Summer Institutes of Statistical Genetics, 2023

Module 2: INTRODUCTION TO GENETICS AND GENOMICS

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Lecture 9: PERSONALIZED MEDICINE

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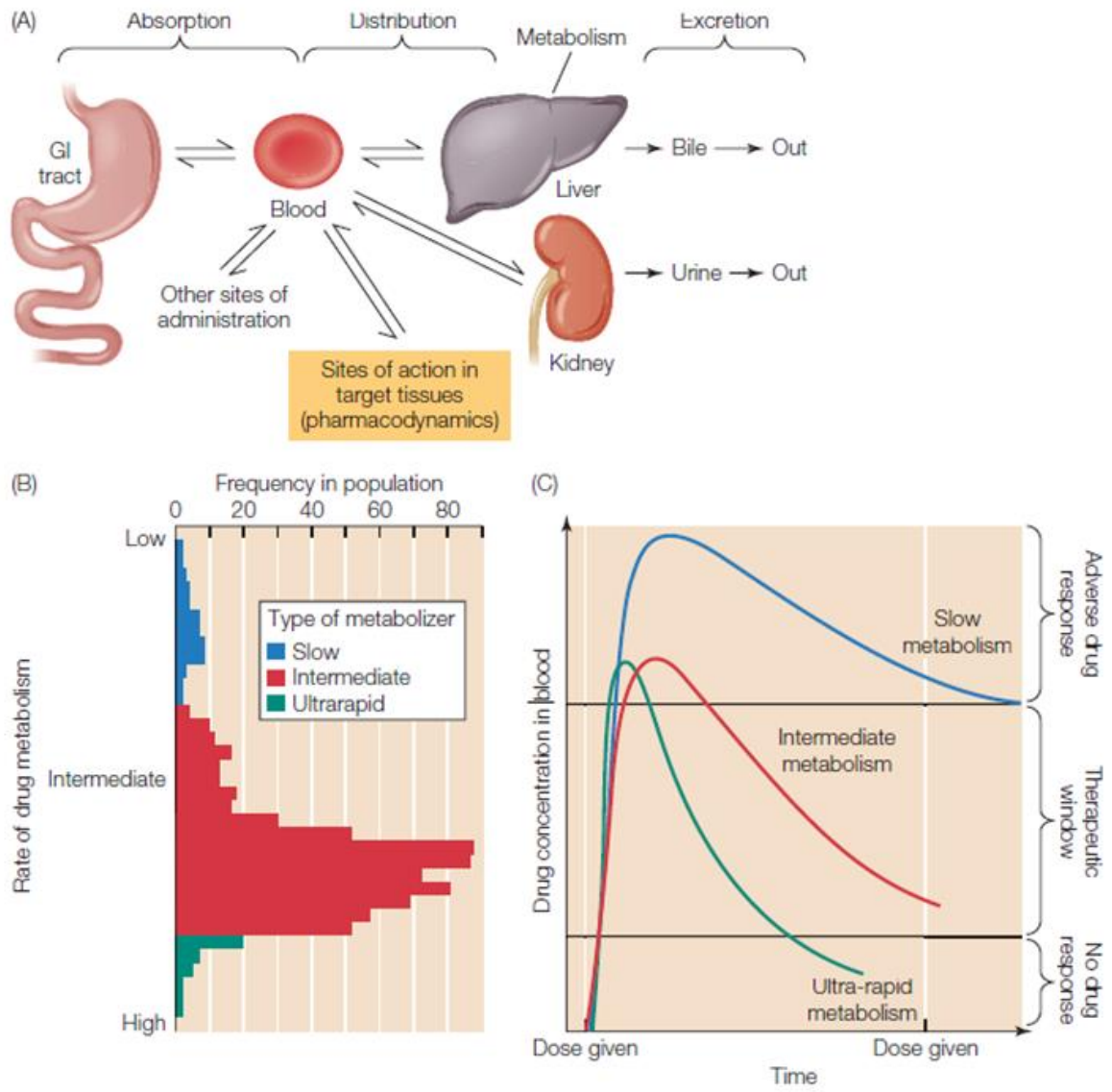
PHARMACOGENETICS

