Development and Application of Polygenic Risk Scores

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Why Do We Study Human Genomics?

1. Teaches us a little bit about who we are and where we came from…

2. The biology of disease and novel therapeutic strategies…

3. Prediction…

"It's Difficult to Make Predictions, Especially About the Future."

Niels Bohr (maybe)

Some editorial comments about GRS/PRS:
1. They are not new.

XV.—**The Correlation between Relatives on the Supposition of Mendelian Inheritance.** By **R. A. Fisher, B.A.** *Communicated by* Professor J. Arthur Thomson. (With Four Figures in Text.)

(MS. received June 15, 1918. Read July 8, 1918. Issued separately October 1, 1918.)

European Journal of Internal Medicine
Volume 13, Issue 8, December 2002, Pages 485-492
ELSEVIER

Original article

Analysis of several hundred genetic polymorphisms may improve assessment of the individual genetic burden for coronary artery disease

American Journal of Epidemiology

Vol. 166, No. 1
DOI: 10.1093/aje/kwm060 Advance Access publication April 18, 2007

Original Contribution

Prediction of Coronary Heart Disease Risk using a Genetic Risk Score: The Atherosclerosis Risk in Communities Study

Ann Hum Genet. 2005 March ; 69(0 2): 176–186. doi:10.1046/j.1529-8817.2005.00155.x.

Generating Genetic Risk Scores from Intermediate Phenotypes for Use in Association Studies of Clinically Significant Endpoints

Steps of Genetic Risk Scores

1. Selection of SNPs from discovery studies (usually large GWAS).
    a. Independent sentinel SNPs
    b. p-value threshold
2. Building/Calculating the GRS/PRS
    a. Weighted vs Unweighted
    b. Parameter estimation
3. Estimation of an individuals risk of disease
    a. Relative
    b. Absolute

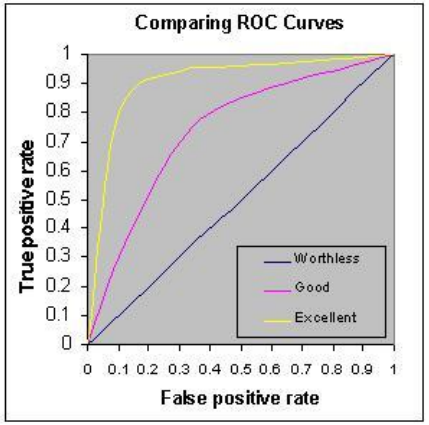
Strong Methodologic Underpinnings

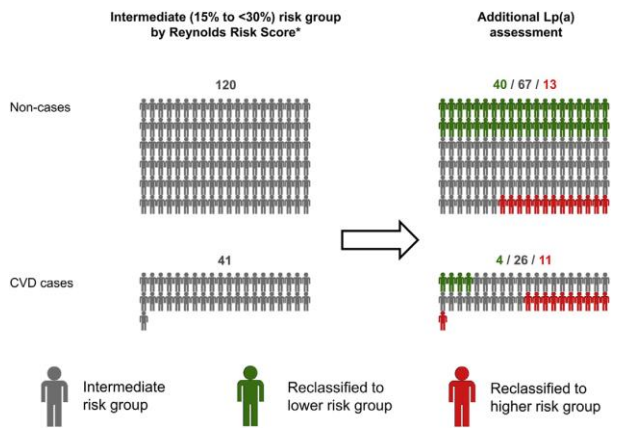
1. Parameter estimation
   Shrinkage (take into account other info)

2. Relative risk to absolute risk

$$R_{a,a+s} = \int_a^{a+s} l(u|Z) \exp\left(-\int_a^u \{l(v|Z) + m(v|Z)\} dv\right) du$$

3. Evaluation

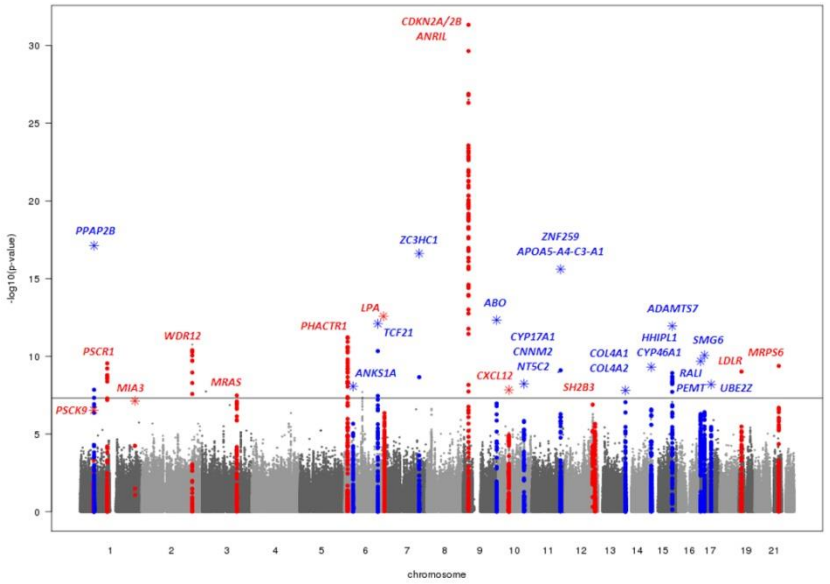




GWAS of CHD

A Common Allele on Chromosome 9 Associated with Coronary Heart Disease
Ruth McPherson, *et al.*
Science **316**, 1488 (2007);
DOI: 10.1126/science.1142447

