Imperial College London

MRC Laboratory of Medical Sciences

Genetics for early detection and diagnosis of CVD

Global Heart Hub Annual Summit

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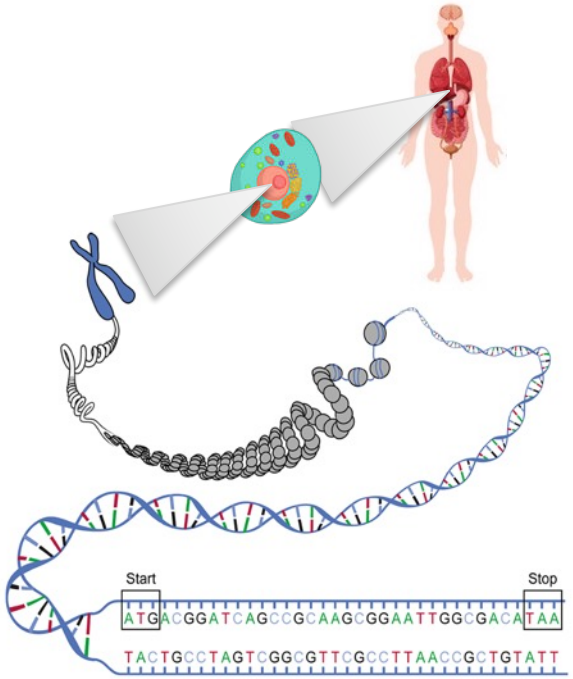
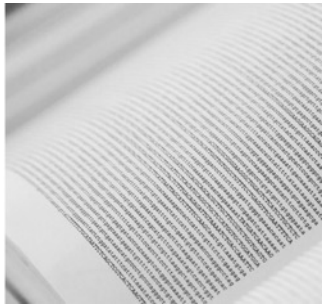
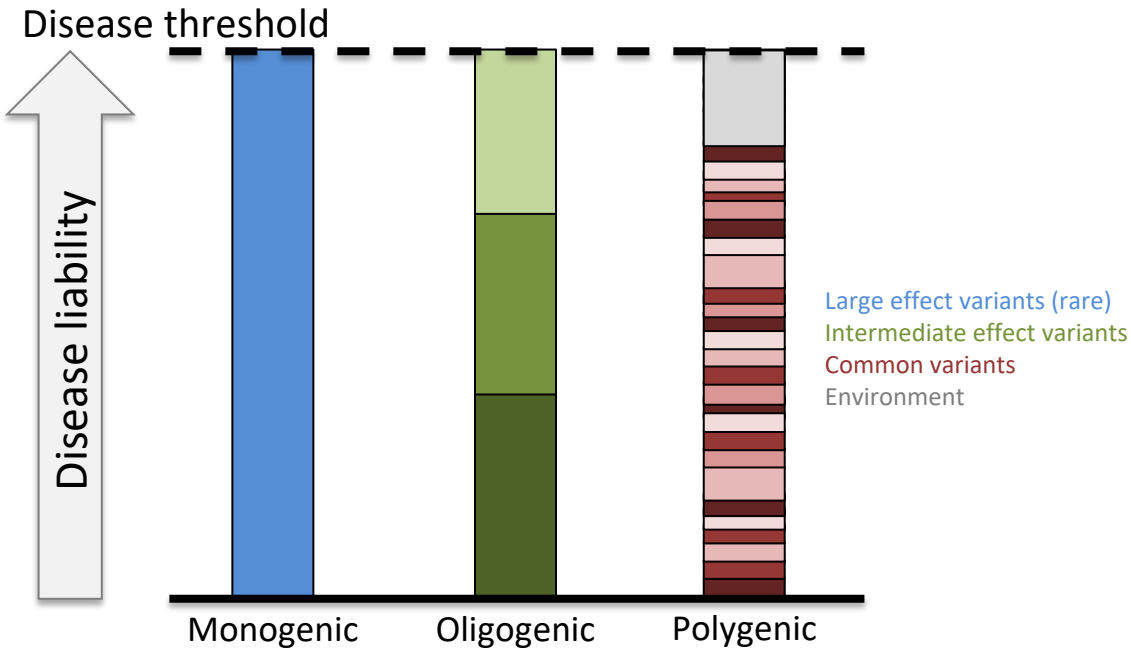
8th November 2023

