single test: monogenic + polygenic

Genome-wide polygenic score for myocardial infarction
Opportunity to deliver on 'genomic medicine'

color

Single test: monogenic + polygenic

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Reporting: genetic and nongenetic factors

Genome-wide polygenic score for myocardial infarction
Opportunity to deliver on 'genomic medicine'

color

Single test: monogenic + polygenic

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Reporting: genetic and nongenetic factors

PREVENTIVE GENOMICS CLINIC

Infrastructure: enable genome-first medicine at MGH

Recognition and treatment of high polygenic score important public health opportunity

@amitvkhera

"Flying under the radar" in clinical practice

	↑Risk
Monogenic	3.8-fold
High polygenic	3.7-fold

Two interventions to mitigate risk

Lifestyle

Khera| *NEJM* | 2016

Statins

Mega | *Lancet* | 2015
Natarajan | *Circ* | 2017