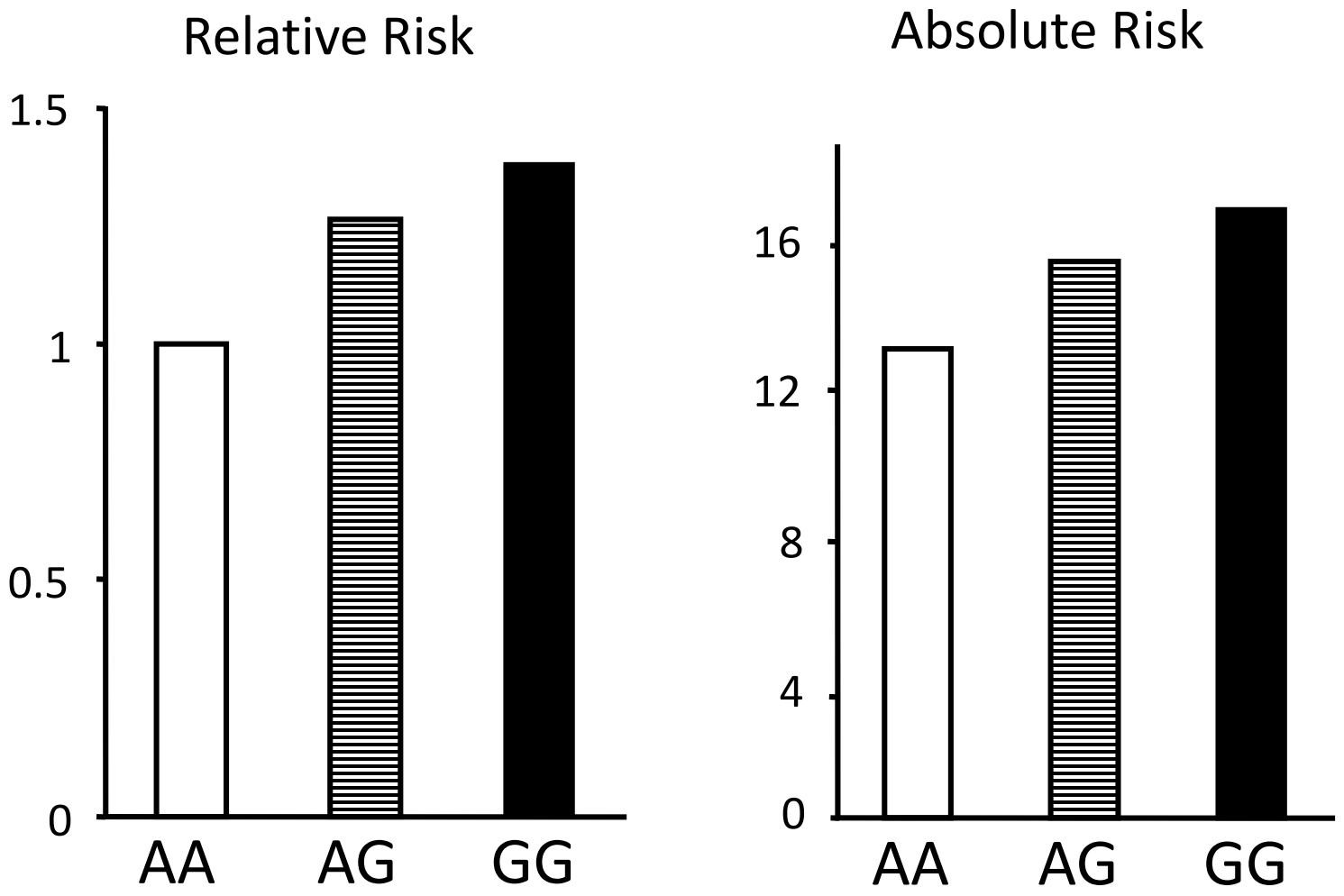
Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease.
Schunkert, et al.
Nature Genet 43, 333 (2011)



Now Surpassed the 1 million person mark

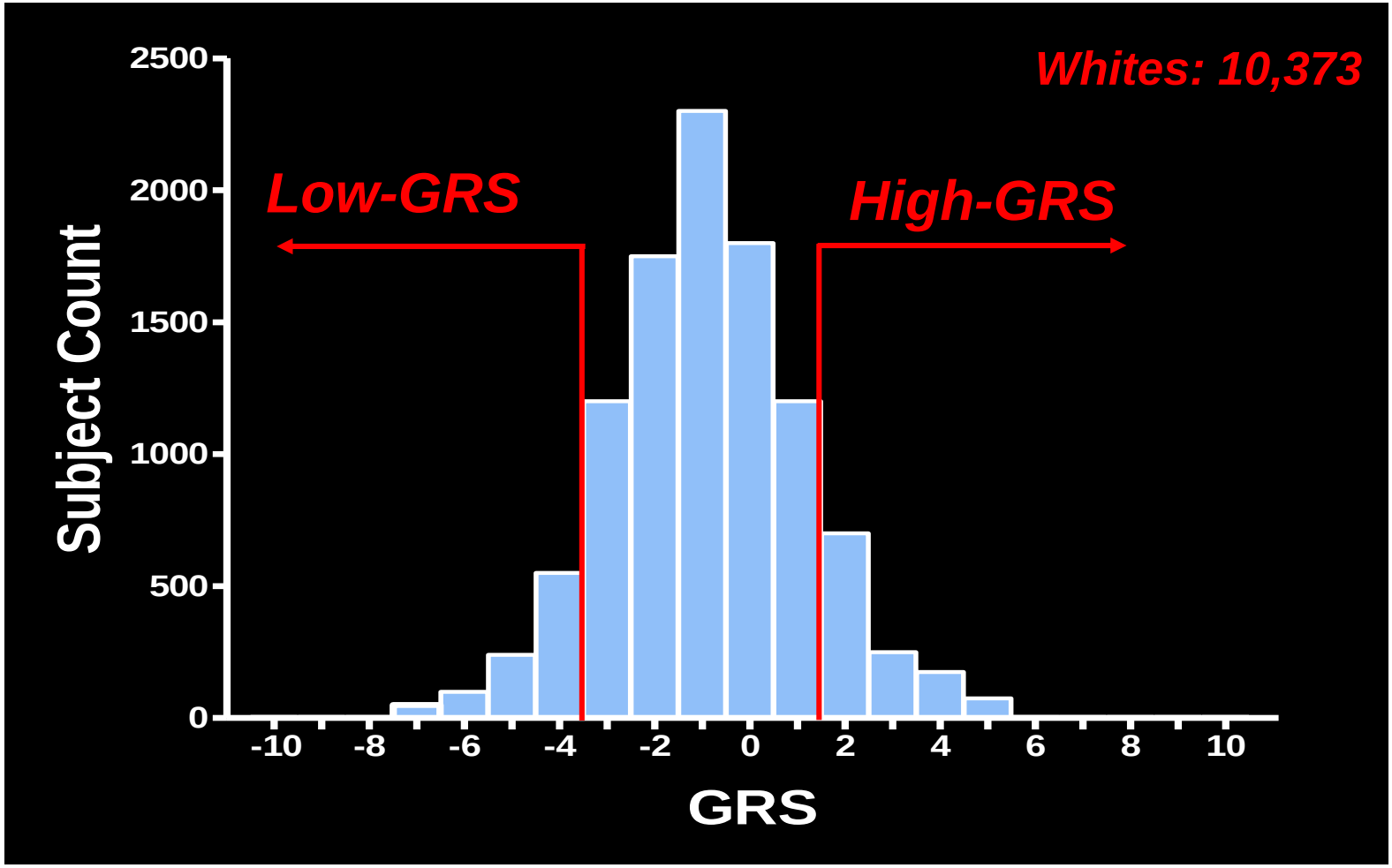
Genome-Wide Association Study of Coronary Heart Disease and Its Risk Factors in 8,090 African Americans: The NHLBI CARe Project
Lettre et al. 2011. Plos Genetics

9p21 SNP rs10757274 and CHD Risk



Genetic Risk Score Cut Points

Whites in ARIC



- GRS ranges from minus 10 to plus 10
- High-GRS group comprises 18% of the ARIC population
- The HRR for CHD was 2.1 for the high GRS group compared to the low GRS group