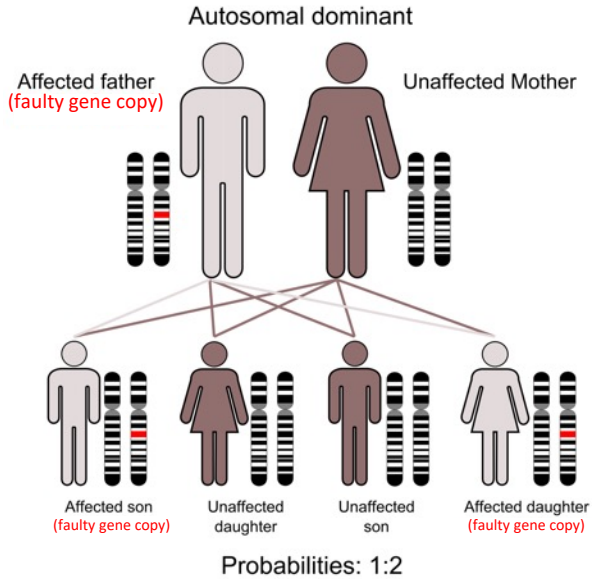
What is a gene?





Genetic influences on the heart





Clinical applications of genetic testing

For the patient

- diagnostic
- prognostic
- therapeutic

Table 5 Impact of genetic testing for the proband

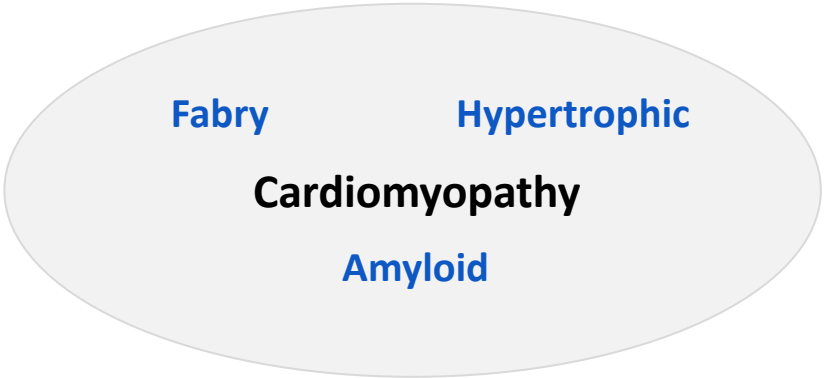
Disease	Diagnostic	Prognostic	Therapeutic
Arrhythmia syndromes			
Long QT syndrome	+++	+++	+++
CPVT	+++	+	+
Brugada syndrome	+	+	+
Progressive cardiac conduction disease	+	+	+
Short QT syndrome	+	+	+
Sinus node disease	–	+	–
Atrial fibrillation	–	+	–
Early repolarization syndrome	–	–	–
Cardiomyopathies			
Hypertrophic cardiomyopathy	+++	++	++
Dilated cardiomyopathy	++	+++	++
Arrhythmogenic cardiomyopathy	+++	++	++
Left ventricular non-compaction	+	+	–
Restrictive cardiomyopathy	+	+	+
Congenital heart disease			
Syndromic CHD	+++	+	–
Non-syndromic CHD	+	–	–
Familial CHD	++	–	–

+++	is indicated / useful
++	can be useful
+	may be considered
-	not recommended

2022 consensus statement on genetic testing for cardiovascular diseases

Precision diagnosis

→ Precision therapy



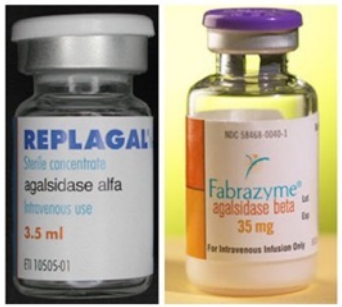
Precision diagnosis

⟶ Precision therapy

Fabry **Hypertrophic**

Cardiomyopathy

Amyloid



~2001

OCTOBER 5, 2023 / NEWS RELEASES

Cleveland Clinic Performs World's First In-Human Gene Therapy for Hypertrophic Cardiomyopathy

