Welcome! While waiting for **our day's session** to start:

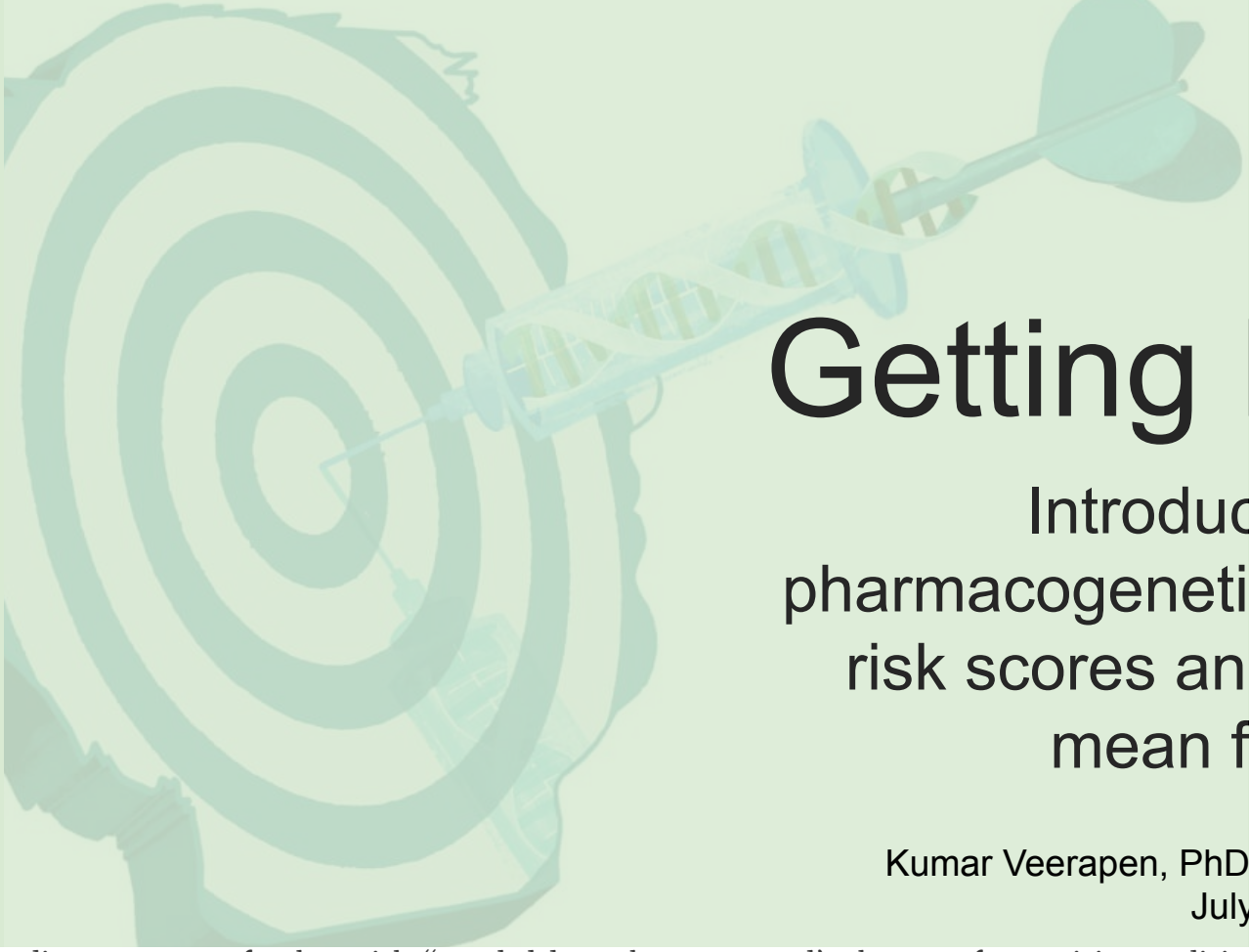
•Please ensure that your microphone is muted during the presentation. **But** we'd love if you could unmute yourself temporarily (by pressing the *spacebar* or CMD+A):

- •To giggle or laugh (we think the presenters may be funny)
- •To comment / ask questions

•If you would like to turn on your video, great! It would be nice to see everyone. Otherwise, we respect your privacy and prerogative :)

•Issues with the Zoom? Please use the zoom chat box. Caitlin and I will check it periodically.


