Update on Genetic Prediction of Future Cardiovascular Disease

Wendy S. Post, MD, MS

Professor of Medicine and Epidemiology

Director of Cardiovascular Research

Division of Cardiology, Department of Medicine

Johns Hopkins University, Baltimore, MD

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Financial Disclosures

- I have no financial relationships with a commercial entity that is relevant to the content of this presentation.

Genetics

- Genetic discoveries lead to insights into biology
- Targets for therapy
- Polygenic Risk Scores
  - Are they useful for risk prediction?
- Clinical Genetic Testing for CVD
- Direct to consumer marketing

Personalized Genomic Medicine

“Personalized genomic medicine is that knowledge of a person’s gene sequences and activity will facilitate more appropriate medical interventions, particularly drug prescriptions, to reduce the burden of disease.”

Gibson G. PLOS Genetics 2019, April 25.

163 CAD risk loci from Genome Wide Association Studies (GWAS)

Explain ~30-40% of heritability of CHD

Common variants each with small effect size

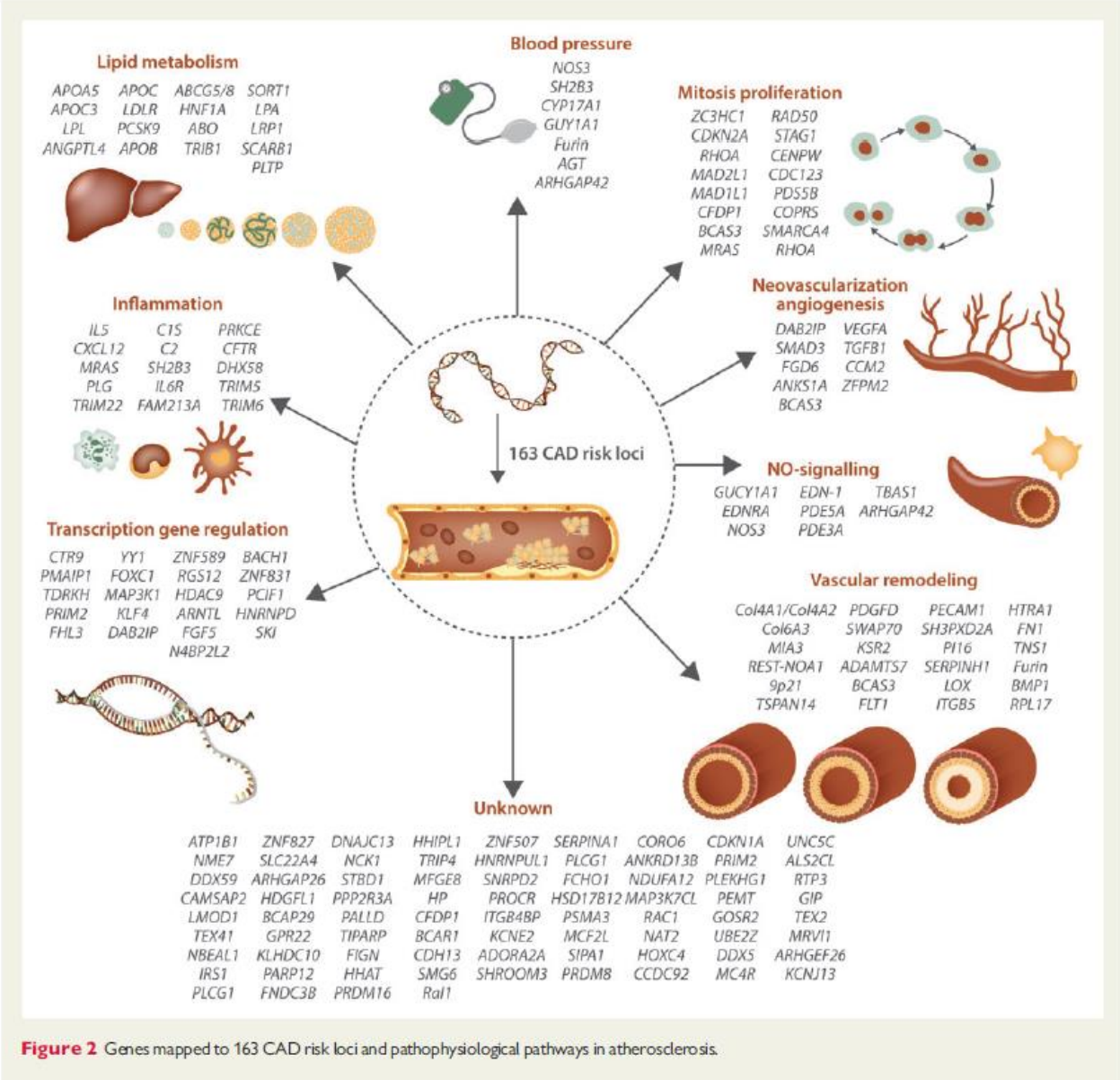


Figure 2 Genes mapped to 163 CAD risk loci and pathophysiological pathways in atherosclerosis.

Erdmann J et al. Cardiovasc Research 2018; 114: 1241-57

Genetic Discoveries and Medical Therapies for CAD

Table 2 Examples of genes affecting CAD and MI risk identified by large-scale array-based or deep-sequencing projects with relevance for therapeutic development

Gene	*PCSK9*	*NPC1L1*	*LPA*	*LPL*	*APOC3*	*ANGPTL4*	*ANGPTL3*
Frequency	1 in 50 blacks	1 in 150	1 in 13	1 in 10	1 in 150	1 in 500	1 in 300
Phenotype	LDL	LDL	Lp(a)	TG	TG	TG	TG, LDL
Risk	80% lower risk	53% lower risk	14% higher risk	17% lower risk	40% lower risk	57% lower risk	34% lower risk
Therapy	Evolocumab, Bococizumab, Alirocumab	Ezetimibe	Antisense in development	?	Antisense in development	Monoclonal antibodies in development	Monoclonal antibodies in development
References	115	116	117	118	119	118, 120	121–123

Beneficial effect not only in those with genetic variants.

Erdmann J et al. Cardiovasc Research 2018; 114: 1241-57

Drug targets

- But most identified genetic loci are in non-coding regions.
- Most are near multiple genes.
- Don’t know biological meaning or downstream pathways.

Coronary artery disease

- Common complex disorder
- Rare monogenic disorders- Familial Hypercholesterolemia
  - 0.4% of general population
- Loss of function variants in FH- 4 fold risk for CAD
  - LDLR
  - APOB
  - PCSK9
  - Others

- Polygenic risk scores
  - Calculated for each individual- precision medicine
  - Sum of risk variant alleles weighted by impact of each allele on disease risk

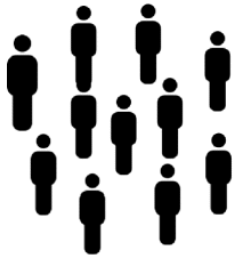
Cardiomyopathy

- Hypertrophic Cardiomyopathy
- Dilated Cardiomyopathy
- ARVC
- Familial Amyloid Heart Disease

Monogenic Risk

High Risk Variants
Rarely Observed
Binary Testing Result

~2%



Average Risk
~98%

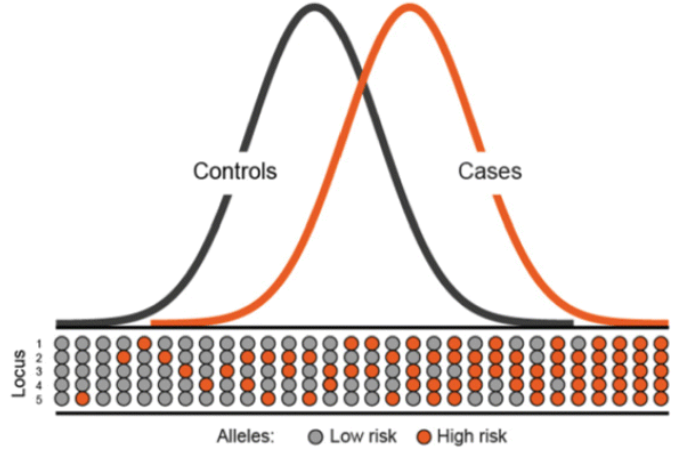
High Risk
~2%

Yes or No?

Σ

Polygenic Risk

Low Risk Variants
Numerous Common Variants
Continuous Testing Result



Low Risk **High Risk**

Muse ED et al. Curr Cardiolog Rep 2021 Jul 1;23(8):107

Genetic Risk, Adherence to a Healthy Lifestyle, and CHD

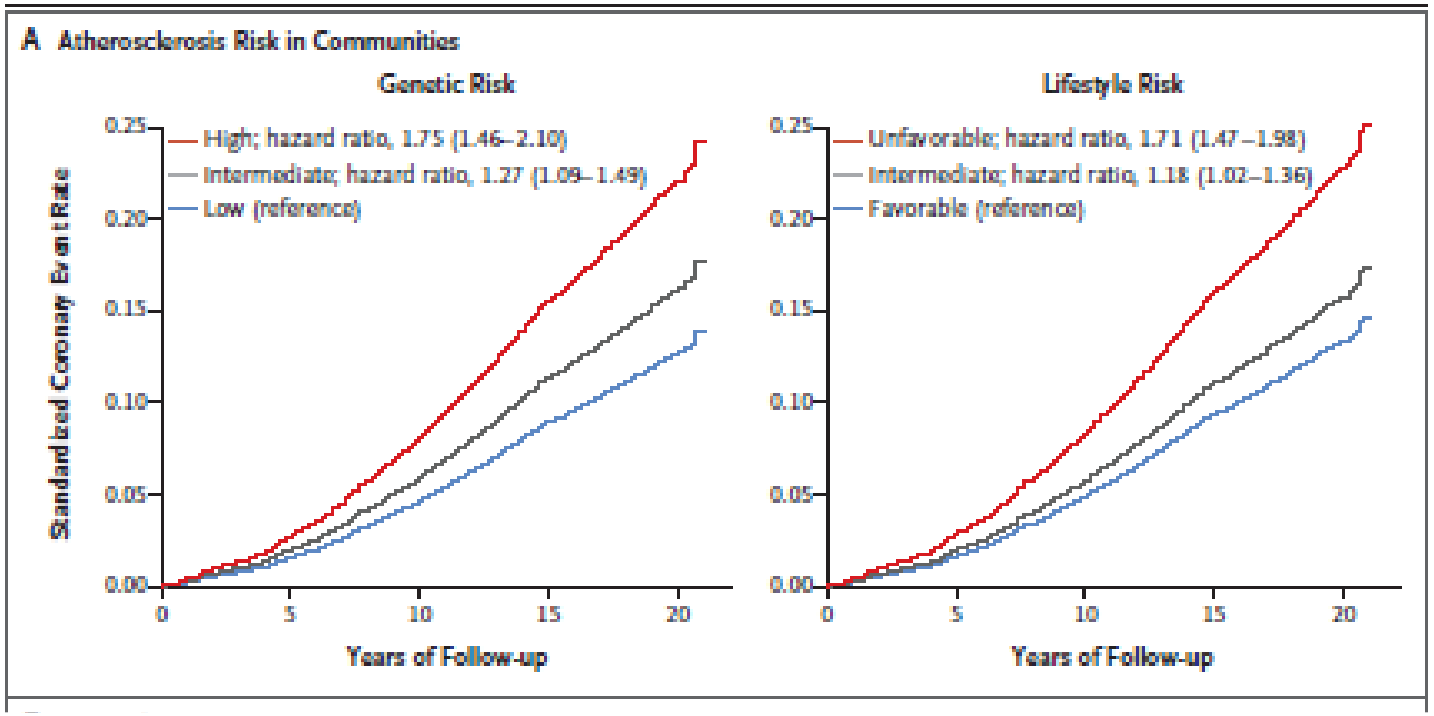
Lifestyle Risk:
no current smoking
no obesity (BMI< 30)
regular physical activity (at least once a week)
healthy diet*