Pharmacodynamics and Pharmacokinetics



PRECISION MEDICINE

Peri-Natal Screening

Genetic carrier screening

Noninvasive prenatal testing

Fetal sex testing

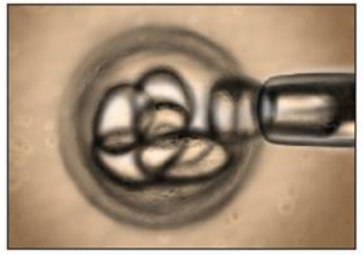
natera™

Harmony™ PRENATAL TEST

sequenom. Laboratories

Prenatal paternity testing

Miscarriage testing



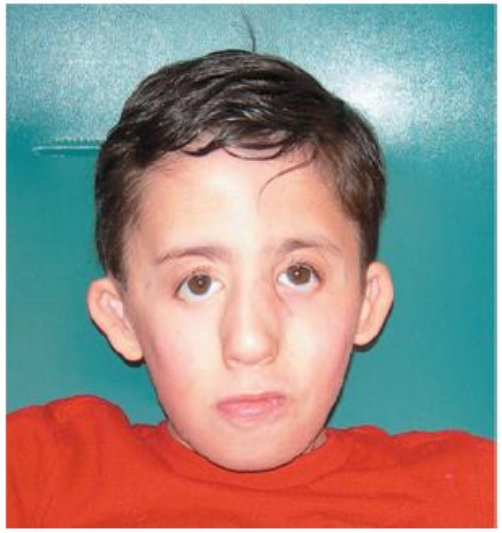
Preimplantation genetic screening

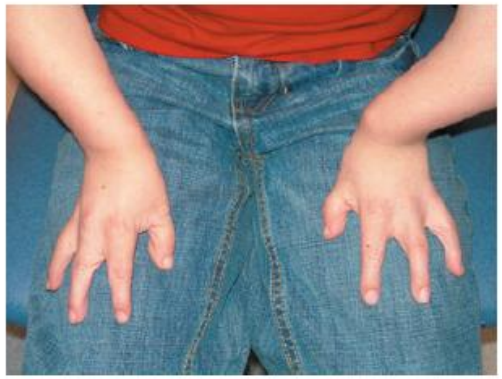
Newborn Screening

Type of Disorder	Disease	Gene	Prevalence
Red blood cells	Sickle-cell anemia	*HB* (coding)	1/400 (African American)
	β-Thalassemia	*HB* (regulatory)	1/50,000
Inborn errors of amino acid metabolism	Tyrosinemia	*FAH/TAT/HPD*	1/100,000
	Argininosuccinic aciduria	*ASL*	1/100,000
	Citrullinenmia	*ASS/SLC25A13*	1/100,000
	Phenylketonuria	*PAH*	1/25,000
	Maple syrup urine disease	*DBT/BCKDH*	1/100,000
	Homocysteinuria	*CBS*	
Inborn errors of organic acid metabolism	Glutaric academia type I	*GCDH*	1/75,000
	HMG-lyase deficiency	*HMGCL*	1/100,000
	Isovaleric academia	*IVD*	1/100,000
	3MCC deficiency	*MCCC1,2*	1/75,000
	MM-CoA mutase deficiency	*MUT*	1/75,000
	Methylmalonic aciduria	*MMA A,B,C,D*	1/100,000
	Beta-ketothiolase deficiency	*ACAT1*	1/100,000
	Propionic academia	*PCC A,B*	1/75,000
	Multiple-CoA carboxylase deficiency	*HLCS/BTD*	1/100,000
Inborn errors of fatty acid metabolism	LCHAD	*HADHA*	1/75,000
	MCAD	*ACADM*	1/25,000
	VLCAD	*ACADVL*	1/75,000
	Trifunctional protein deficiency	*HADH A,B*	1/100,000
	Carnitine uptake defect	*OCTN2 (SLC22A5)*	1/100,000
Miscellaneous multisystem diseases	Cystic fibrosis	*CFTR*	1/5000
	Congenital hypothyroidism	*TSHR/TSHB/PAX8*	1/5000
	Biotinidase deficiency	*BTD*	1/75,000
	Congenital adrenal hyperplasia	*CYP21A*	1/25,000
	Classical galactosemia	*GAL E,K1,T*	1/50,000
Screened by other methods	Severe combined immune deficiency		1/50,000
	Congenital deafness		1/5000
	Critical congenital heart defects		1/100

Source: American College of Medical Genetics 2006.