Good Morning!



Getting Personal

Introduction into pharmacogenetics and polygenic risk scores and what do they mean for you?

Kumar Veerapen, PhD. Caitlin Cooney, CGC
July 2020

Credit: Eva Vazquez for the article "Headed down the wrong road': The quest for precision medicine distracts us from what already works." Genetic Literacy Project. March 2020
https://geneticliteracyproject.org/2020/03/02/headed-down-the-wrong-road-why-the-quest-for-precision-medicine-distracts-us-from-what-already-works/

What are we doing today?

10:00 - 10:05 am : people settle in

10:05 - 10:15 am : Recap from day one

10:15 - 11:00 pm : Lecture 2a. Instructor: Kumar

Genetics to Genomics
Introduction to genetic epidemiology
Polygenic risk score (PRS)

11:00 - 12:30 pm : **Computing PRS lab**

12:30 - 1:00 pm : Lunch break

1:00 - 2:00 pm : Lecture/Discussion 2b.
Instructor: Caitlin

Clinical application of PRS
Ethical implications of PRS

Recap from Day 1

- What is pharmacogenetics?
- Which gene is the most commonly used gene to identify drug metabolizers?
- How can you use genetics resources e.g. PharmGKB, to interpret direct to consumer genetic testing kits?

Learning Objectives for today

- To describe the difference between pharmacogenetics and pharmacogenomics
- To define polygenic risk scores (PRS)
- To compute PRS
- To understand statistical and clinical interpretation of PRS
- To understand and describe ethical issues in the interpretation of PRS

When poll is active, respond at **PollEv.com/gspacepgx**

Text **GSPACEPGX** to **37607** once to join

Do you think that a single gene can always control how medications metabolize in the body?

Yes

No

Unsure

Genetics vs Genomics

Genetics

- A study of heredity.
- “Gene” refers to a specific sequence of DNA on a single chromosome.
- Genetics involves the study of functions and composition of the single gene.

Genomics

- Genomics is the study of the entirety of the organism's genes.
- “Genome” refers to an organism’s entire genetic makeup.
- Genomics addresses all genes and their inter relationships.

Pharmacogenetics vs Pharmacogenomics

Pharmacogenetics

- Single/panel gene approach
- Focused on patient variability.
- One drug, one gene, many patients.
- Ability to predict drug toxicity.
- Useful in patient/disease specific healthcare.

Pharmacogenomics

- Whole genome approach
- Focused on drug variability.
- Many drugs, one genome.
- Ability to predicts drug efficacy.
- Useful in drug discovery and development or selection.