*increased amount of fruits, nuts, vegetables, whole grains, fish, and dairy products and a reduced amount of refined grains, processed meats, unprocessed red meats, sugar-sweetened beverages, trans fats and sodium

Genetic Risk Score: 50 top SNPs from GWAS multiplied by effect size

High= top quintile of polygenic risk score
Intermediate- quintiles 2,3,4
Low- bottom quintile

Favorable= 3 or 4
Intermediate 2 or 3
Unfavorable = 0 or 1



Khera AV et al.. N Engl J Med 2016;375:2349-2358

Cox regression models adjusted for age, sex (in ARIC and MDCS),randomization to vit E or aspirin (WGHS), education, and principal components of ancestry

Genetic and lifestyle factors independently associate with coronary artery disease risk

Participants at high genetic risk

- favorable lifestyle associated with a nearly 50% lower relative risk of coronary artery disease than an unfavorable lifestyle

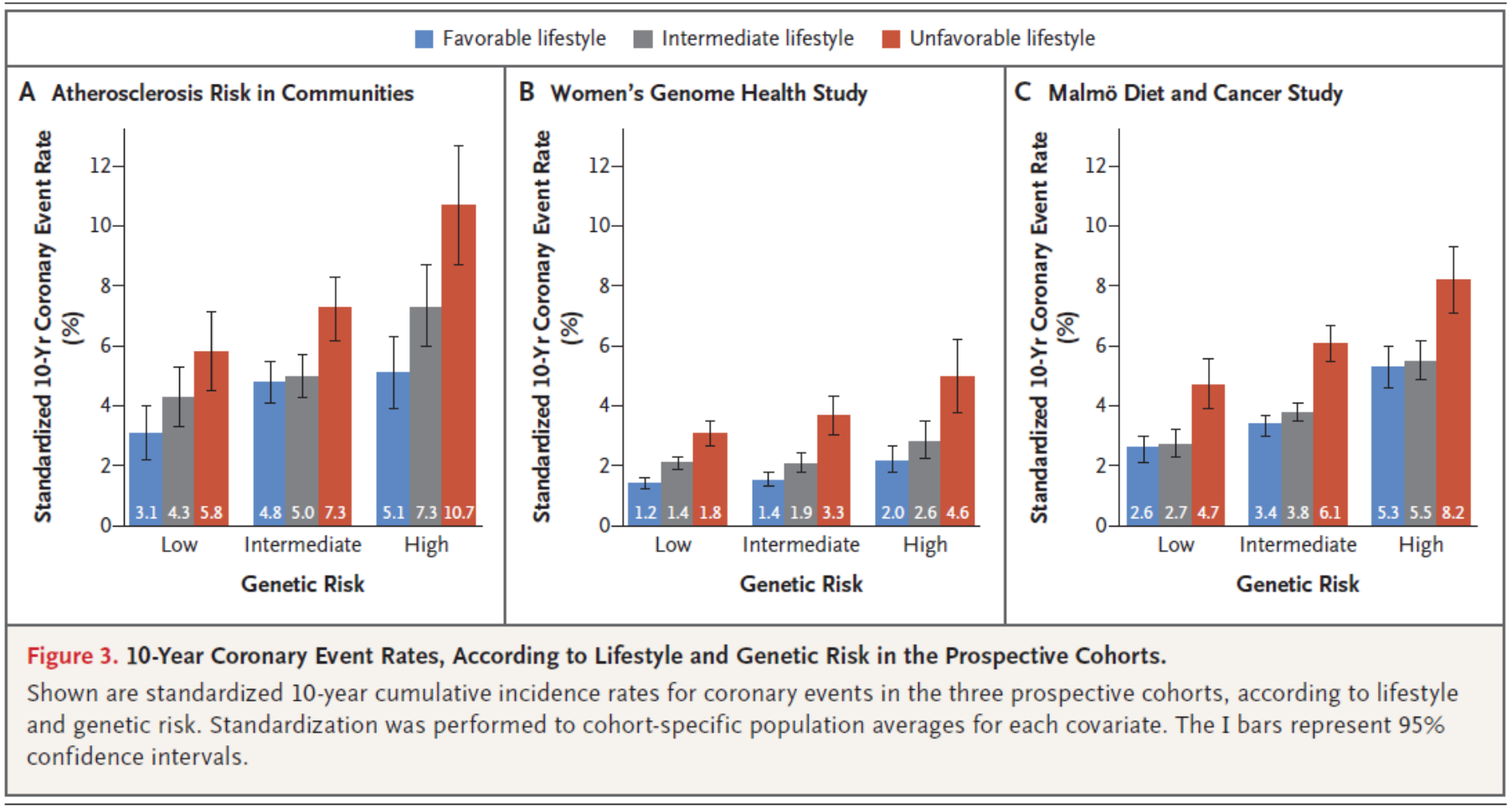


Figure 3. 10-Year Coronary Event Rates, According to Lifestyle and Genetic Risk in the Prospective Cohorts.

Shown are standardized 10-year cumulative incidence rates for coronary events in the three prospective cohorts, according to lifestyle and genetic risk. Standardization was performed to cohort-specific population averages for each covariate. The I bars represent 95% confidence intervals.

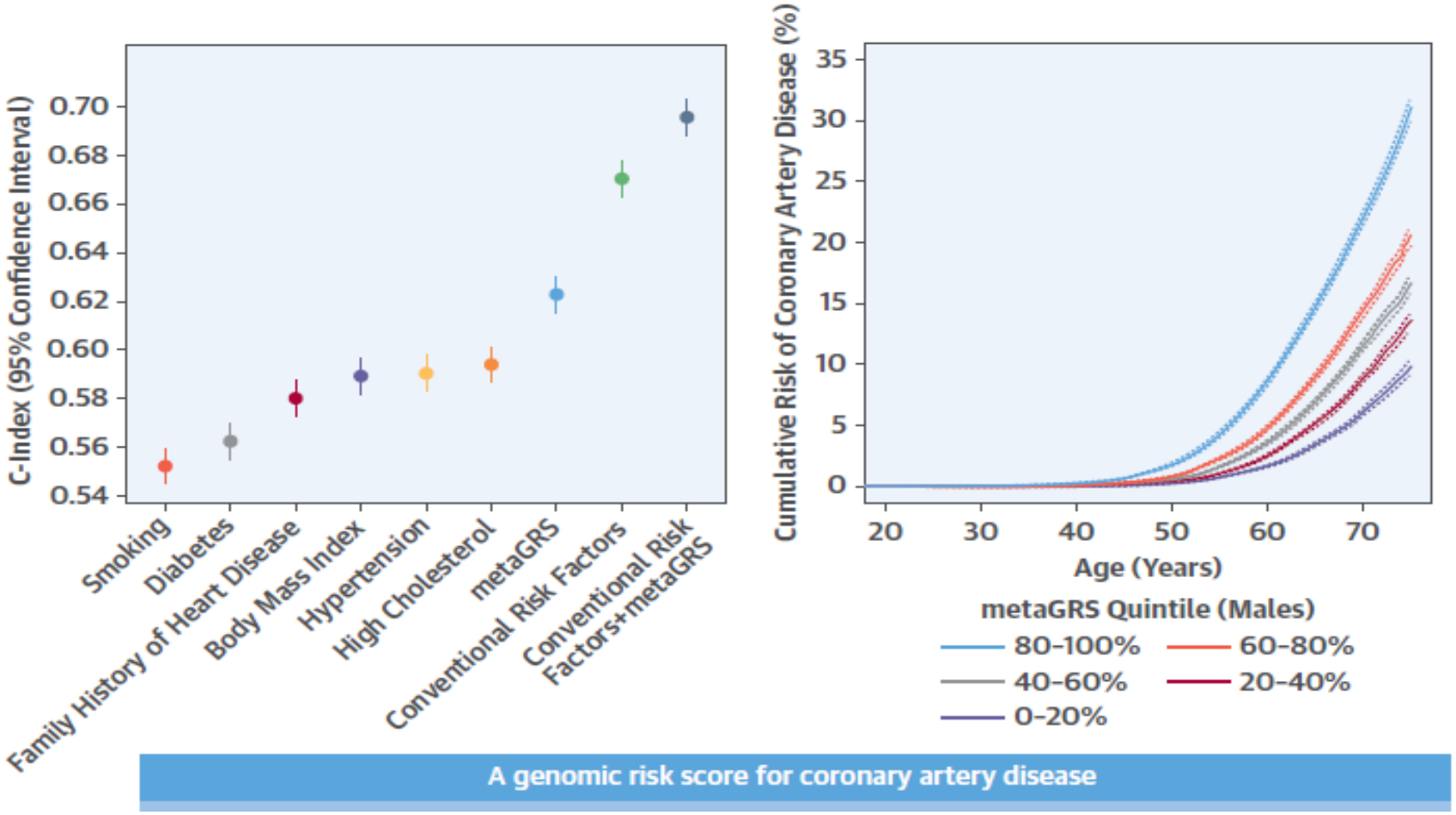
Khera AV et al.. N Engl J Med 2016;375:2349-2358

UK Biobank- Meta Genetic Risk Score (GRS)

Meta GRS
1.7 million genetic variants

22,242 CAD cases
460,387 non-cases
UK Biobank

Top 20% of metaGRS distribution
HR of 4.17 (95% CI: 3.97 to 4.38)
compared the bottom 20%.