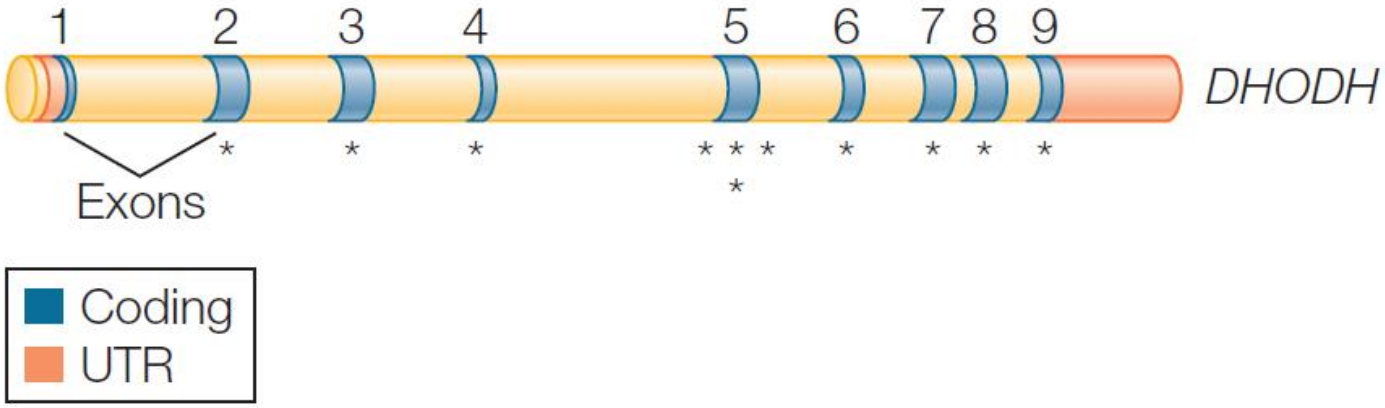
Diagnostic Sequencing: Miller Syndrome



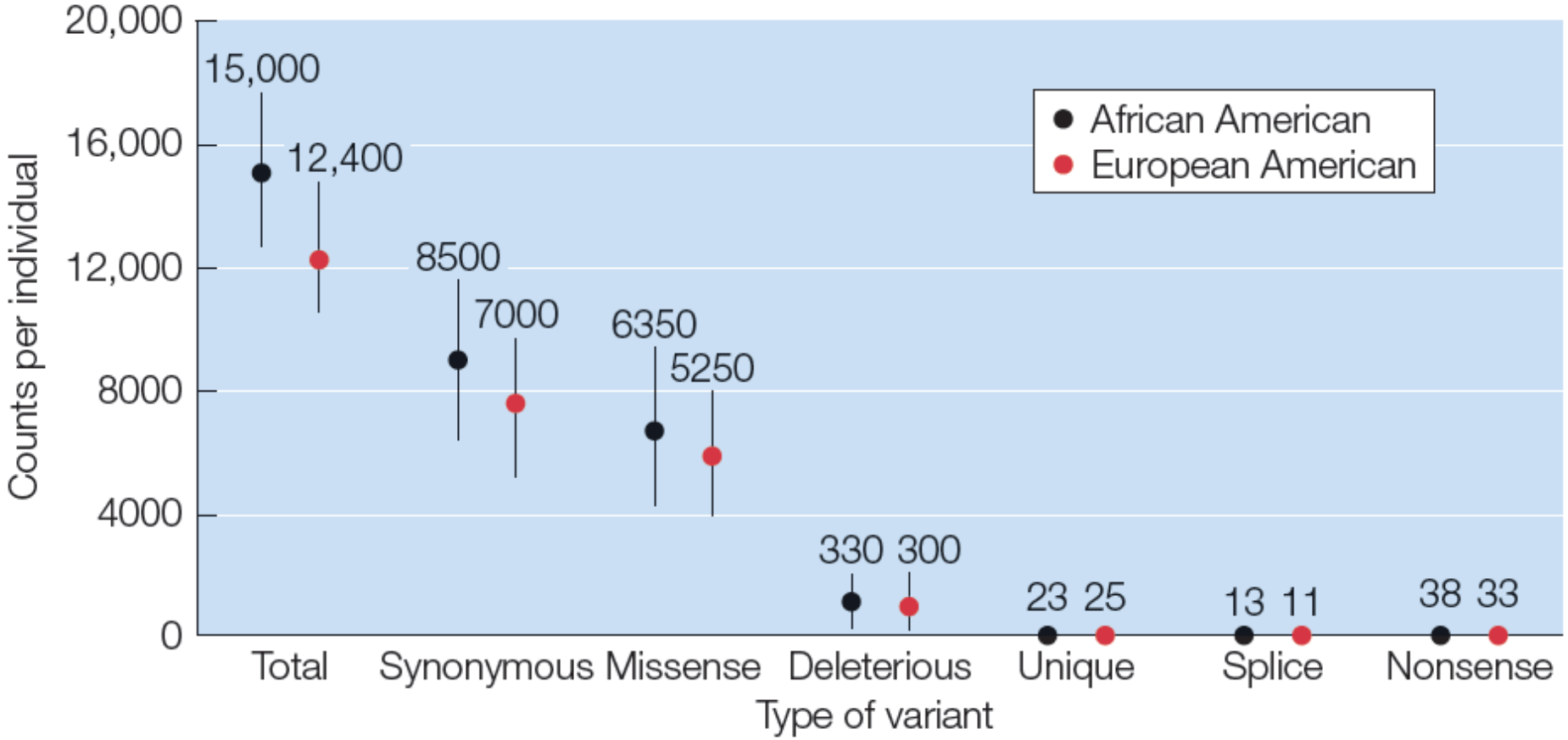


	1 individual		3 kindreds	
Filter	**Dominant**	**Recessive**	**Dominant**	**Recessive**
NS/SS/I	4650	2850	2650	1525
Novel	460	32	8	1
Damaging	228	9	2	0

(B)



Number of Variants in a Typical Human Genome



N=1 Genetics

How do we know if a newly identified mutation is pathogenic?

1. Previously ascribed clinical function
2. Bioinformatic prediction from protein structure or attributes
3. Evolutionary conservation
4. Experimental validation (animal models, cellular manipulation, in vitro studies)

What could possibly go wrong?

5. It is easy to get trapped in a genetically deterministic worldview:
    - even Mendelian variants have incomplete penetrance
    - expressivity is modified by genetics and environment
    - deleterious to the protein is not necessarily deleterious to the organism