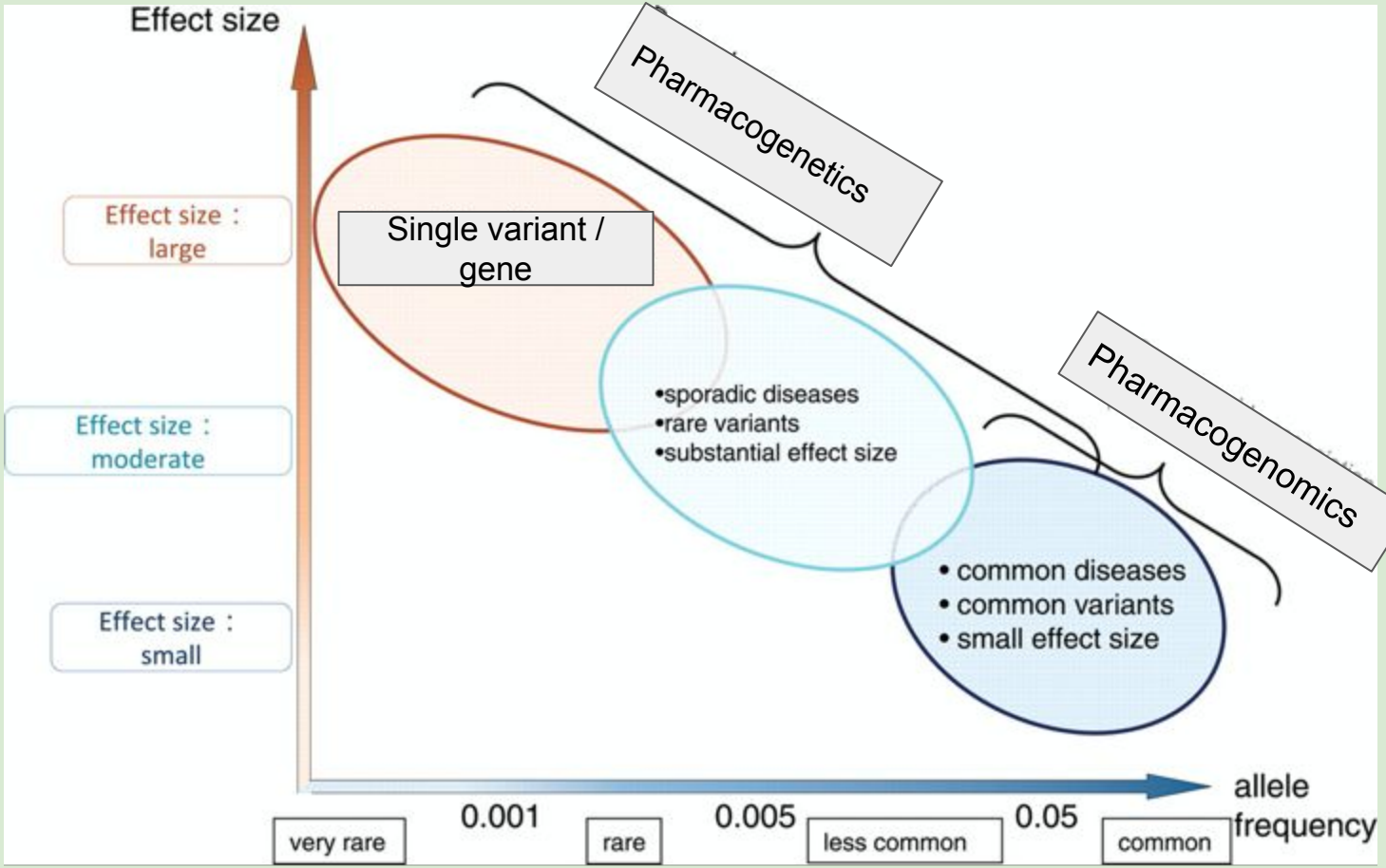
A few terminologies before we move on...

Allele frequency: frequency of a variant at a population on a scale of 0-1. Something closer to 0 is very rare and may be very damaging and vice versa.

Effect size: quantifying size difference between two groups such as people who have a certain trait vs people who do not. Used to tell us how “good” or “bad” a variant is in a population.

Variance: the amount of difference observed in the data.