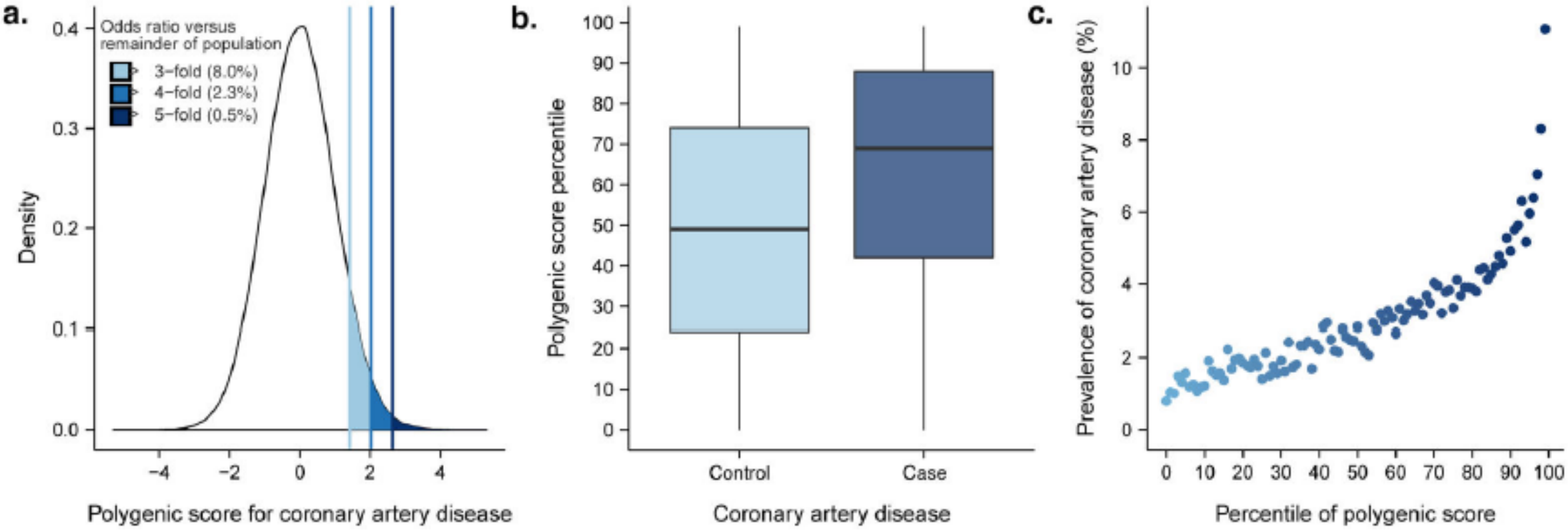


A genomic risk score for coronary artery disease

The genomic score substantially advances the concept of using genomic information to stratify individuals with different trajectories of CAD risk and the potential for genomic screening in early life to complement conventional risk prediction.

Inouye M et al. JACC 2018; 72 (16); 1883-93.

Genome-wide Polygenic Risk Score- CAD



UK Biobank- European Ancestry

6 million genetic variants

Khera AV et al. Nat Genet 2018; 50 (9):1219-24

Genome-wide Polygenic Risk Score

UK Biobank- European Ancestry

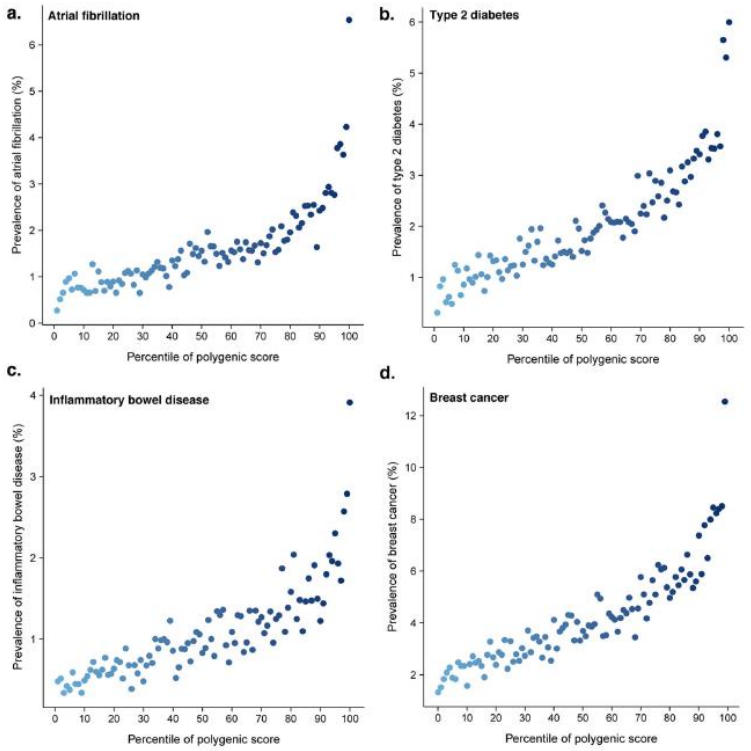
6 million genetic variants

A fib

DM

Inflammatory Bowel Disease

Breast Cancer



Khera AV et al. Nat Genet 2018; 50 (9):1219-24

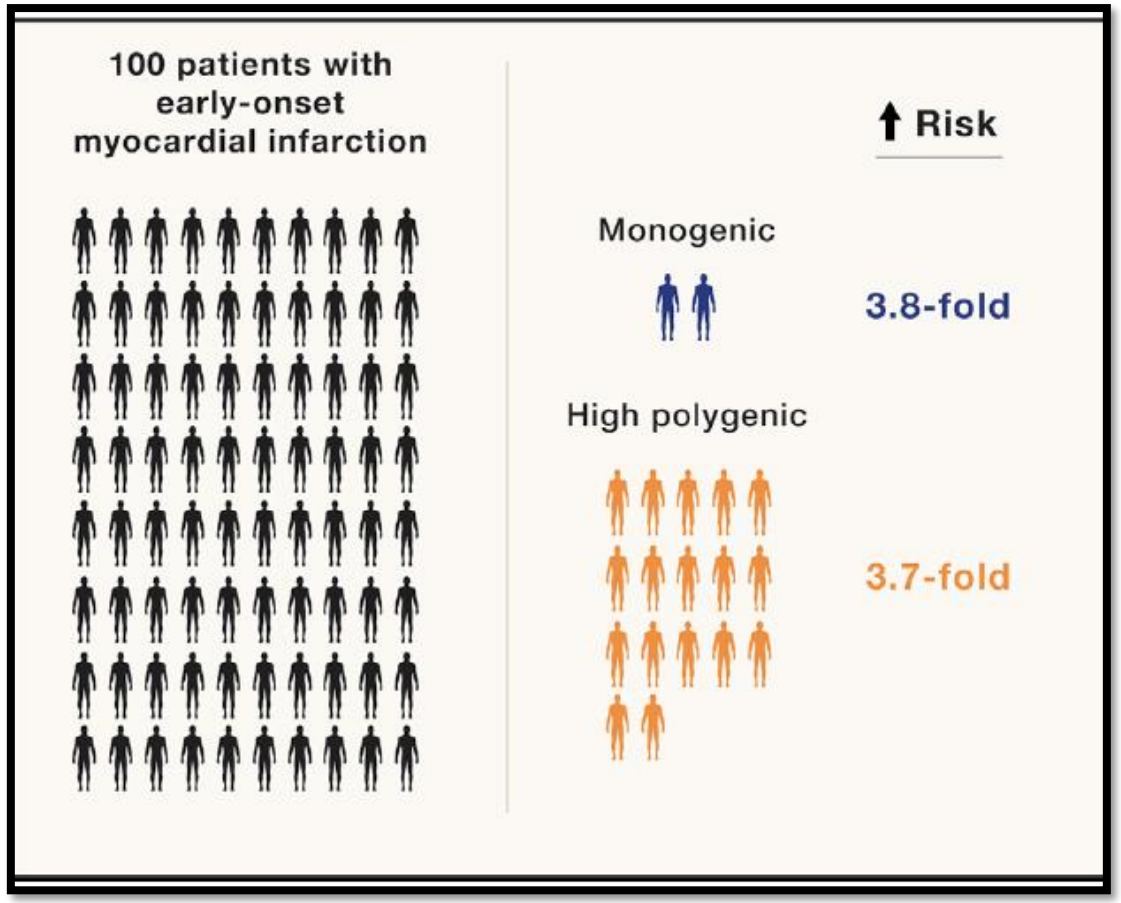
Polygenic risk scores

Polygenic risk scores can identify a substantially larger fraction of the population than found by rare monogenic (single-gene) mutations, at comparable or greater disease risk.

Combined influence of multiple pathways.