Predictive Ability of Risk Scores

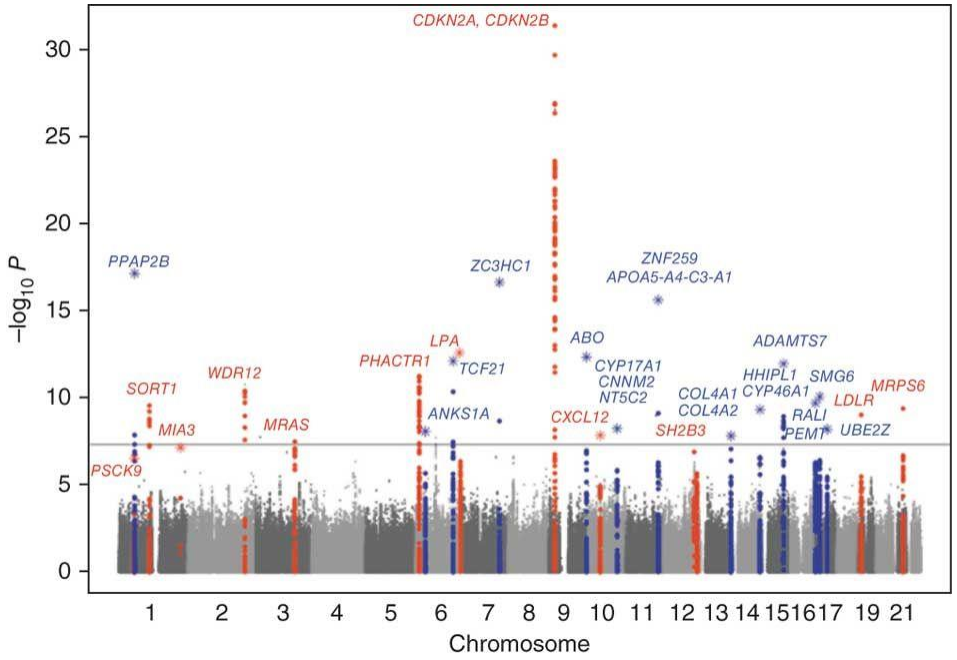
Blacks

	AUC	ΔAUC	P value
CHD Risk Score only	0.7588		
Add GRS	0.7719	0.013	Significant
Remove Hypertension	0.6988	0.06	Significant
Remove LDL	0.7578	0.001	Not significant
Add CRP	0.7608	0.002	Not significant

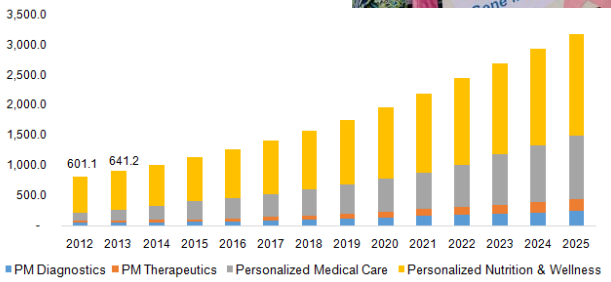
Individual risk factors do not cause large changes in the area under the CHD Risk Score ROC curve

Some editorial comments about GRS/PRS:
2. So, why now?