6. We do not have parallel methods for evaluating function of regulatory variants

7. Ethical concerns: reporting incidental findings, prescribing off-label drugs, false positives

Project Baby Bear

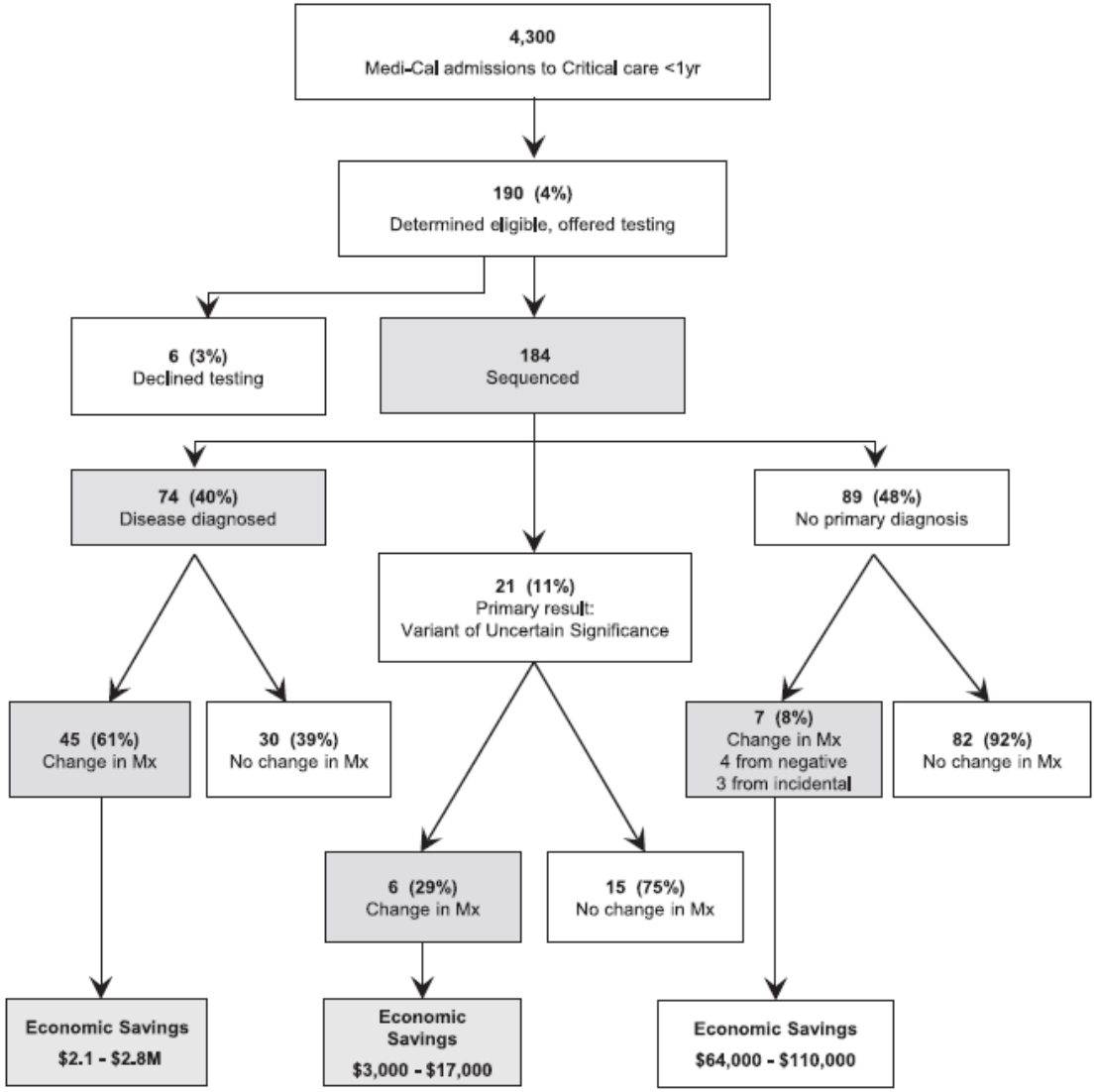


Table 2. Number of infants with a change in care due to an rWGS result

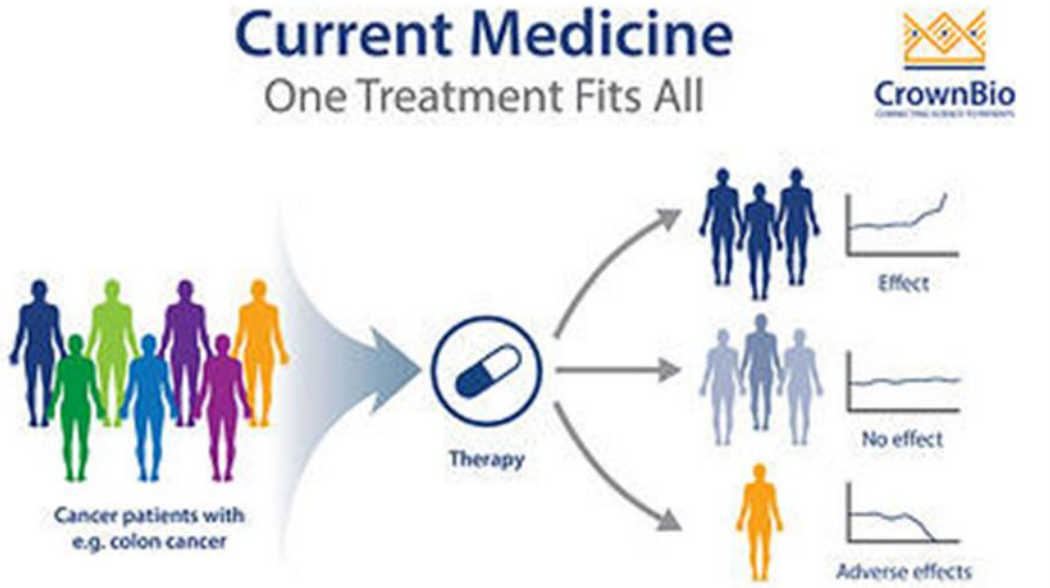
Intervention type	n
Any change	58
Surgical (n = 24)	
Surgical procedure added	5
Surgical procedure removed	16
Surgical procedure changed	5
Medication (n =23)	
Medication added	16
Medication stopped	8
Medication changed	0
Dietary (n = 9)	
Diet changed	9
Length of hospital course (n = 30)	
Hospital days added	0
Hospital days avoided	30

Please note that children may have experienced more than one change, for example, a medicine added and a medicine stopped.