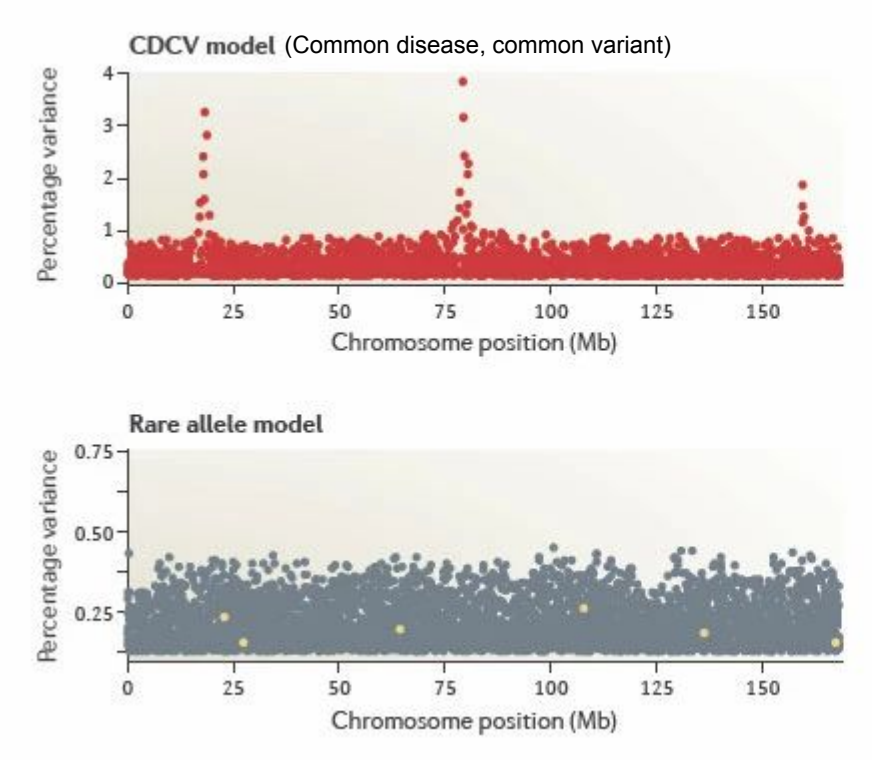
Heritability: degree of genetic variance that contributes to a specific trait. The higher the value in %, the more genetic a trait is.