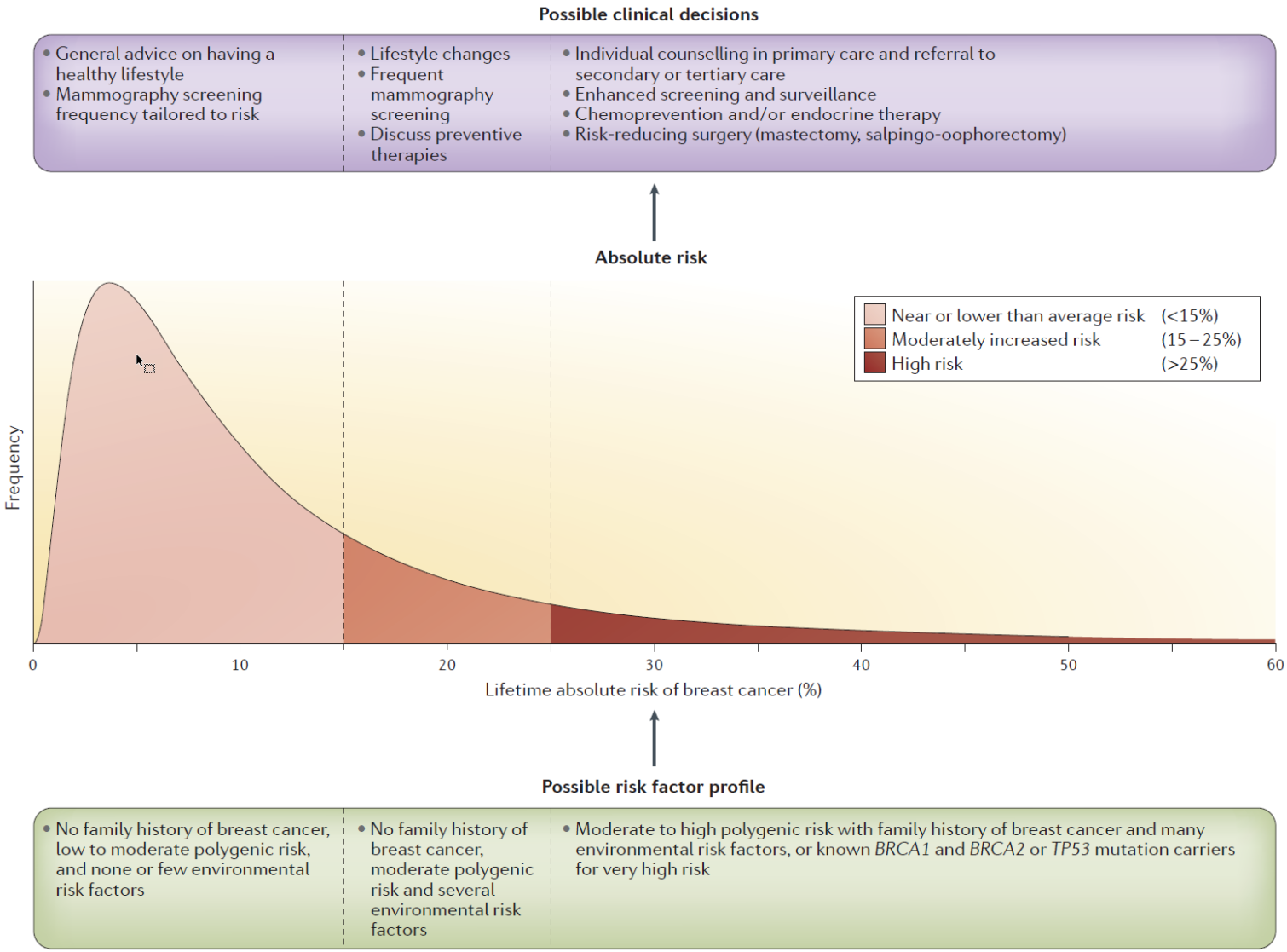
A. We have genes (maybe?)……



B. …now do something with them.



Putting the Pieces Together



Chatterjee et al. Nat Rev Genet 17: 392

Example Patient #1

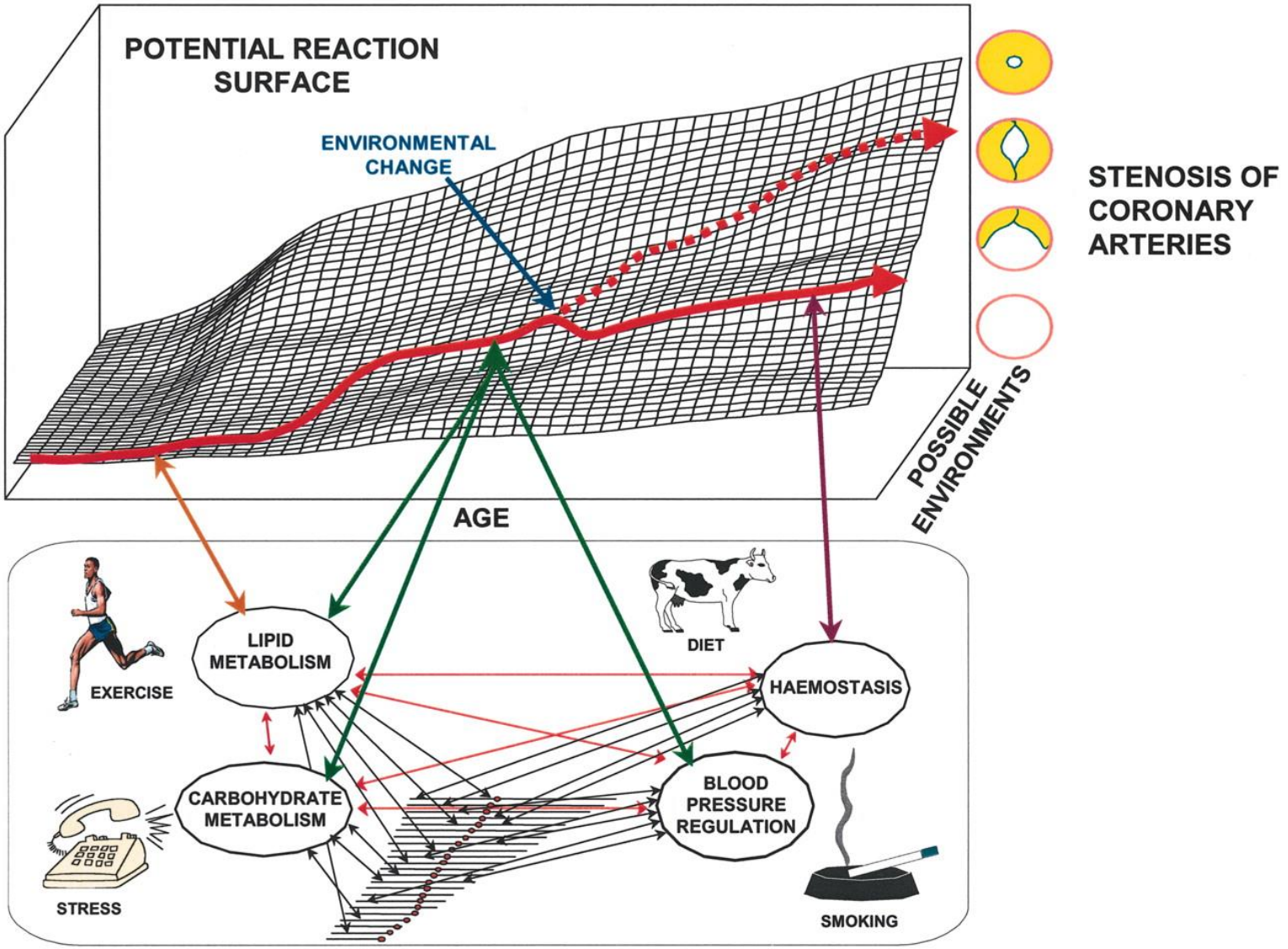
- Female, age 57, taking hypertension medications
- LDL-C of 150 mg/dL
- 10-year CHD risk of 15%
- According to ATP III, “intermediate high” category
- The addition of 9p21 genotype (GG) for this women puts her 10–year risk at 21%
- Recommend initiating drug therapy at >130 mg/dL, with a goal of <100 mg/dL

ATP III Guidelines

				ATP III classification using ACRS + 9p21 allele			
		ATP III classification using ACRS alone		High	Mid-high	Mid	Low
CHD and CHD risk equivalents 10-year risk >20% LDL-C goal <100 mg/dL	High	1,870 (372) 18.69%		1760 (360)	109 (12) 3.95%*	0	0
Multiple (2+) risk factors 10-year risk 10–20% LDL-C goal <130 mg/dL	Mid-high	2,049 (219) 20.48%		217 (27) 10.59%*	1,701 (179)	131 (13) 6.39%*	0
Multiple (2+) risk factors 10-year risk <10% LDL-C goal <130 mg/dL	Mid	1,737 (80) 17.36%		0	179 (17) 10.31%*	1,558 (63)	0
0–1 risk factor 10-year risk <10% LDL-C goal <160 mg/dL	Low	4,349 (107) 43.47%		0	0	0	4,349 (107)
	Total	10,004 (778) (100%)		1,977 (19.76%)	1989 (19.88%)	1,689 (16.88%)	4,349 (43.47%)

* Percentage of people re-classified. (Number of events on 10 years of follow-up.)