Dimmock et al (2021) *Am J Hum. Genet*. **108**: 1231-1238

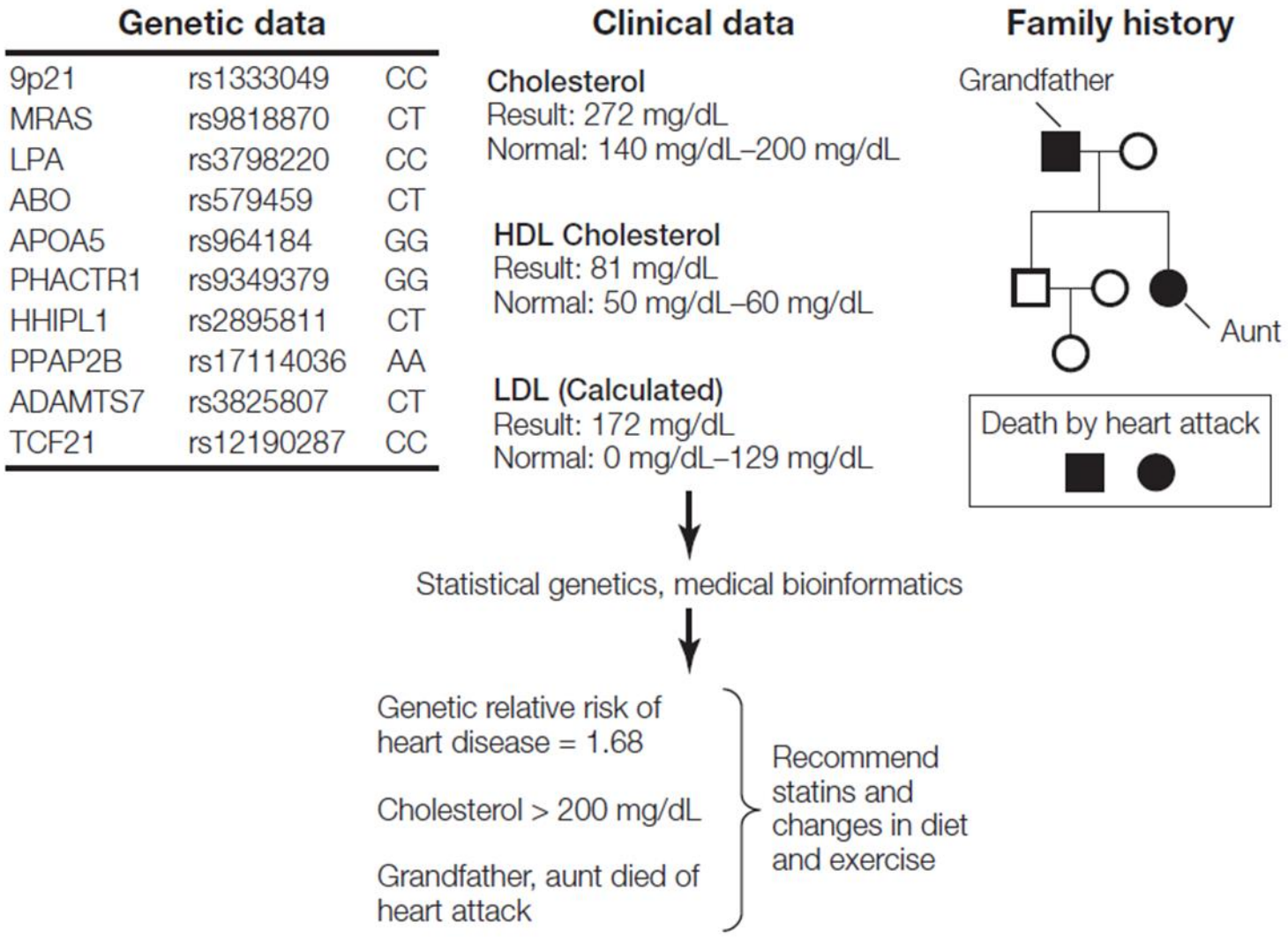
PREDICTIVE HEALTH

Personalized Diagnostics Rationale



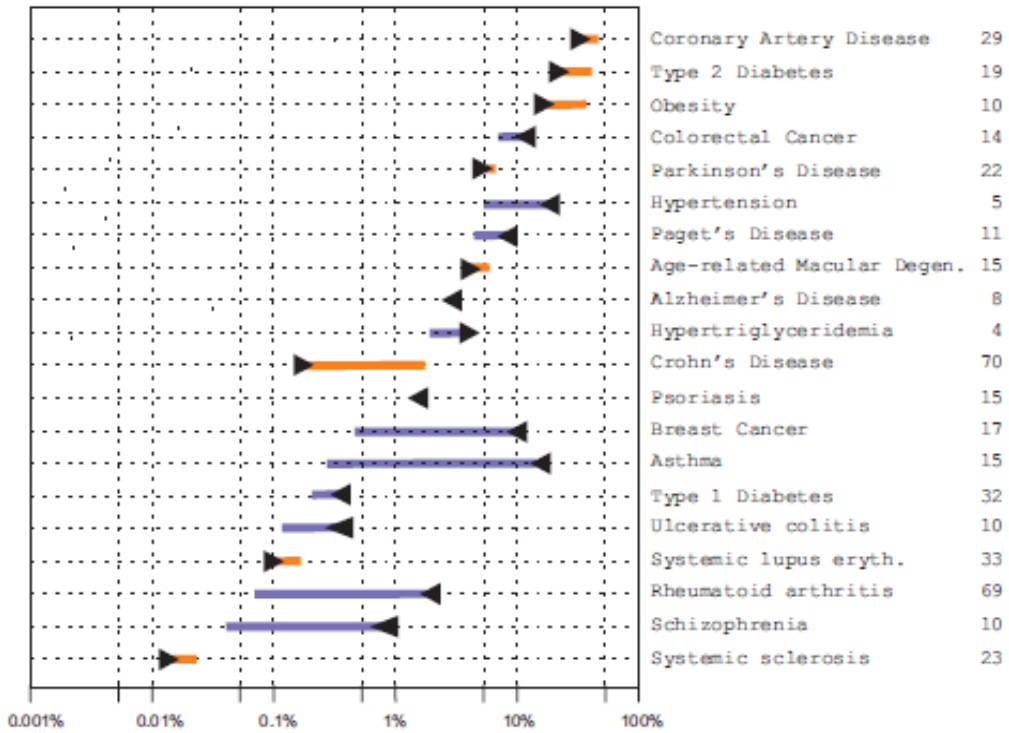
https://blog.crownbio.com/pdx-personalized-medicine

The Western Approach to Predictive Health

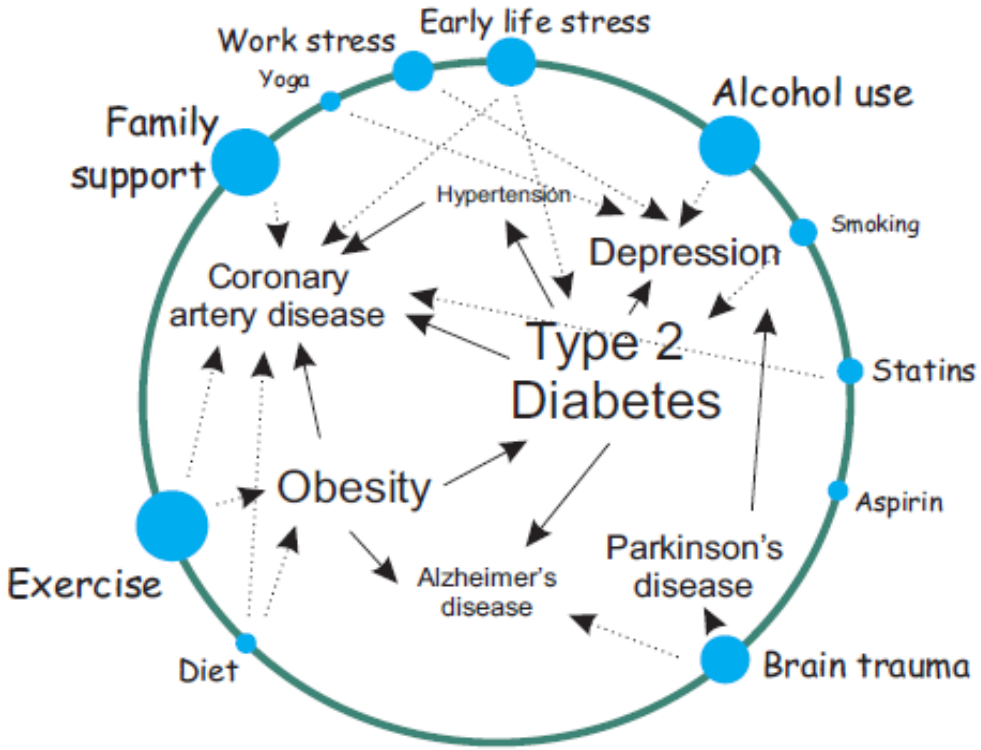


Risk-o-Grams

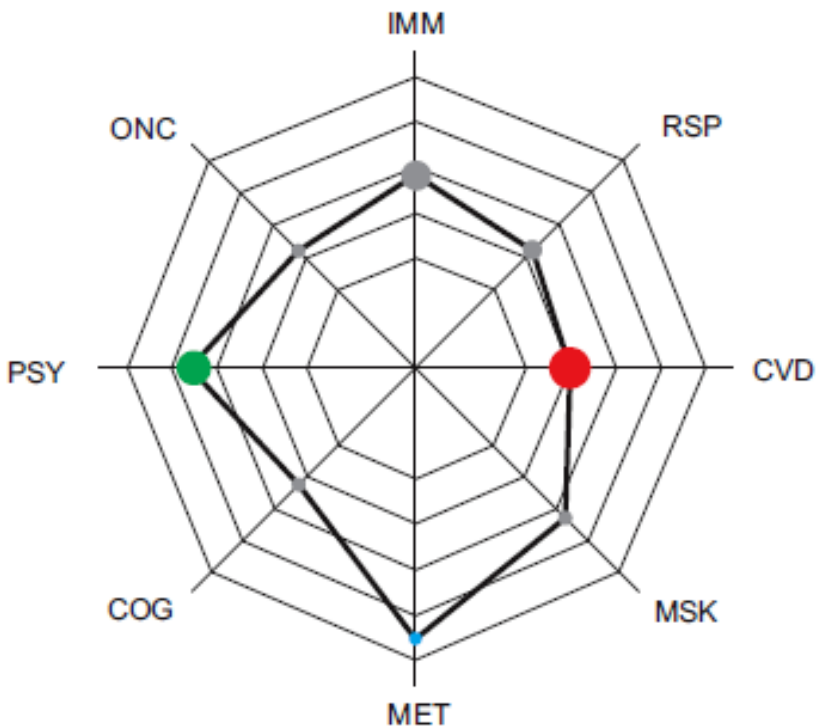
A.