Patient is first person dosed in clinical trial

Media Contact

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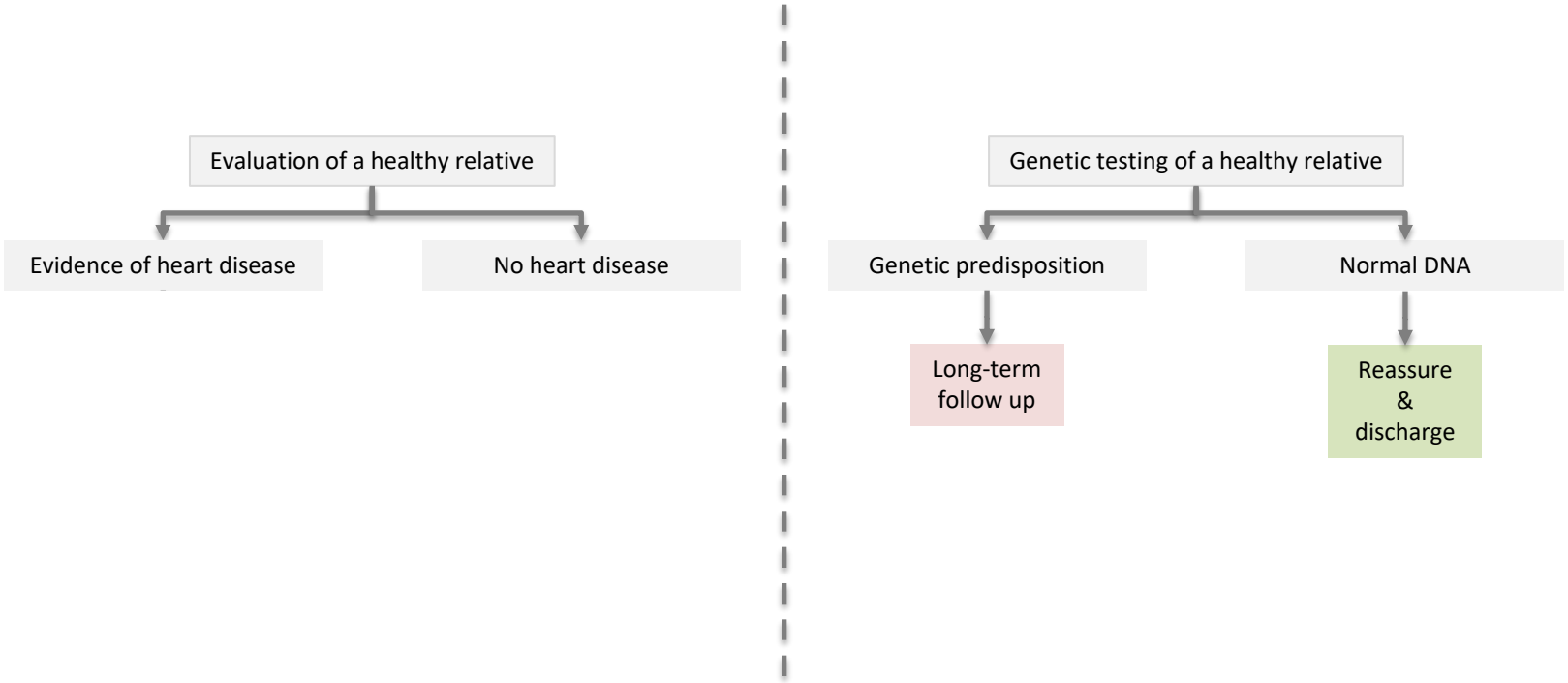
Hope Buggey | 216.213.6192

Cleveland Clinic has infused a new gene therapy to deliver a working gene to address the leading cause of hypertrophic cardiomyopathy (HCM) in the first patient in the world as part of a clinical trial.