Khera AV et al. Nat Genet 2018; 50 (9):1219-24

Monogenic Diseases compared with Polygenic Risk Scores



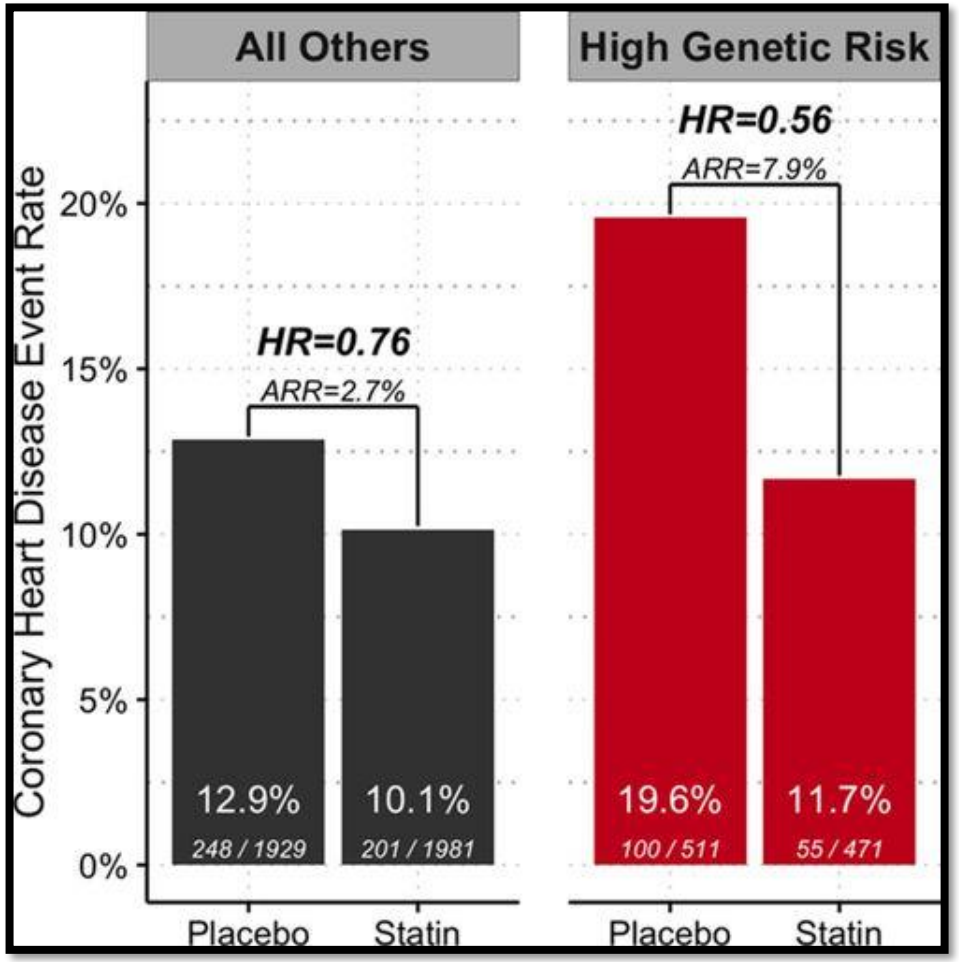
- High PRS more likely to explain early onset MI than monogenic diseases
- 100 individuals with premature CAD
  - 17 had a high polygenic risk score
  - 2 had a monogenic pathogenic variant

Khera AV, et al. *Circulation.* 2019

Guide Medical Management

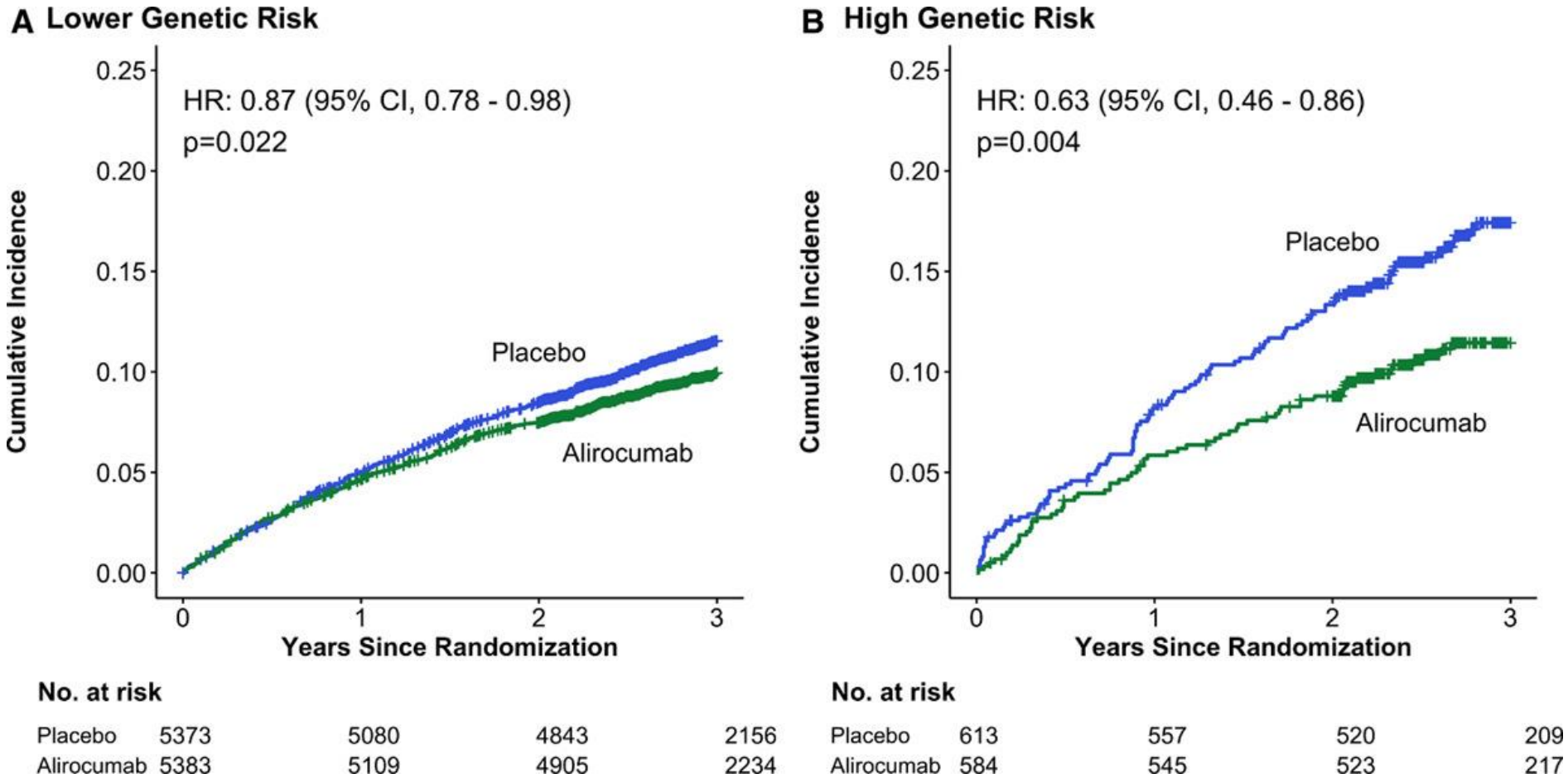
- WOSCOPS - primary prevention statin randomized trial
- Polygenic risk score derived from up to 57 common DNA sequence variants previously associated with coronary heart disease
- Top quintile of PRS= high genetic risk
- Statins confer greatest benefit to individuals at high genetic risk

- CHD events= non-fatal MI or CHD death



Natarajan P, et al., *Circulation*, 2017; 135:2091–2101.

Patients With High GRS for CAD May Receive Greater Clinical Benefit From Alirocumab Treatment: ODYSSEY OUTCOMES Trial



Patients with history of Acute Coronary Syndrome
LDL> 70 mg/dl on high dose statin therapy

Randomized to PCSK9i vs placebo

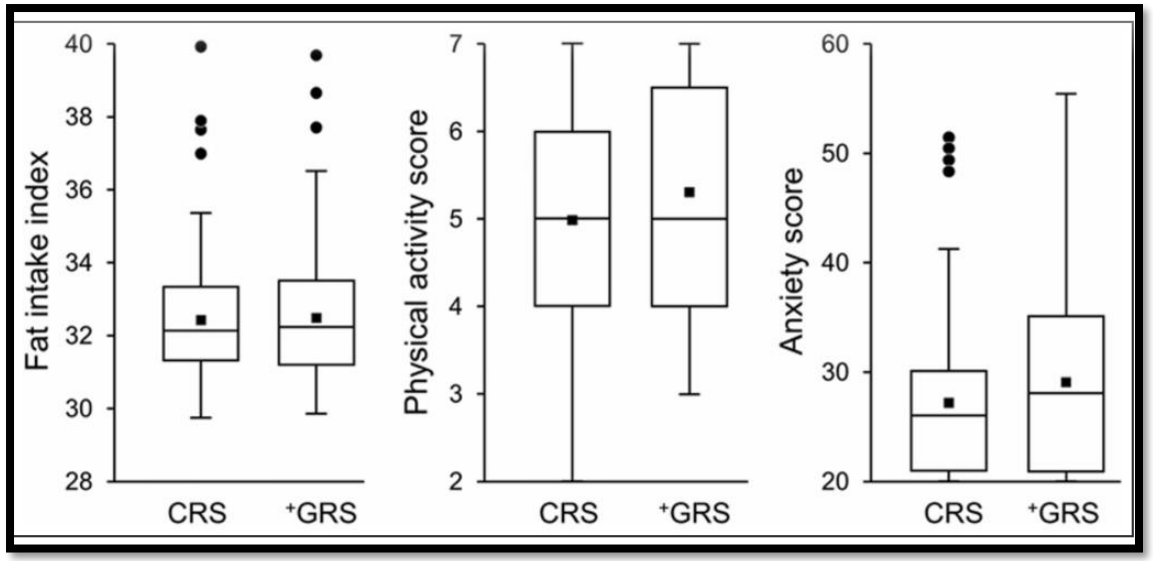
High genetic risk
>90th percentile
GRS with > 6 million variants

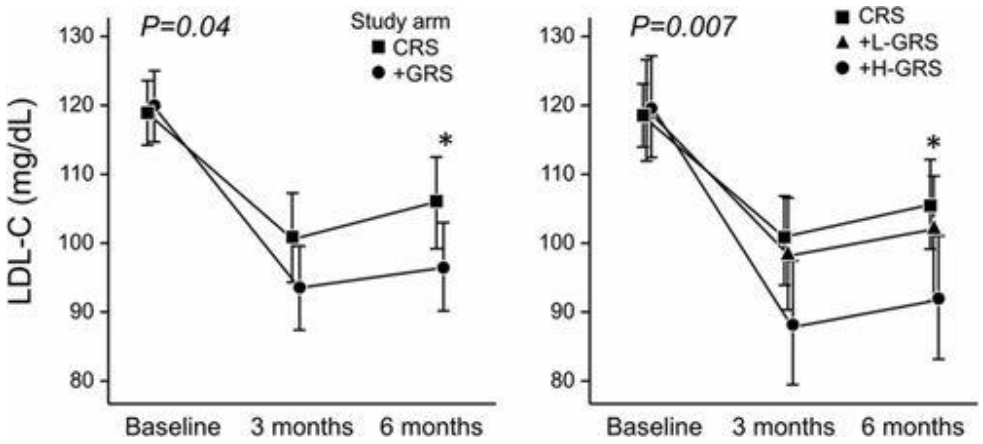
Outcome= CAD death, nonfatal MI, ischemic stroke, or unstable angina

Damask A et al. Circulation. 2020 Feb 25;141(8):624-636

Does knowledge of genetic risk lead to change?