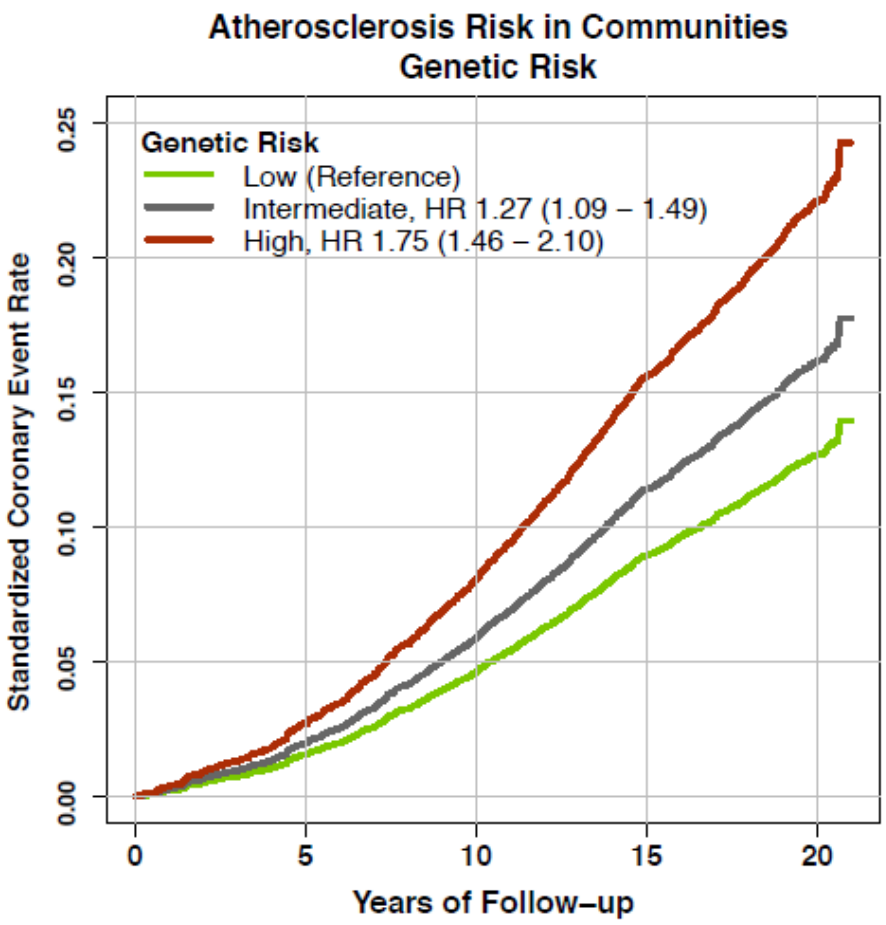
Genes, Environments and Time

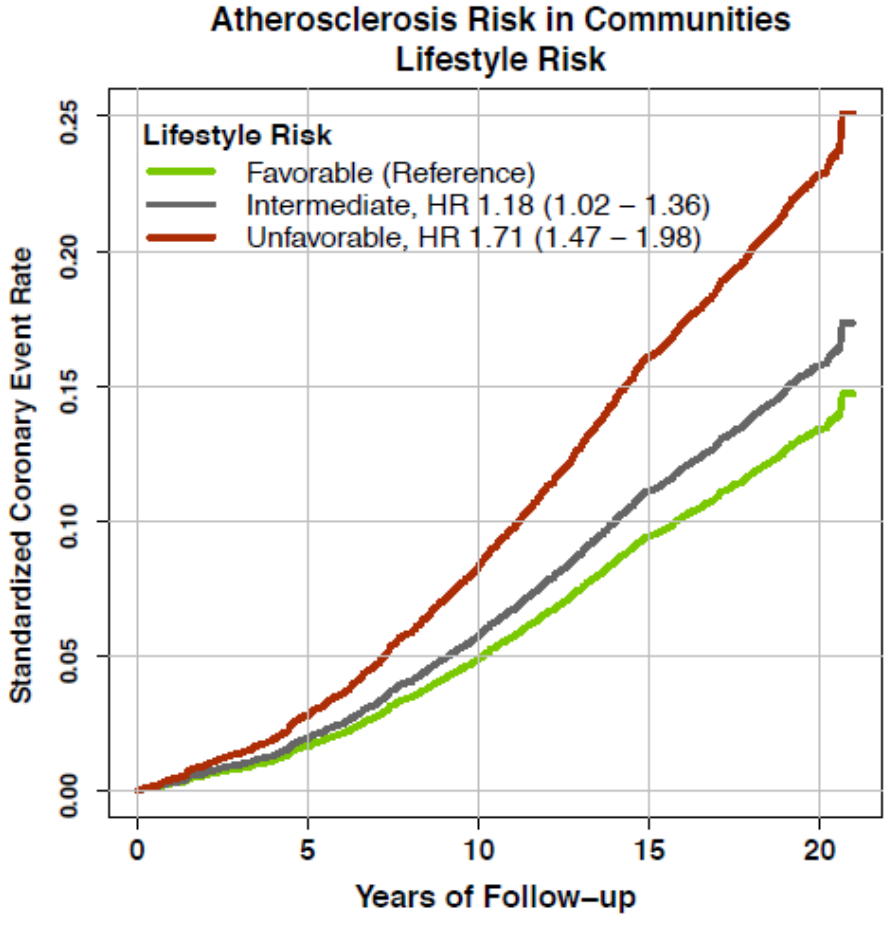


Genes & Life Style & Risk

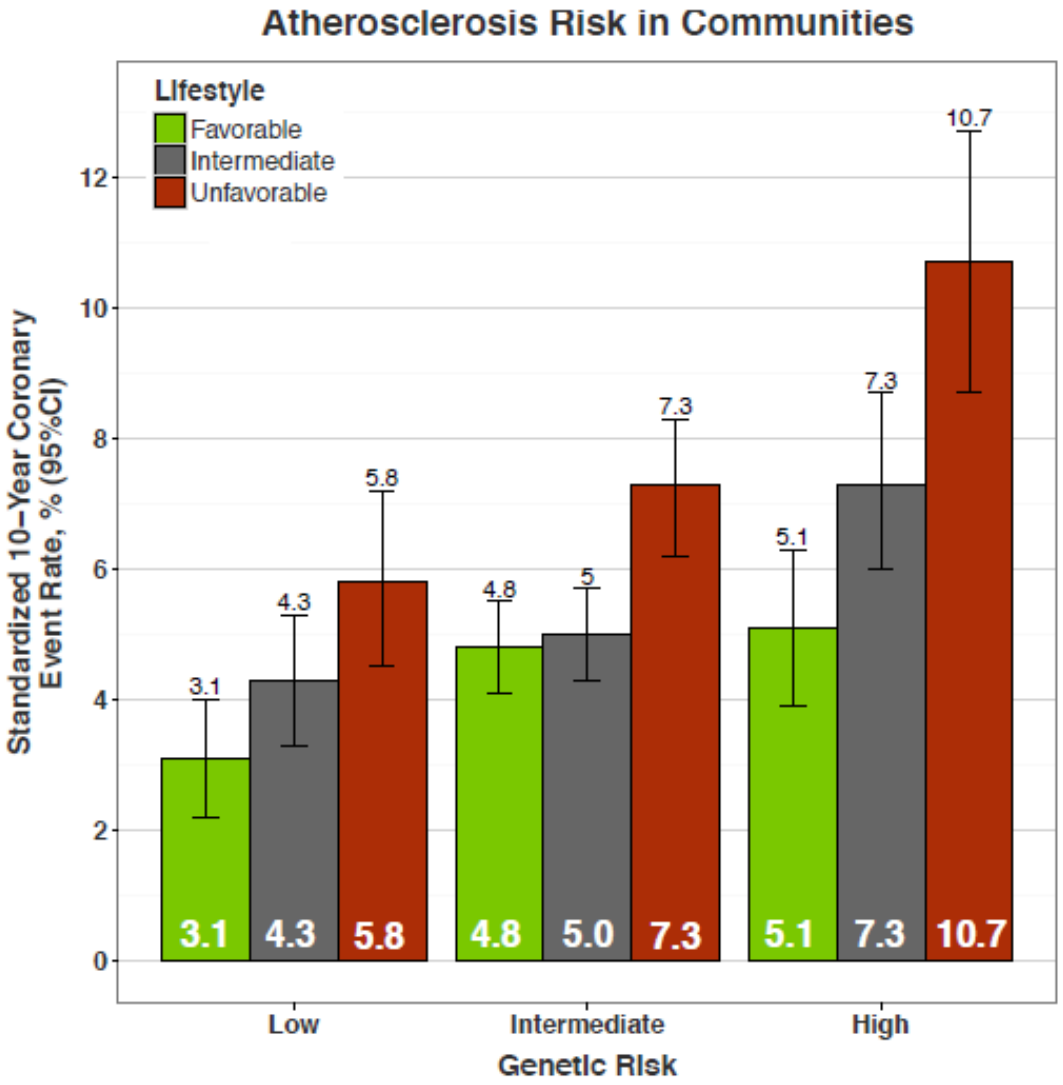
A 50 Locus GRS

Smoking, BMI, Exercise, Diet



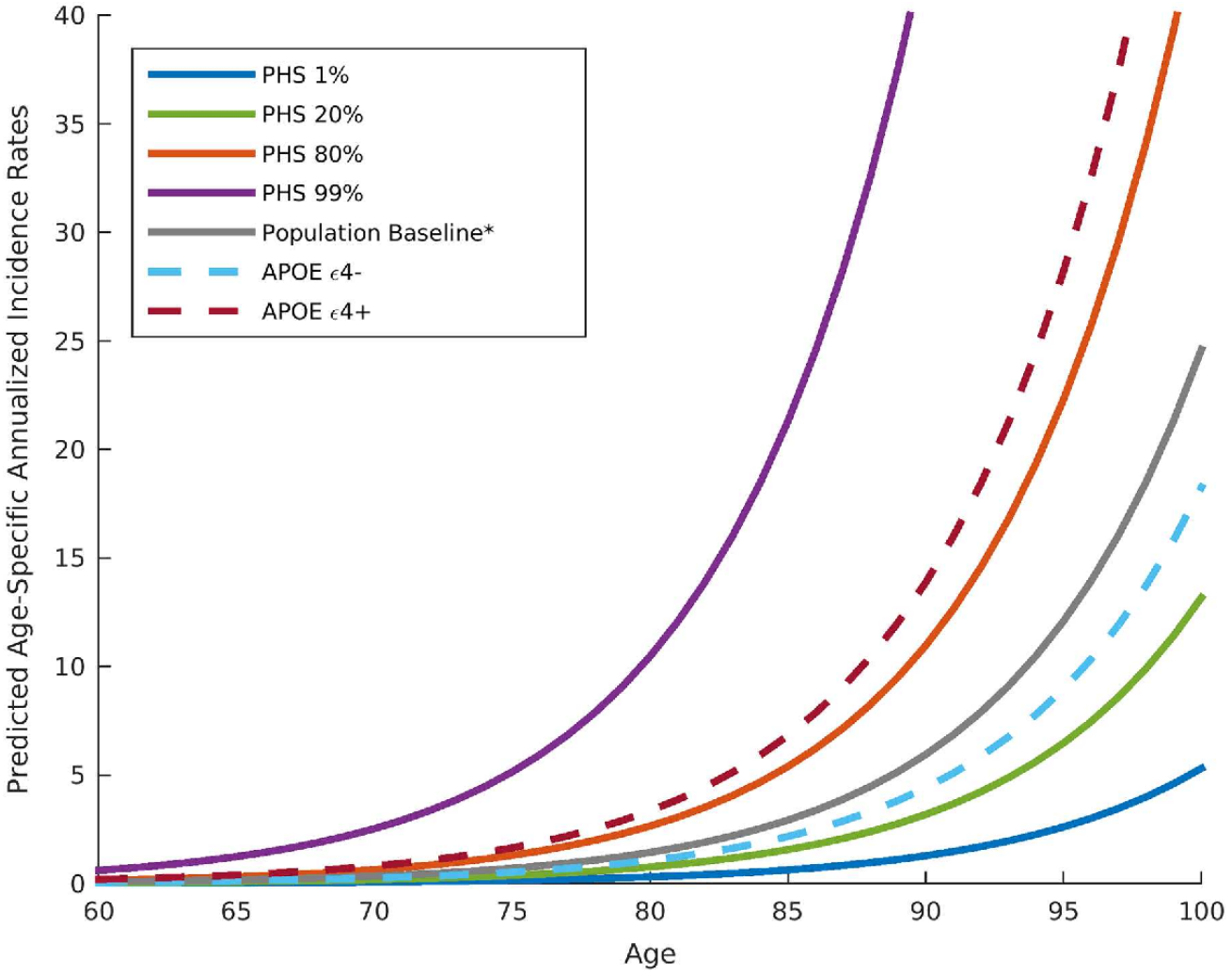


Genes & Life Style & Risk



Data from Khera et al, (NEJM)

AD Rates by ApoE and GRS



Early Genotype-Directed Primary Prevention Clinical Trials

Trial	Participants	Treatment	Outcome Measures
API: Alzheimer's Prevention Initiative	300 members of Colombian families, including 100 carriers of a mutated *PSEN1* gene	Crenezumab (Genentech)	Primary: Cognitive. Secondary: Biomarkers, including brain scans to measure amyloid accumulation and brain atrophy
DIAN: Dominantly Inherited Alzheimer Network	240 members of families with early-onset Alzheimer's; 60 have a mutation in one of three genes	Three anti-amyloid therapies to be determined	An initial phase will use biomarkers to identify the most promising drug candidate for a follow-up phase to examine cognitive effects
A4: Anti-Amyloid Treatment of Asymptomatic Alzheimer's	1500 healthy seniors, including 500 with amyloid-positive brain scans	One anti-amyloid therapy to be determined	Primary: Cognitive Secondary: Biomarkers