Myosin binding protein C3 *(MYBPC3)* gene mutations are the most common genetic cause of HCM. The gene therapy is designed to deliver a working MYBPC3 to the heart muscle through a one-time infusion of TN-201, which is a first-in-class adeno-associated virus-based gene therapy. The hope is that this new gene will restore normal levels of the protein, which regulates the contraction and relaxation of the heart muscle. In preclinical studies, a single dose restored normal levels of the protein which led to disease reversal.

Research nurse coordinator Danielle Kellner readies the infusion.

Genetics for screening of family members



Early detection or prevention?
reproductive counselling and prenatal genetics

A genetic diagnosis allows us to evaluate

- risk of recurrence (siblings)
- risk to future generations

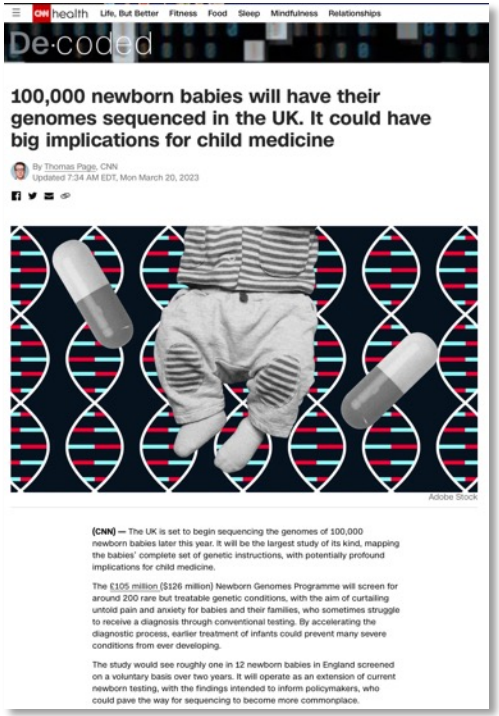
for pre-conception counselling

Allows for pre-natal diagnosis or assisted reproduction

- pre-implantation genetic diagnosis
- donor gametes

Genetics for population screening

population sequencing – secondary findings – recreational genomics



CNN health Life, But Better Fitness Food Sleep Mindfulness Relationships

De-coded

100,000 newborn babies will have their genomes sequenced in the UK. It could have big implications for child medicine

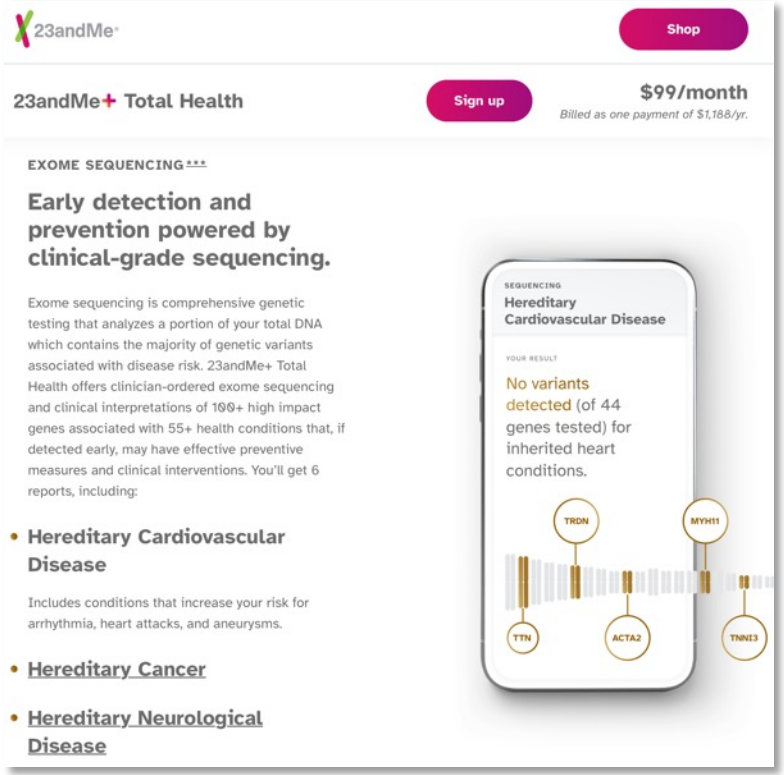
By Thomas Page, CNN
Updated 7:34 AM EDT, Mon March 20, 2023