- Participants (n=203, 45–65 years of age, at intermediate risk for CHD, and not on statins) randomly assigned to receive their 10-year probability of CHD based either on a conventional risk score (CRS) or CRS + GRS (+GRS). Shared decision making about therapy with a physician after talking to genetic counselor.
- Receiving a high PRS score was not significantly associated with dietary or exercise changes compared to standard of care.
- Physicians were more likely to prescribe statins if they knew individuals had a high PRS





Kullo IJ, et al., *Circulation*, 2016;133:1181–1188

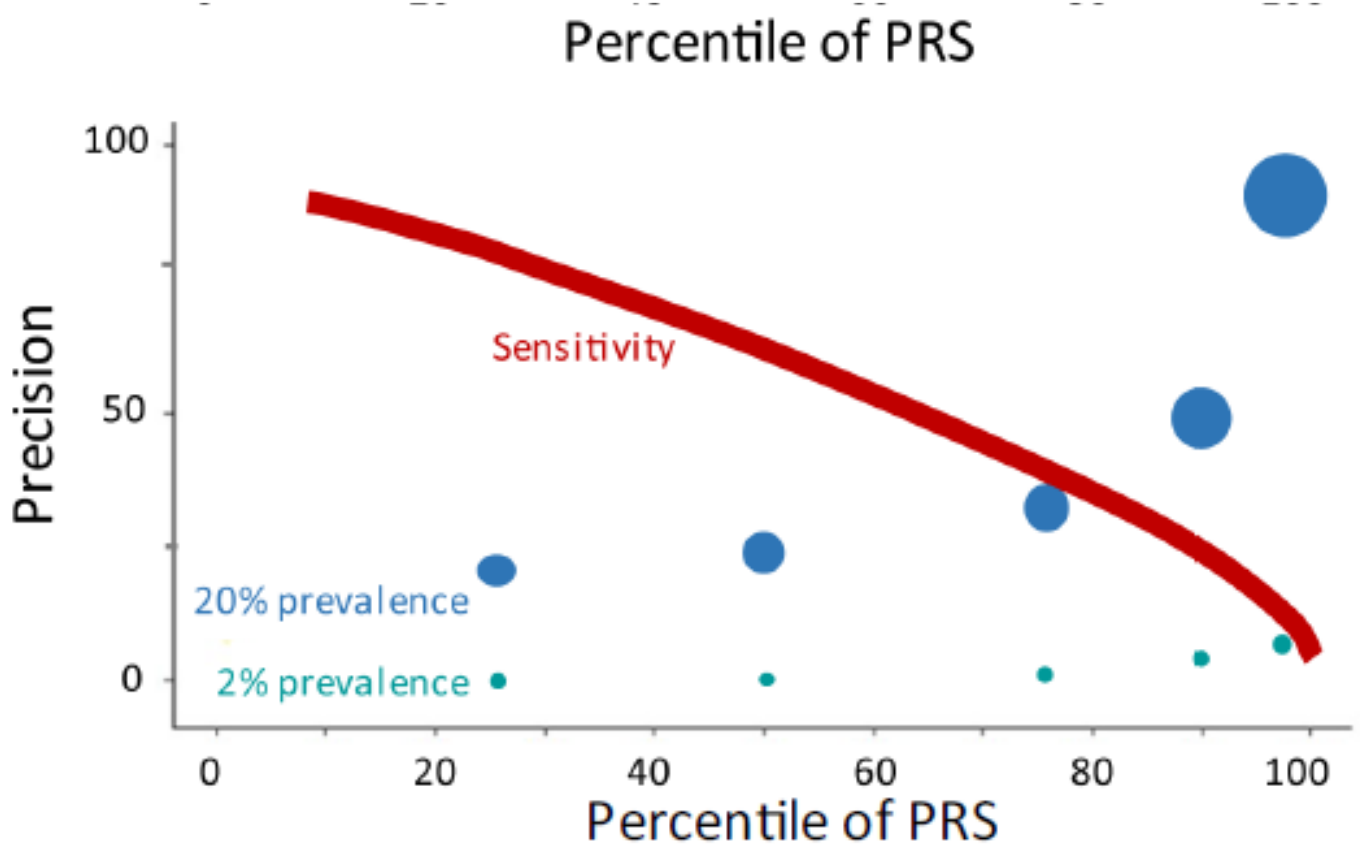
Positive Predictive Value (PPV) and Prevalence of Disease

Precision (PPV) =
Proportion of individuals
called positive who have the disease

Sensitivity=
proportion of cases captured by the PRS at the indicated percentile.

PPV depends on the prevalence of disease. Low prevalence of disease= Low PPV.

Sensitivity depends on the cut-off used to define the positive test.
High threshold= low sensitivity
Low threshold- high sensitivity



Gibson G. PLOS Genetics 2019, April 25.

JAMA | Original Investigation

Predictive Accuracy of a Polygenic Risk Score Compared With a Clinical Risk Score for Incident Coronary Heart Disease

Jonathan D. Mosley, MD, PhD; Deepak K. Gupta, MD, MSCI; Jingyi Tan, MA; Jie Yao, MD, MS; Quinn S. Wells, MD, PharmD; Christian M. Shaffer, BS; Suman Kundu, DSc; Cassianne Robinson-Cohen, PhD; Bruce M. Psaty, MD; Stephen S. Rich, PhD; Wendy S. Post, MD, MS; Xiuqing Guo, PhD; Jerome I Rotter, MD; Dan M. Roden, MD; Robert E. Gerszten, MD; Thomas J. Wang, MD

IMPORTANCE Polygenic risk scores comprising millions of single-nucleotide polymorphisms (SNPs) could be useful for population-wide coronary heart disease (CHD) screening.

OBJECTIVE To determine whether a polygenic risk score improves prediction of CHD compared with a guideline-recommended clinical risk equation.

DESIGN, SETTING, AND PARTICIPANTS A retrospective cohort study of the predictive accuracy of a previously validated polygenic risk score was assessed among 4847 adults of white European ancestry, aged 45 through 79 years, participating in the Atherosclerosis Risk in Communities (ARIC) study and 2390 participating in the Multi-Ethnic Study of Atherosclerosis (MESA) from 1996 through December 31, 2015, the final day of follow-up. The performance of the polygenic risk score was compared with that of the 2013 American College of Cardiology and American Heart Association pooled cohort equations.

EXPOSURES Genetic risk was computed for each participant by summing the product of the weights and allele dosage across 6 630 149 SNPs. Weights were based on an international genome-wide association study.

MAIN OUTCOMES AND MEASURES Prediction of 10-year first CHD events (including myocardial infarctions, fatal coronary events, silent infarctions, revascularization procedures, or resuscitated cardiac arrest) assessed using measures of model discrimination, calibration, and net reclassification improvement (NRI).

RESULTS The study population included 4847 adults from the ARIC study (mean [SD] age, 62.9 [5.6] years; 56.4% women) and 2390 adults from the MESA cohort (mean [SD] age, 61.8 [9.6] years; 52.2% women). Incident CHD events occurred in 696 participants (14.4%) and 227 participants (9.5%), respectively, over median follow-up of 15.5 years (interquartile range [IQR], 6.3 years) and 14.2 (IQR, 2.5 years) years. The polygenic risk score was significantly associated with 10-year CHD incidence in ARIC with hazard ratios per SD increment of 1.24 (95% CI, 1.15 to 1.34) and in MESA, 1.38 (95% CI, 1.21 to 1.58). Addition of the polygenic risk score to the pooled cohort equations did not significantly increase the C statistic in either cohort (ARIC, change in C statistic, −0.001; 95% CI, −0.009 to 0.006; MESA, 0.021; 95% CI, −0.0004 to 0.043). At the 10-year risk threshold of 7.5%, the addition of the polygenic risk score to the pooled cohort equations did not provide significant improvement in reclassification in either ARIC (NRI, 0.018, 95% CI, −0.012 to 0.036) or MESA (NRI, 0.001, 95% CI, −0.038 to 0.076). The polygenic risk score did not significantly improve calibration in either cohort.

CONCLUSIONS AND RELEVANCE In this analysis of 2 cohorts of US adults, the polygenic risk score was associated with incident coronary heart disease events but did not significantly improve discrimination, calibration, or risk reclassification compared with conventional predictors. These findings suggest that a polygenic risk score may not enhance risk prediction in a general, white middle-aged population.