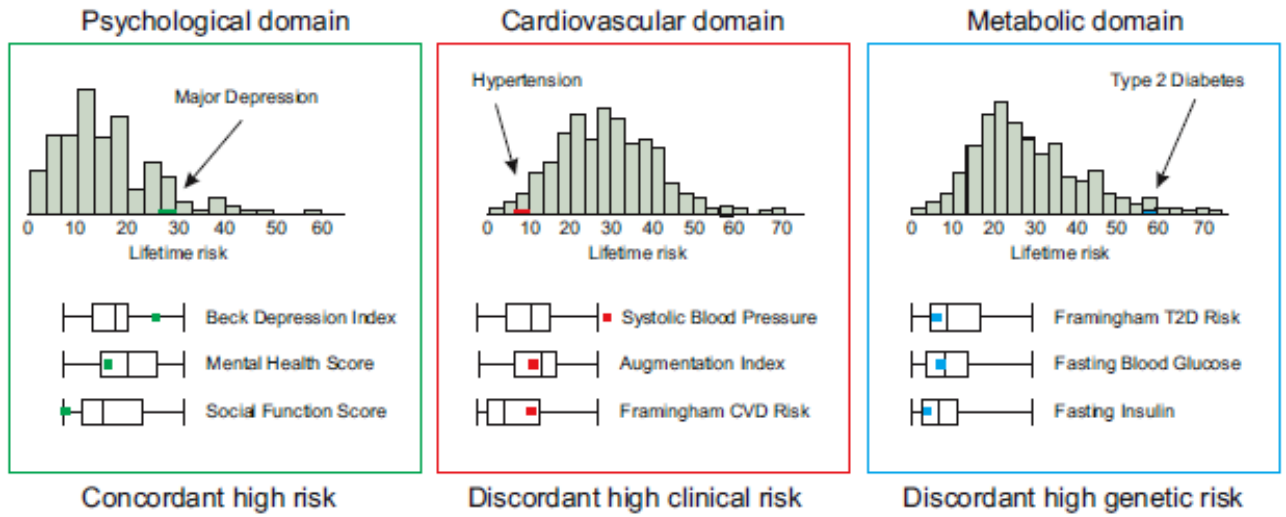


B.

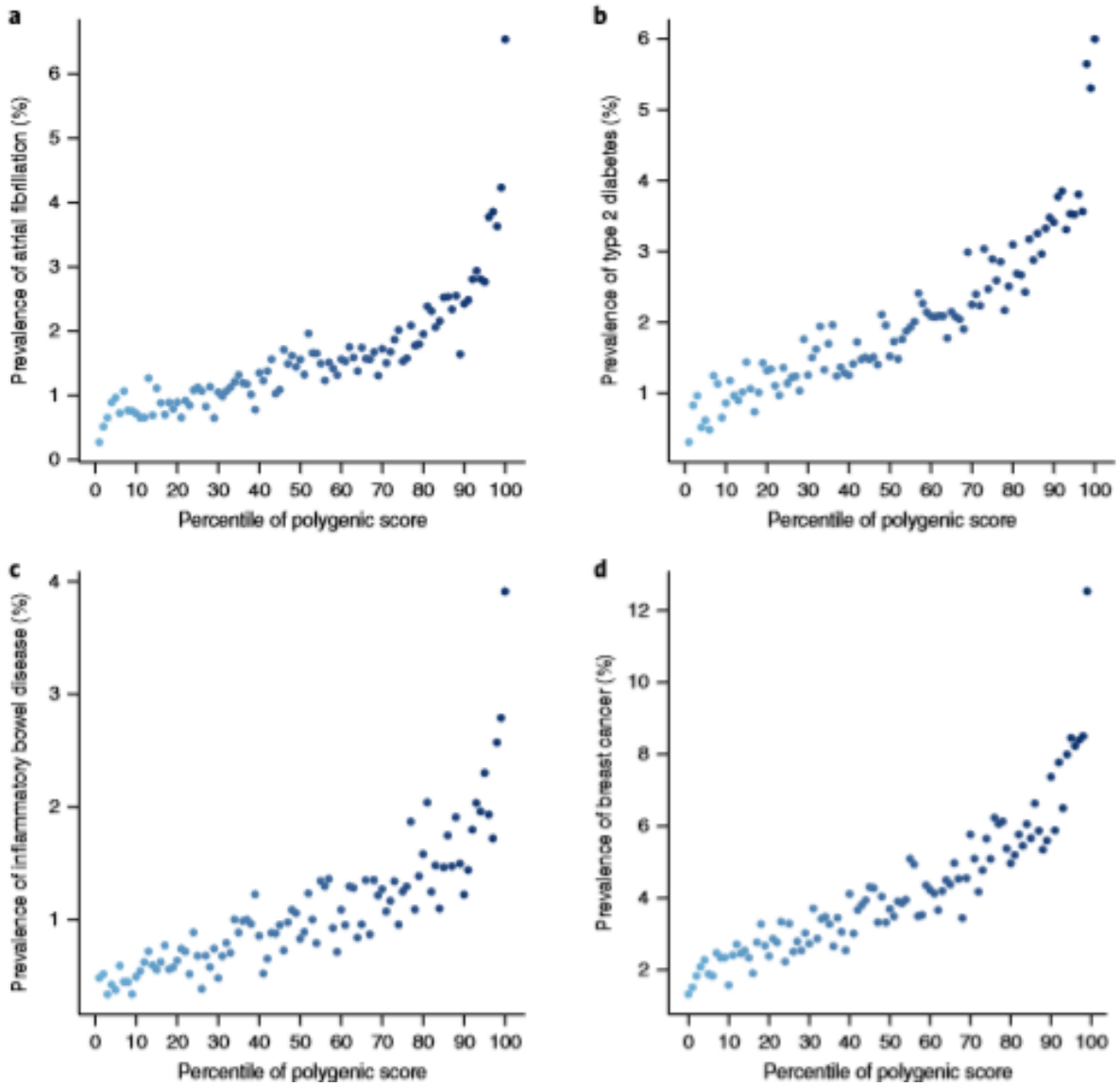


Risk Radars


IMM
RSP
CVD
MSK
MET
COG
PSY
ONC


Psychological domain
Major Depression
0 10 20 30 40 50 60
Lifetime risk
Beck Depression Index
Mental Health Score
Social Function Score
Concordant high risk
Cardiovascular domain
Hypertension
0 10 20 30 40 50 60 70
Lifetime risk
Systolic Blood Pressure
Augmentation Index
Framingham CVD Risk
Discordant high clinical risk
Metabolic domain
Type 2 Diabetes
0 10 20 30 40 50 60 70
Lifetime risk
Framingham T2D Risk
Fasting Blood Glucose
Fasting Insulin
Discordant high genetic risk