Adobe Stock

(CNN) — The UK is set to begin sequencing the genomes of 100,000 newborn babies later this year. It will be the largest study of its kind, mapping the babies' complete set of genetic instructions, with potentially profound implications for child medicine.

The £105 million ($126 million) Newborn Genomes Programme will screen for around 200 rare but treatable genetic conditions, with the aim of curtailing untold pain and anxiety for babies and their families, who sometimes struggle to receive a diagnosis through conventional testing. By accelerating the diagnostic process, earlier treatment of infants could prevent many severe conditions from ever developing.

The study would see roughly one in 12 newborn babies in England screened on a voluntary basis over two years. It will operate as an extension of current newborn testing, with the findings intended to inform policymakers, who could pave the way for sequencing to become more commonplace.



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EXOME SEQUENCING***

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Exome sequencing is comprehensive genetic testing that analyzes a portion of your total DNA which contains the majority of genetic variants associated with disease risk. 23andMe+ Total Health offers clinician-ordered exome sequencing and clinical interpretations of 100+ high impact genes associated with 55+ health conditions that, if detected early, may have effective preventive measures and clinical interventions. You'll get 6 reports, including:

- **Hereditary Cardiovascular Disease**

  Includes conditions that increase your risk for arrhythmia, heart attacks, and aneurysms.

- **Hereditary Cancer**
- **Hereditary Neurological Disease**

SEQUENCING
Hereditary Cardiovascular Disease

YOUR RESULT

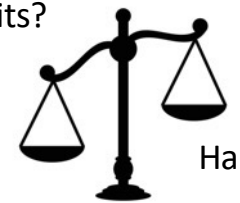
No variants detected (of 44 genes tested) for inherited heart conditions.

TRDN MYH11 TTN ACTA2 TNNI3

Genetics for population screening

population sequencing – secondary findings – recreational genomics

Benefits?