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Mosley JD, et al. *JAMA.* 2020;323(7):627–635

Eurocentric bias

Genetic risk scores derived largely from European ancestry populations

Don’t work as well in other populations

Potential for greater improvements in health in European descent populations

Greater diversity needed in genetic research studies

Newer studies include trans-ethnic meta-analyses

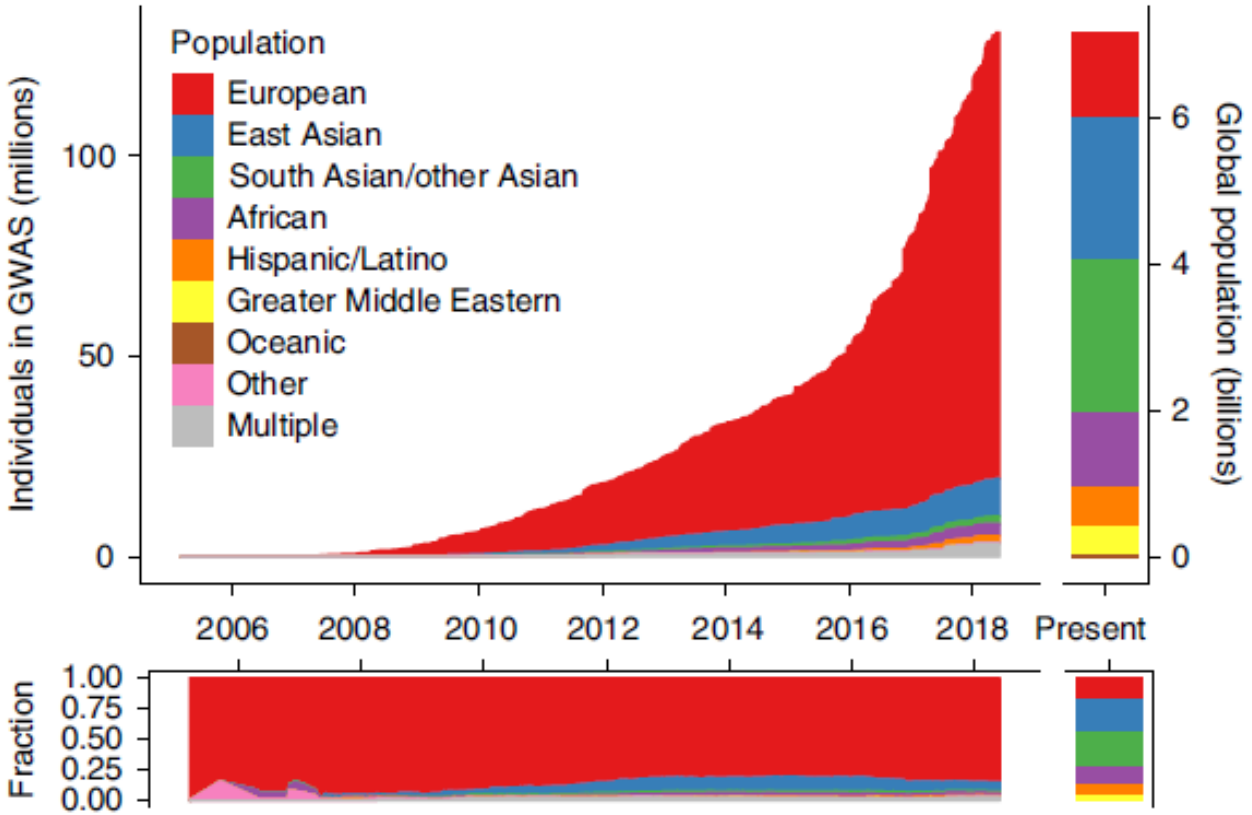


Fig. 1 | Ancestry of GWAS participants over time, as compared with the global population. Cumulative data, as reported by the GWAS catalog[76].

Martin AR et al. Nat Genet 2019:51, 584-591

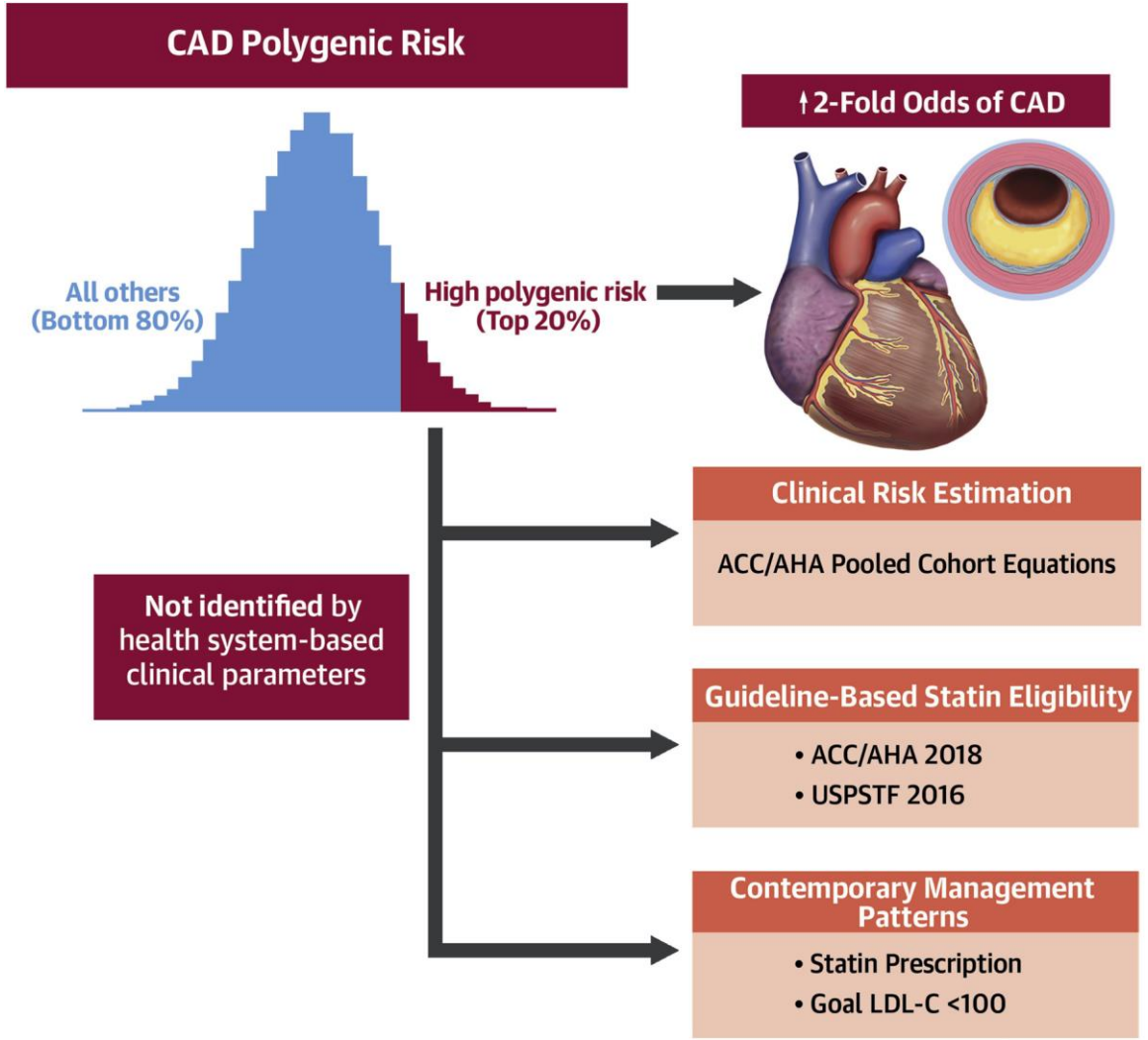
GRS- Potential limitations

- Psychological distress
- Fatalism
- Insurance discrimination
- Treatment costs
- Limited information
  - non-European populations
  - Gene x Environment interactions

GRS- Additional research needed

- Can genetic risk scores motivate behavior change or identify individuals most likely to benefit from an intervention?
- Need to prove that disclosing results to patients will lead to decreased risk
  - Randomized trial?
- Prevention strategies at earlier stage?
- Lifestyle modification or disease screening?
- Low PPV- false positives. Value may be with identifying low risk
- Need more information about interactions with environment

Limitations of Contemporary Guidelines for Managing Patients at High Genetic Risk of Coronary Artery Disease



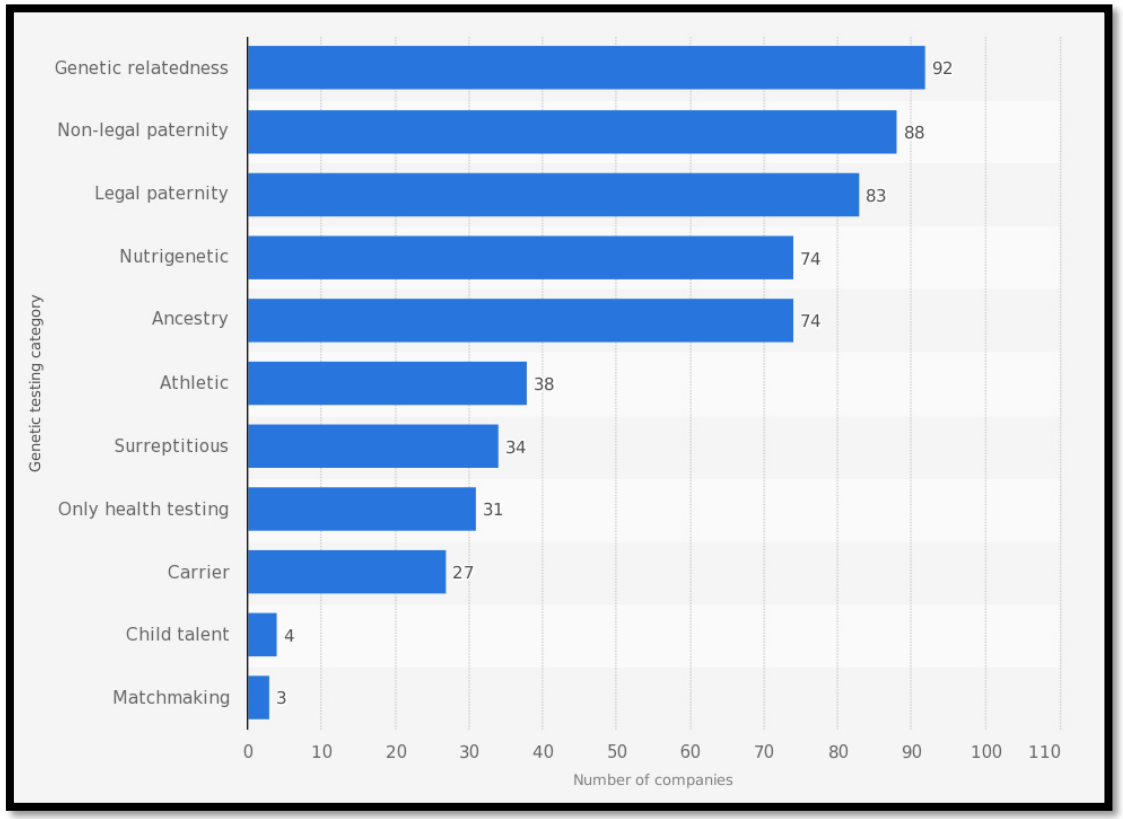
Aragam KG et al. JACC 2020;75(22):2769-2780