Performance of GRS/PRS across ancestry groups

1. Selection of SNPs from large GWAS.

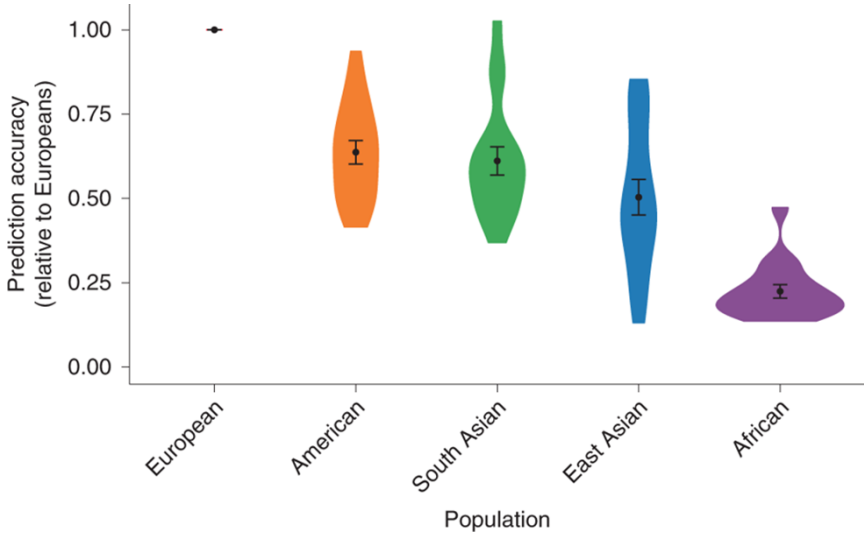
Different SNPs

2. Building/Calculating the GRS/PRS

Different parameter estimates

3. Estimation of an individuals risk of disease

Different absolute risk equations and inputs



From Martin et al, Nature Genetics, 51: 584.

“PRS are of burgeoning interest to the clinical community”

1. Risk score use was dependent on several factors, including IT support, clinical relevance for daily practice, rotation of staff and workload.
2. The scores were seen as valuable support systems in improving uniformity in treatment practices, educating interns, conducting research and quantifying a practitioner’s own risk assessment.

1. No evidence of harm.
2. No evidence of improved endpoint outcomes
3. Evidence of improved risk factor control.

1. 34% report regular use of risk scores.
2. Use correlates with increased use of prescribed meds.

Sposito et al. Curr Med Res Opin. Engel et al. BMC Hlth Serv Res
Sheridan and Crespo. BMC Hlth Serv Res

Some editorial comments about GRS/PRS:

3. But what is their future?

Time to take a Deep Dive into Healthcare!

1. Hierarchical Conditional Categories (HCC).

2. Determines per member per month
   for CMS and many ACO plans.

3. How's it calculated? You guessed it…….

But Don’t Despair: Dive into the Deep End!

1. Hierarchical Conditional Categories.

2. Determines per member per month for CMS and many ACO plans.

3. It is based on risk scores, which are then used to calculate a risk adjustment factor.

4. The RAF is used to estimate prospective health care costs which turn into monthly payments.

HCC: Critical Element of Risk Management

Implement an HCC Best Practice – PYA's HCC Checkup

Since 2004, Hierarchical Condition Categories (HCC) have been a foundational element of the Centers for Medicare & Medicaid's (CMS) capitated payments, value-based reimbursement methodology.

HCC risk-adjusted framework is used through private and public plan contracts to better manage and modulate payments.

Risk Adjustment Factors (RAFs)

HCCs use RAFs to

- **Capture** complex health conditions
- **Determine** capitated payments with reimbursement rates based on 12-month retrospective patient diagnostic record
- **Renew** HCC scores every year

> Our second goal is for virtually all **Medicare** fee-for-service payments to be tied to **quality and value**; at least 85% in 2016 and **90% in 2018**.
>
> - Sylvia Burwell, the Secretary of HHS