Harms

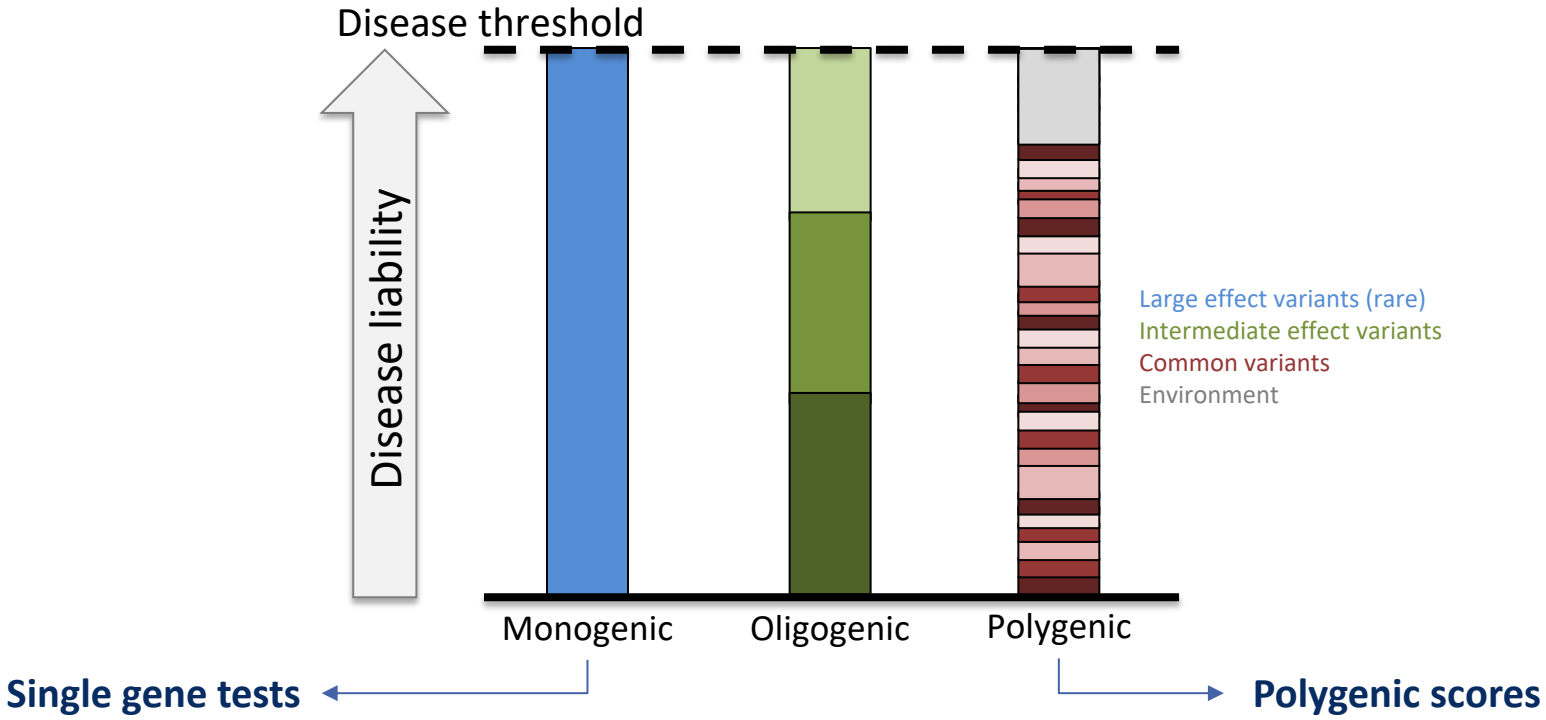
Cost-effectiveness?

Genetic testing in inherited conditions

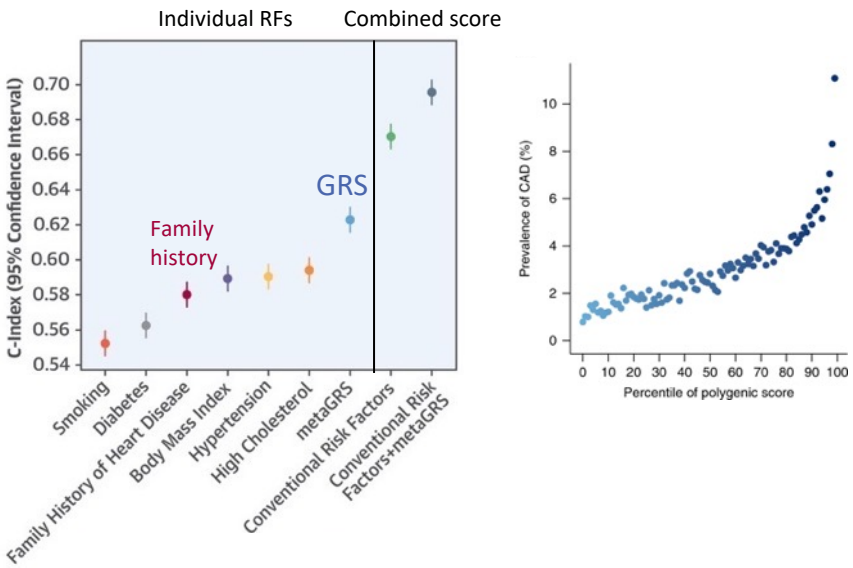
- Useful for care of families
  can be cost effective, even cost saving
- Increasingly useful for prognostication & targeted therapies in patients with rare disease
- *Wider opportunity for screening?*

- Still expensive from global perspective
- Requires high level of training
  (medical, counselling, laboratory, computational)
- Research bias to European ancestry
  Inequality in genome interpretation
- Knowledge gaps:
  Natural history
  Incomplete penetrance
  Variable severity