GRS- Huge potential-
but not ready for prime time

- Present at birth
  - Life-long impact
- Target prevention strategies at earlier stage
  - Before traditional risk factors manifest
  - Some genetic risk not associated with traditional risk factors
- Potentially useful to target aggressive lifestyle modification or disease screening
- Pharmacogenetics- response to therapy
- Value may be with identifying low risk
  - Low PPV- false positives but high NPV
- Need to prove added value above traditional risk assessment and coronary artery calcium screening

Direct-to-Consumer (DTC) Genetic Testing

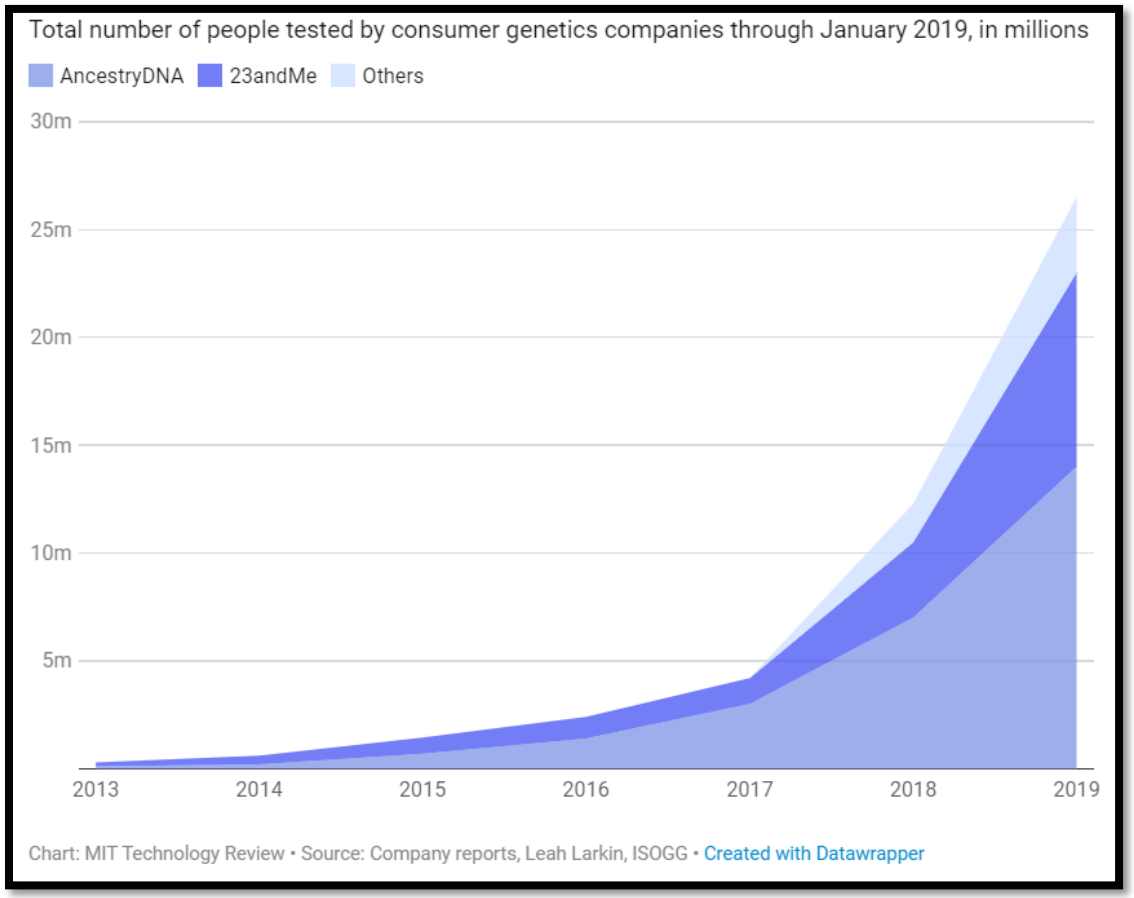
- DTC testing allows the consumer to order genetic testing from home, without a doctor's order
- Variety information provided:
  - Ancestry
  - Ice cream flavor preference
  - Genetic disease mutations
- Beginning in 2013, FDA began to regulate health testing



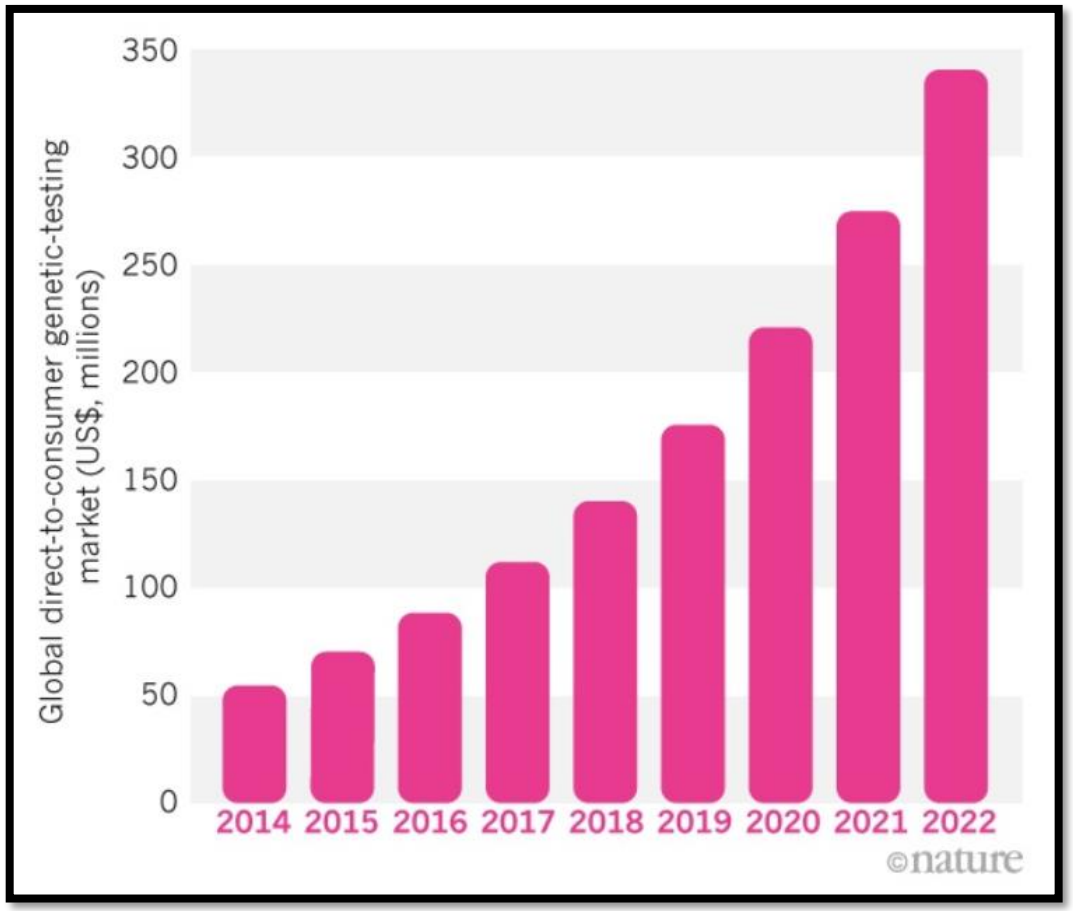
Applied & Translational Genomics; Elsevier; © Statista 2017

Industry is Booming!

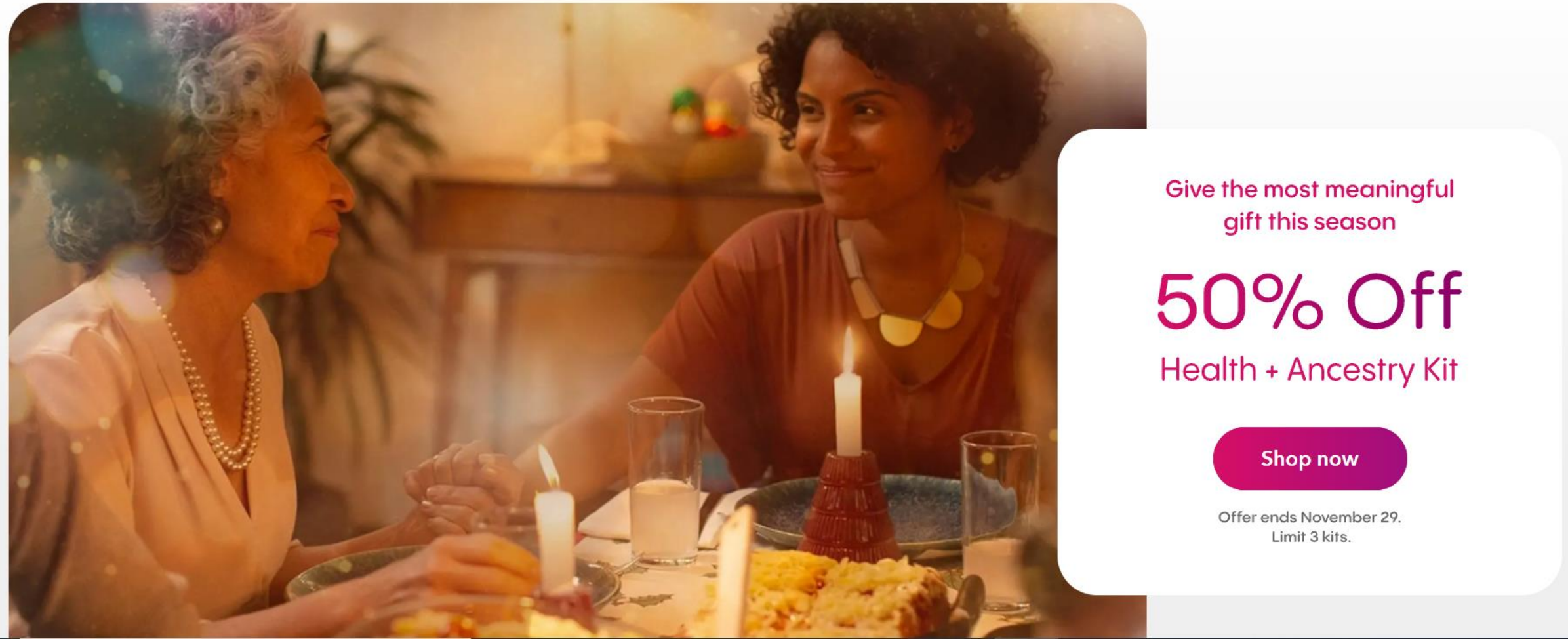
More than 26 million individuals have taken a DTC test