Precise HCC Coding

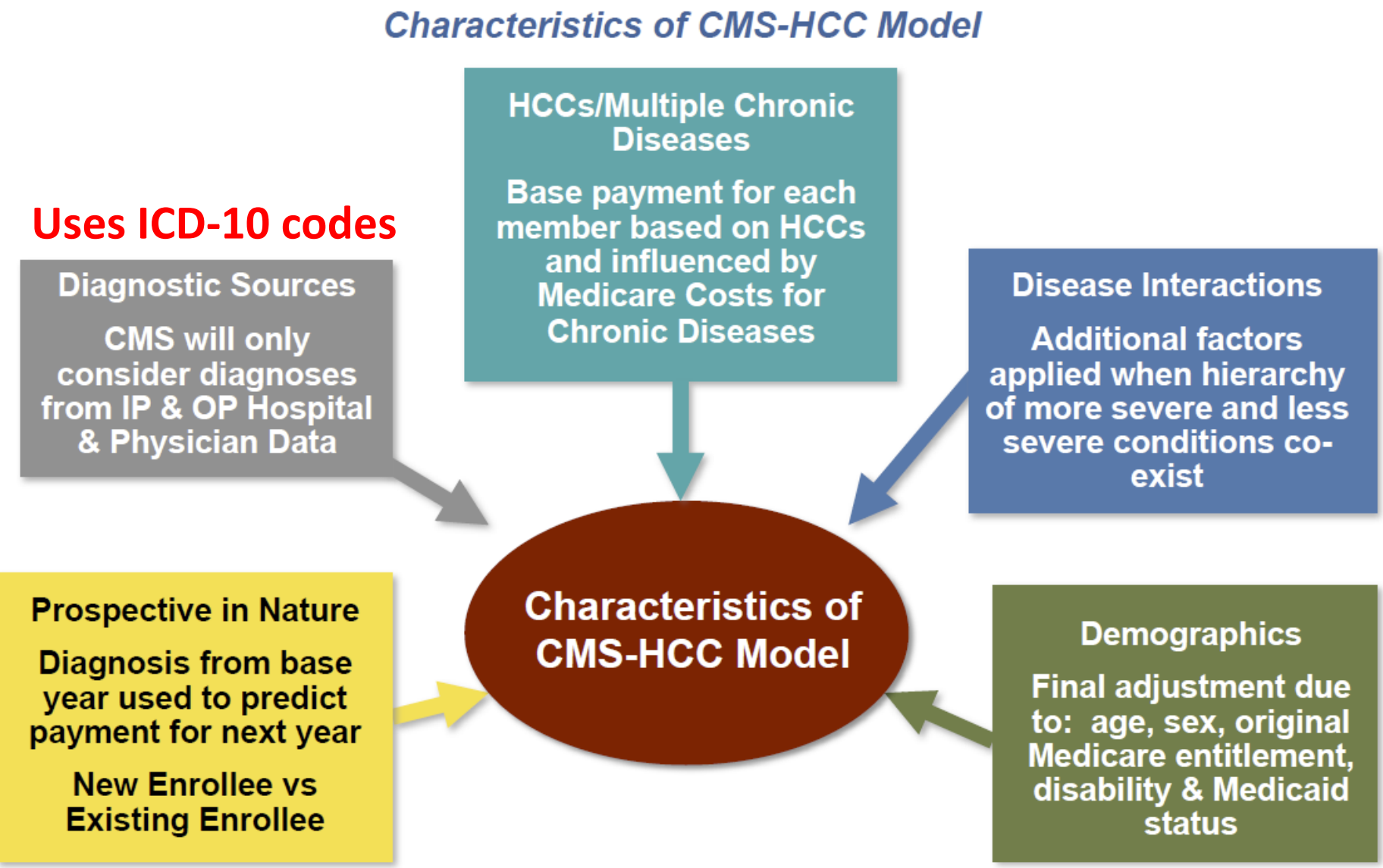
The core of reimbursement

Incomplete

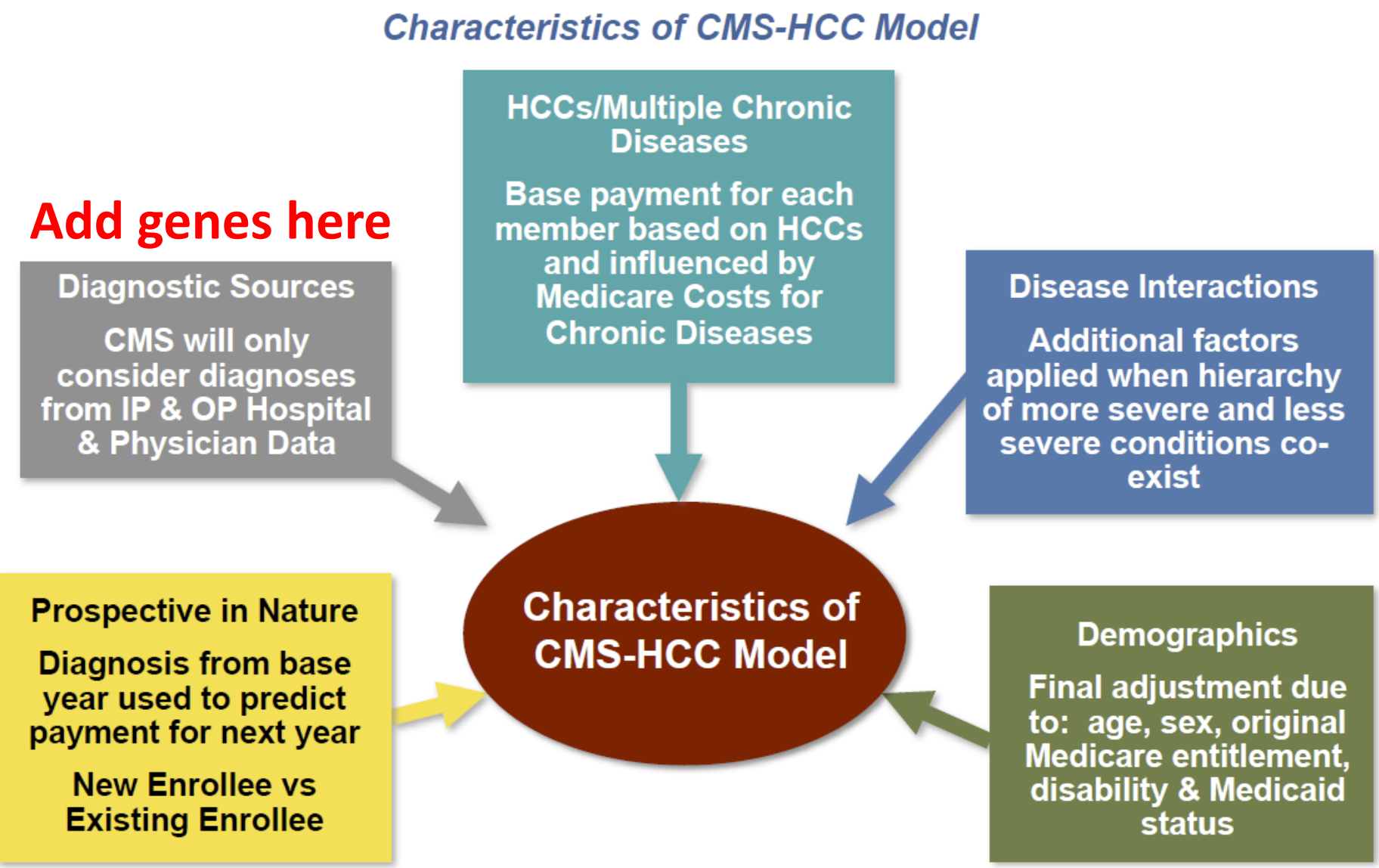
Seismic financial implications are associated with inaccurate HCC coding.

Coding needs to accurately reflect

Inputs into the Risk Score Modeling



Inputs into the Risk Score Modeling



HeartCare

Baylor College of Medicine HGSC Human Genome Sequencing Center Clinical Laboratory

Genetics Report Summary

Patient: PFirstNameTEST6 PMidNameTEST6 PLastNameTEST6

The HeartCare Gene Panel tests 158 genes associated with Cardiovascular Disease. See page 2 for more details.

Patient:	PFirstNameTEST6 PMidNameTEST6 PLastNameTEST6	**Reason for Testing:**	Other, Arrhythmia, Cardiomyopathy
Date of Birth:	01/31/1990	Ordered By:	Dr CHI A
MRN:	CT006		

158 Cardiac Gene Panel: NEGATIVE

Details in Section 1

No pathogenic or likely pathogenic variants were found.

Coronary Artery Disease Polygenic Risk Score: HIGH

Details in Section 2

The patient is in the high genetic risk group (top 5%) for developing coronary artery disease. This result is independent of the high impact variants identified in the 158 Cardiac Gene Panel described above that may provide a more accurate estimation of overall cardiovascular disease risk.

Recommendations: Studies show that a healthy lifestyle like the AHA's Life's Simple 7 is associated with a nearly 50% lower risk of coronary artery disease. Learn more at https://www.heart.org/MyLifeCheck. Other factors may influence risk of developing cardiovascular disease, including environment and ancestry. This score was developed in a group of Caucasian subjects and its applicability to other ethnicities is unclear.

Pharmacogenetics Findings

Details in Section 3

Individual carries two normal function alleles in SLCO1B1.

Recommendations: Prescribe desired starting dose and adjust doses of simvastatin based on disease-specific guidelines. Avoid drugs that are known to interact with simvastatin.

This individual is predicted to be a normal responder to Warfarin.

Recommendations: This individual may respond to normal maintenance Warfarin doses. A Warfarin dosing algorithm based on common genetic variants, race, and clinical information is available at WarfarinDosing.org.

Summary

1. Mendelian and common disease gene discovery are supporting the foundation of GRS/PRS.

2. They are likely a useful research tool, including clinical trials, but their application to healthcare is questionable.

3. Human genomics needs to engage in implementation science focused on real-world healthcare settings