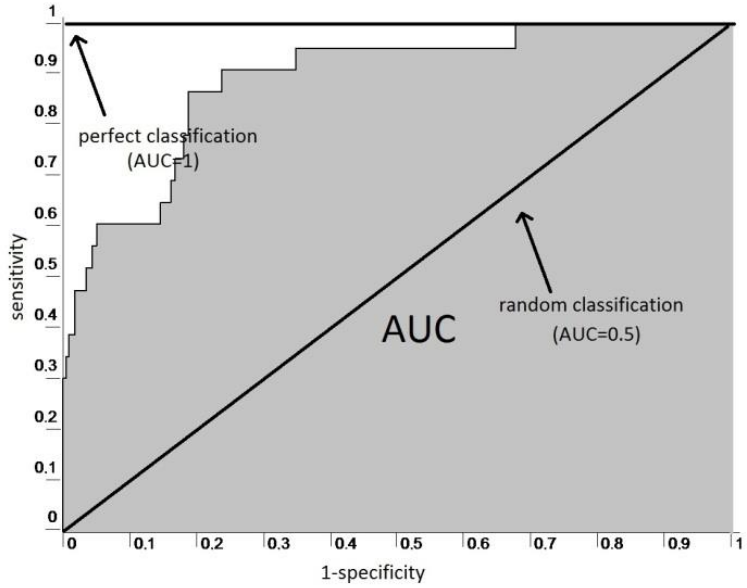
Polygenic Risk Scores



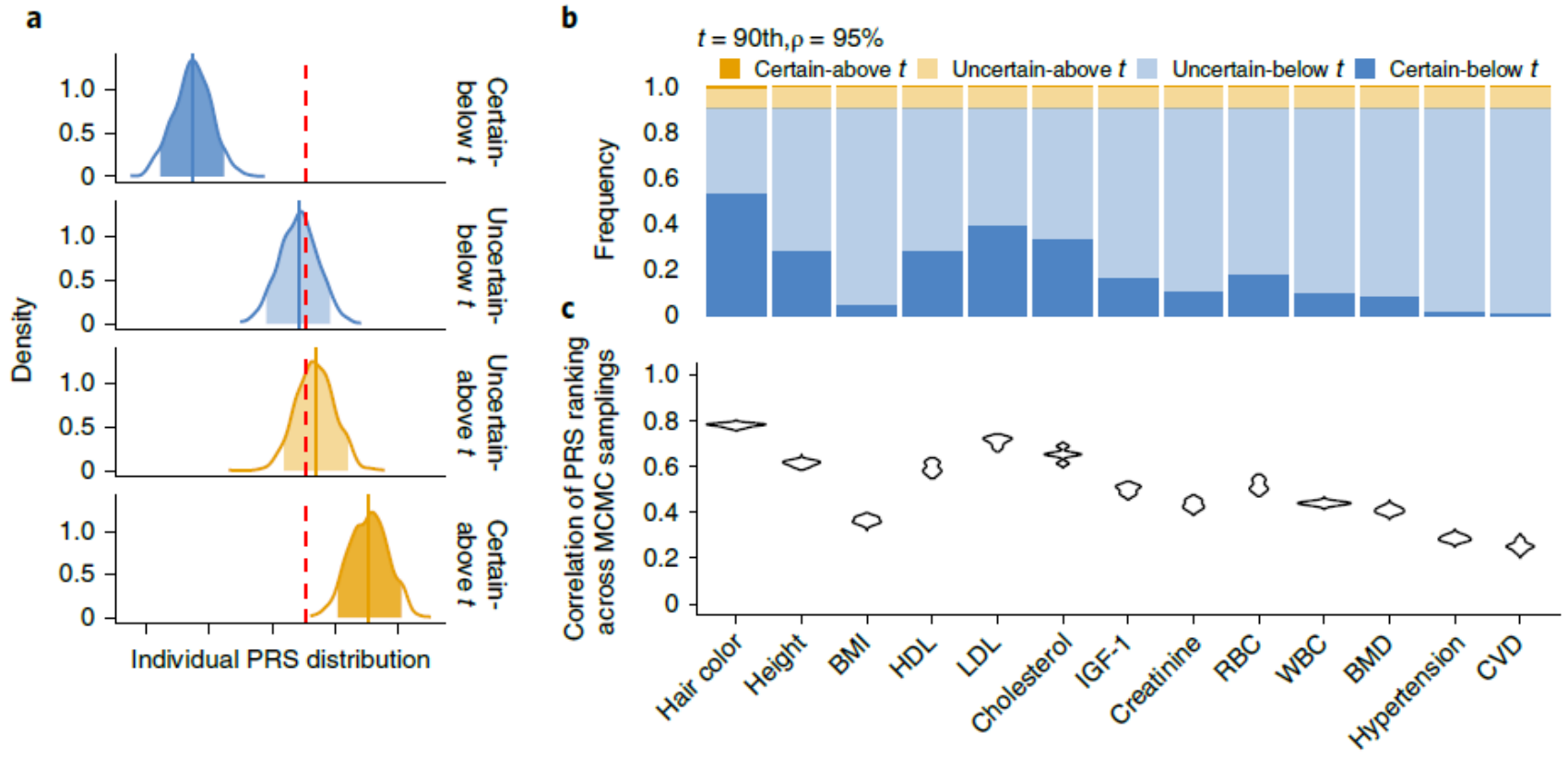
Khera et al,. 2018. *Nature Genetics* **50**: 1219-24

Sensitivity, Specificity, and Precision

	ACTUAL CASES	ACTUAL CONTROLS	
PREDICTED CASES	200	100 (False Positives)	Precision = 67% (FDR = 33%)
PREDICTED HEALTHY	50 (False Negatives)	900	
	Sensitivity = 80%	Specificity = 90%	



PRS Uncertainty is Sobering



Ding et al, 2022. *Nature Genetics* **54**: 30-39

The NNT: Number Needed to Treat

This is the number of people who would need to be treated in order to save one life.

It is computed as 100 over the percent reduction in mortality, namely

$$\text{NNT} = \frac{100}{\text{The \% who die without treatment} \quad \text{minus} \quad \text{The \% who die with treatment}}$$

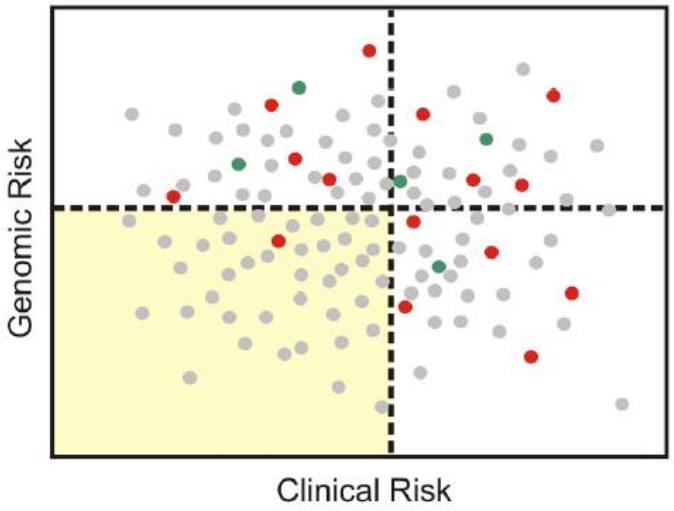
For example if 20% of High Cholesterol patients will die of a heart attack in the next 10 years unless they get a Statin, in which case the proportion is 18%, then NNT is 100/(20-18) = 50

It is solely a function of the difference in numbers, not the proportion (eg 100/(80-78) = 50.