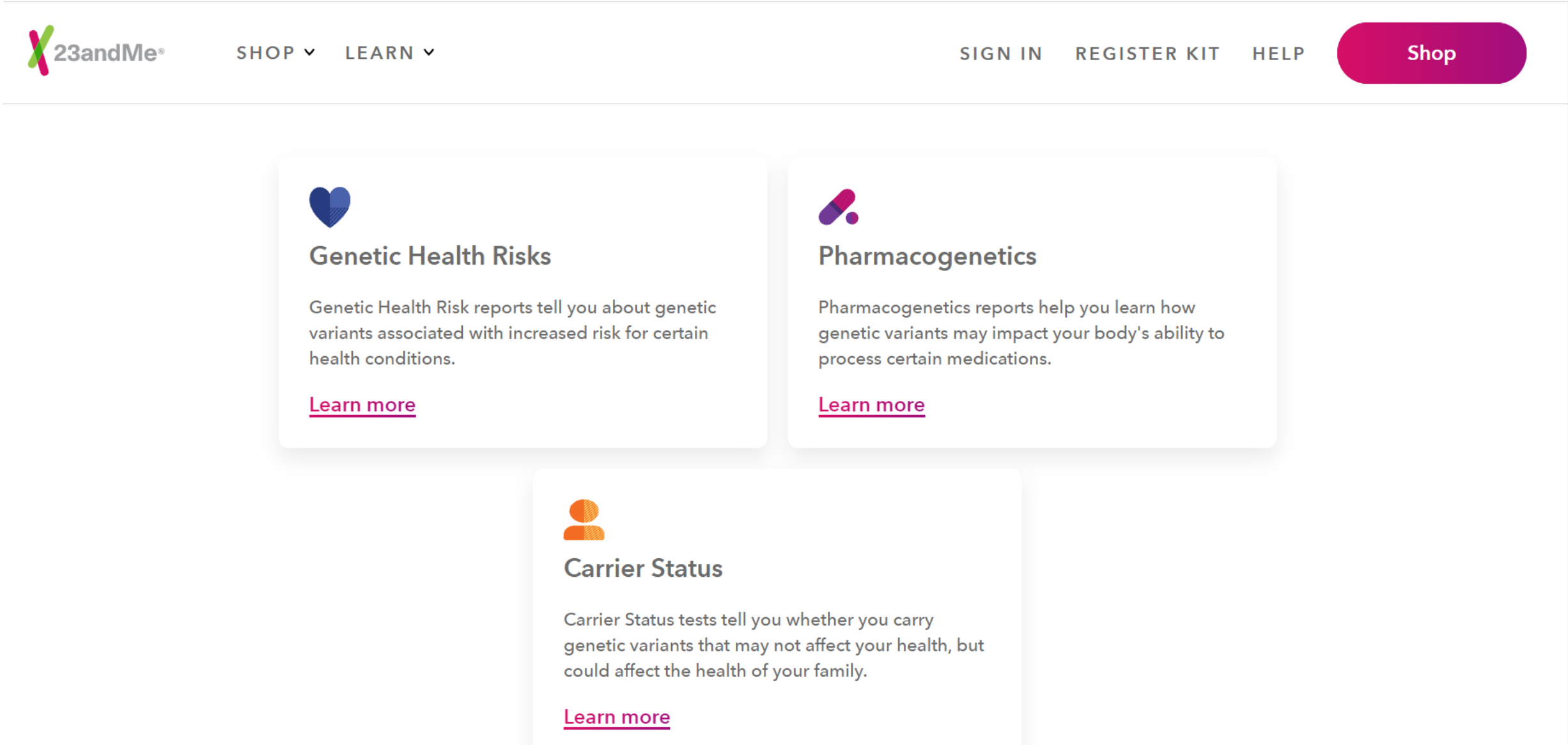
DTC Industry is expected to grow to over $300 million by 2022



Marketing- direct to consumer



Multiple options for testing



Methodology

- Genotyping for specific common variants
- Does not include full gene sequencing or deletion/duplication analysis
- Negative results may be falsely reassuring
- May misdiagnose individuals who are compound heterozygotes
- 23andMe advertises a 99% accuracy for the variants they report
- The company still recommends clinical confirmation of their results

Cardiovascular Genetic Testing- 23andme

Familial Hypercholesterolemia

- Genetic risk for very high cholesterol, which can increase the risk for heart disease
- 24 variants in the LDLR and APOB genes; relevant for European, Lebanese, Old Order Amish descent

Hereditary Amyloidosis (TTR-Related)

- Genetic risk for a form of nerve and heart damage
- 3 variants in the TTR gene; relevant for African American, West African, Portuguese, Northern Swedish, Japanese, Irish, British descent

Late-Onset Alzheimer's Disease

- Genetic risk for a form of dementia
- 1 variant in the APOE gene; variant found and studied in many ethnicities

Hereditary amyloidosis

- Amyloid protein misfolding
- Most common type is familial transthyretin amyloidosis (ATTR)
- Amyloid accumulates in multiple organs including the heart
- Can lead to heart failure
- Autosomal dominant inheritance
- V122I most common variant
- ~3.9% of the African American population
- Very rare in people of European ancestry
- Familial transthyretin amyloidosis is a rare disease
- Many people with this genetic variant will not develop the disease (low penetrance)

Genetic Risk Reports

Based on a genetic model that includes customers' results for thousands of genetic markers; variants found in many ethnicities

Powered by 23andMe Research

- Atrial Fibrillation
- Coronary Artery Disease
- HDL Cholesterol
- High Blood Pressure
- LDL Cholesterol
- Triglycerides

Limitations

23andme.com/test-info/genetic-health

23andMe® SHOP LEARN SIGN IN REGISTER KIT HELP Shop

23andMe Genetic Health Risk Reports: What you should know

Genetic Health Risk reports tell you about genetic variants associated with increased risk for certain health conditions. They do not diagnose cancer or any other health conditions or determine medical action.

Having a risk variant does not mean you will definitely develop a health condition. Similarly, you could still develop the condition even if you don't have a variant detected. It is possible to have other genetic risk variants not included in these reports.

Factors like lifestyle and environment can also affect whether a person develops most health conditions. Our reports cannot tell you about your overall risk for these conditions, and they cannot determine if you will or will not develop a condition.

These reports do not replace visits to a healthcare professional. Consult with a healthcare professional for help interpreting and using genetic results. Results should **not** be used to make medical decisions.

Use of Data by Law Enforcement

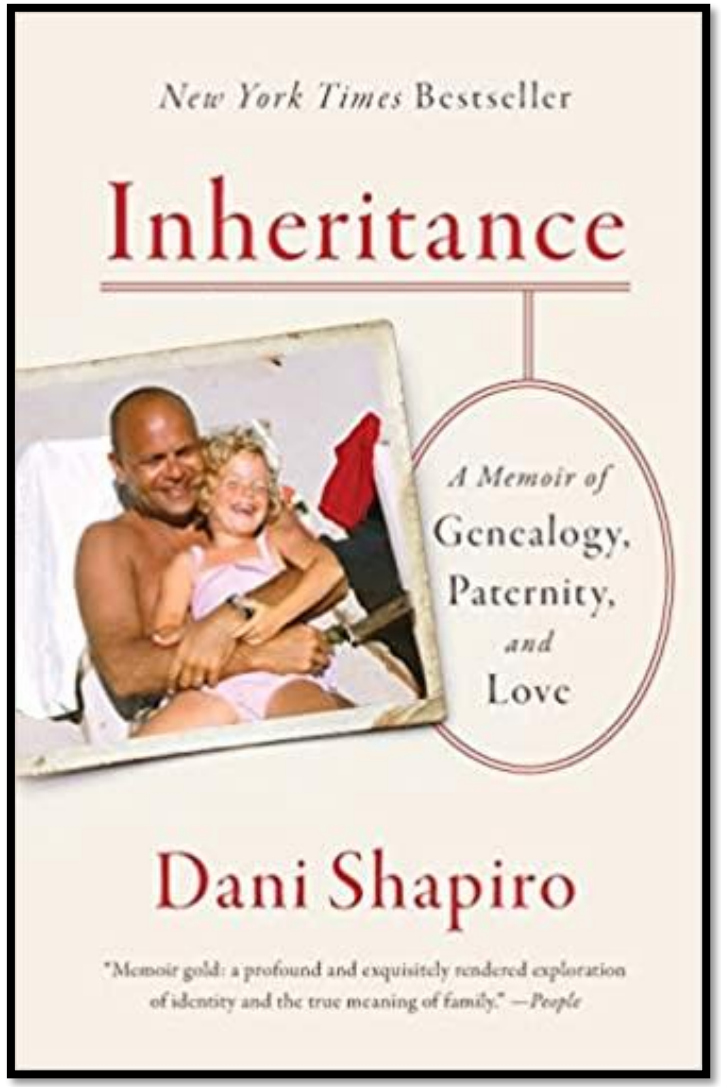
Joseph DeAngelo, the suspected Golden State Killer RANDY PENCH/TNS/NEWSCOM

We will find you: DNA search used to nab Golden State Killer can home in on about 60% of white Americans

By Jocelyn Kaiser | Oct. 11, 2018 , 2:00 PM

Family Secrets

- Nonpaternity
- Half siblings
- Biological parents
  - adoptees, sperm donors



Direct-to-consumer genetic testing

- Should not be used in clinical evaluations and should be confirmed in a clinical lab
- Individuals should fully consider all of the possible implications before submitting a sample
- False positives (genotyping error)
- Low penetrance- positive result does not mean patient will get disease
- False negative may lead to “reassurance” that is not correct
- Patients should consider what type of information they would like to receive and what type of information they may actually receive before taking the test
- Consider referral to genetic counselor if indicated

Thank You for Your Attendance!

Please visit us at:

www.prn.org