Genetic influences on the heart



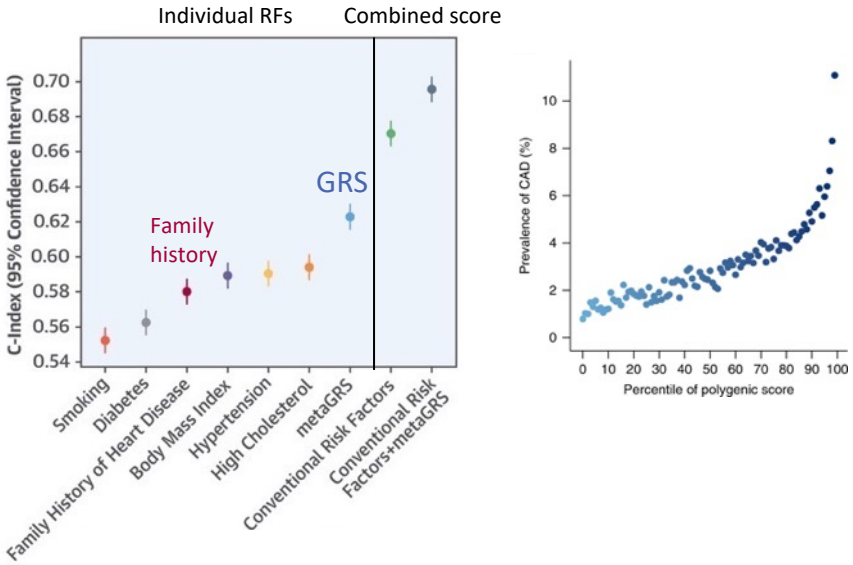
Genomic Risk Scores

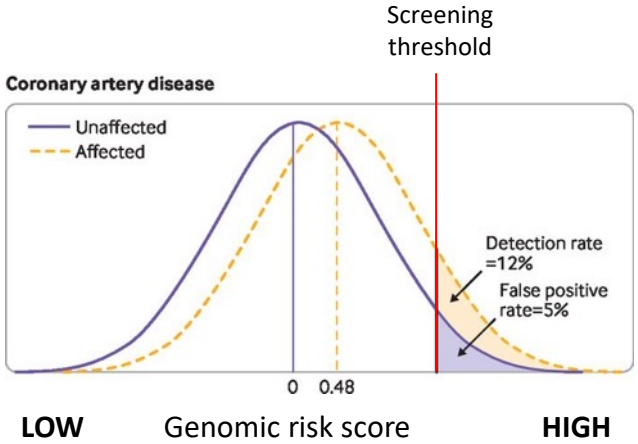


Inouye et al JACC 2018;**17**:1883

Khera et al, Nat Gen 2018

Genomic Risk Scores





Poor performance for individual prediction

Inouye et al JACC 2018;**17**:1883

Khera et al, Nat Gen 2018

Hingorani et al BMJ Med. 2023

Genomic Risk Scores

Pros

- better than any one conventional risk factor (RF)
- combine with conventional RFs
- lifetime risk estimate
- measure from birth ➡
  early interventions including lifestyle

Cons

- Population stratification ≠ individual prediction
  prescribe statin if 10 year risk of CVD >10%
- Number needed to genotype > 5000
  unlikely cost effective?
- Inequality: ancestry affects performance
- Pathways to implementation

- GRS may explain variable penetrance in monogenic diseases (FH, CM, …)
- Genotyping enables pharmacogenomic prediction

Patients

Families

Population

Conclusions

Genetic testing (for variants causing rarer single-gene diseases)

- Precise diagnosis of individuals with ICCs ✅
- Early detection in at-risk family members ✅
- *Opportunity for population screening* ?

Genomic Risk Scores (derived from common genetic variants)

- Improve risk stratification for CVD ✅
- *Unlikely cost effective in isolation* ?
- *Introduce inequality by ancestry* ?

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Cardiomyopathy UK the heart muscle charity