The bigger the difference, the more people benefit: 100/(50-30) = 5

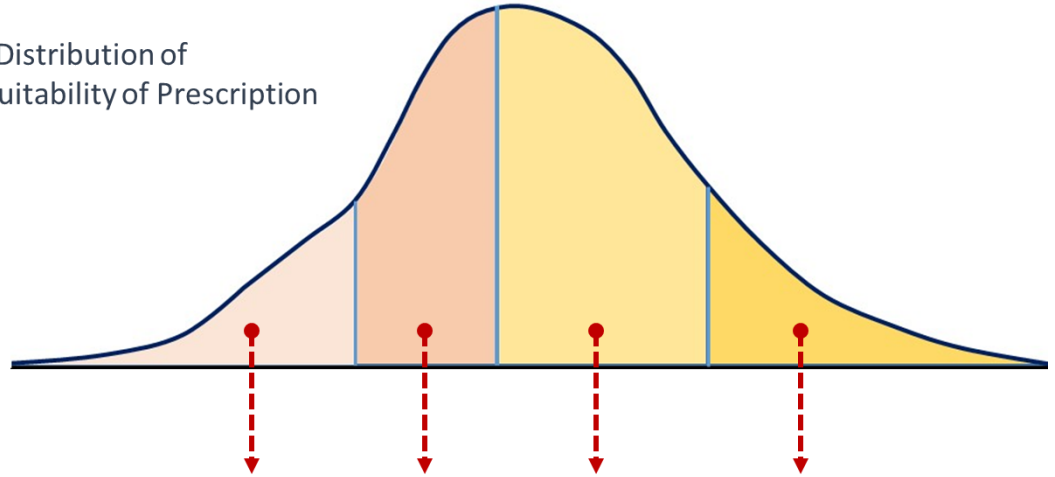
Usually doctors tell you just the relative reduction in risk: (2/20 = 10%; 2/80 = 2.5%)

Going to the Negative



Combined risk = 20/120; Events after treatment = 15/120; NNT = 24

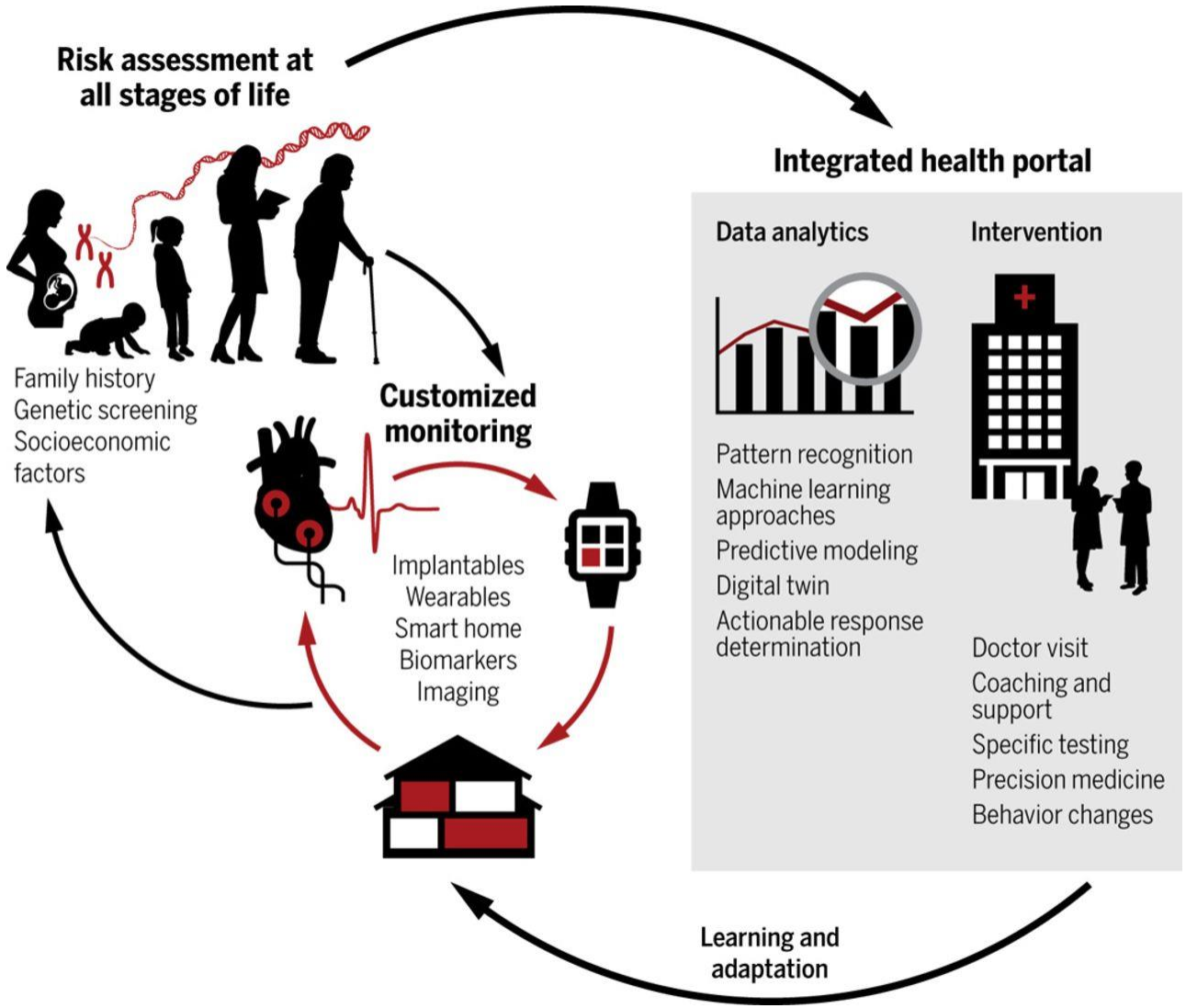
Assessed risk = 19/80; Events after treatment = 14/80; NNT = 16



Events w/o drug	5%	6%	7%	10%
Events with drug	5%	5%	5%	5%
Relative Rate Reduction	0%	15%	30%	50%
Absolute Rate Reduction	0%	1%	2%	5%
Number Needed to Treat	>200	100	50	20
Cost / QALY gained	>>$50K	~$50K	$20K-$50K	<$20K

Gibson G (2019) *Nature Reviews Genetics* **20**: 1-2

Where we are really headed



Gambhir et al (2019) *Science Translational Medicine* **10**: aao3612