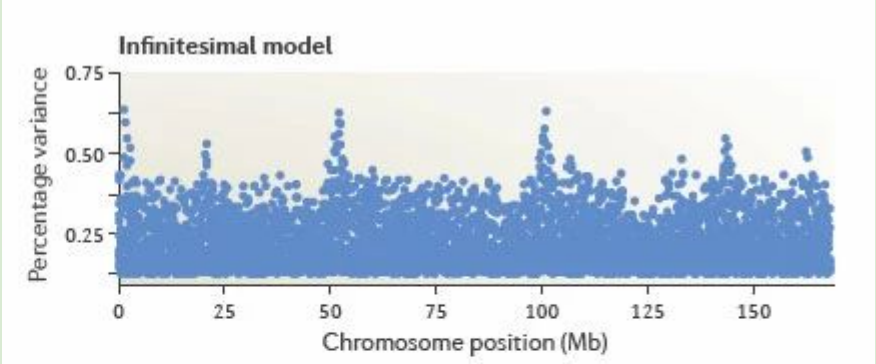


Tsuji S Hum. Mol. Genet. 2010;19:R65-R70

Human Molecular Genetics

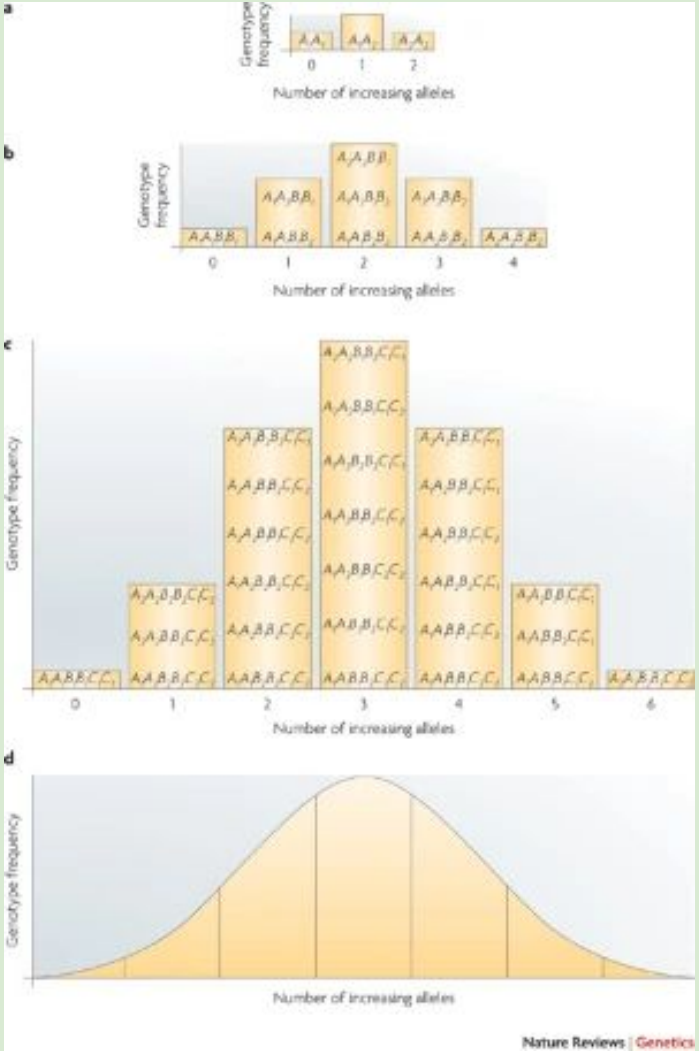
Epidemiology in Genetics and Genomics





Gibson (2012). *Nature Reviews Genetics* **13**, 135-145

Heritability



Least heritability explained
Pharmacogenetics

More heritability explained
Pharmacogenomic applications

Plomin *et al* (2009) *Nat Rev Gen*

Infinitesimal model → Polygenic Risk Score

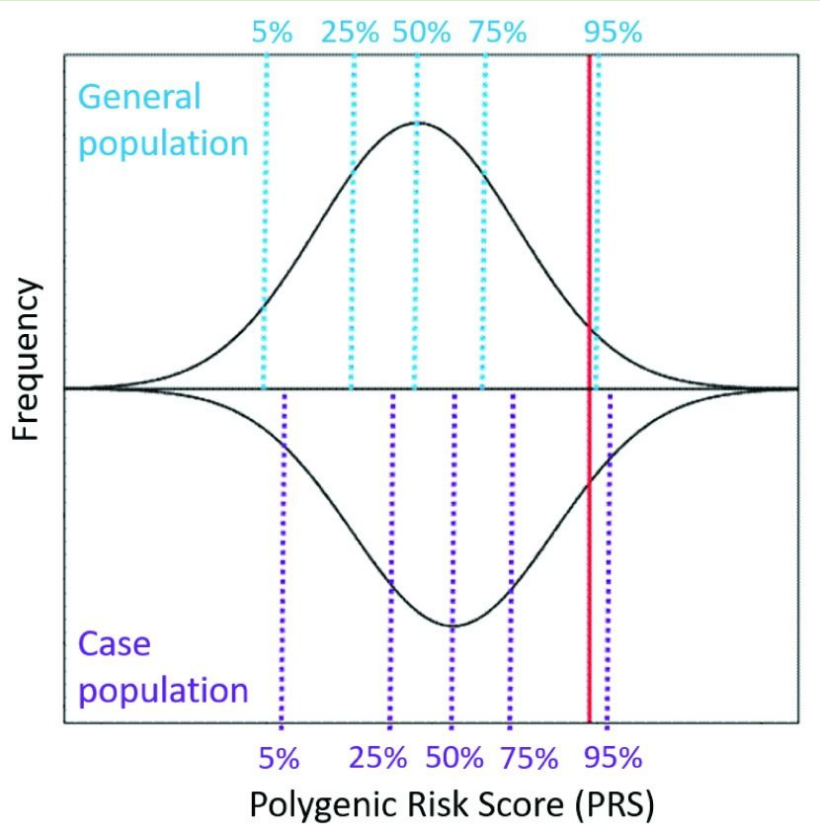
- Polygenic?
  - Many traits are polygenic.
- Polygenic risk score (PRS)?
  - A score that describes a polygenic risk someone carries for a certain trait.
  - It takes into account the effect sizes of multiple variant effect size and sums it up.
- Where do these effect sizes come from?
  - Previous studies that have run CDCV but found low heritability or findings.
- Where has PRS been used to explain traits?
  - Schizophrenia, multiple sclerosis, height, cardiovascular disease, rheumatoid arthritis, body mass index, migraines
  - Improving heritability estimates compared to single variant tests

How do you compute PRS?

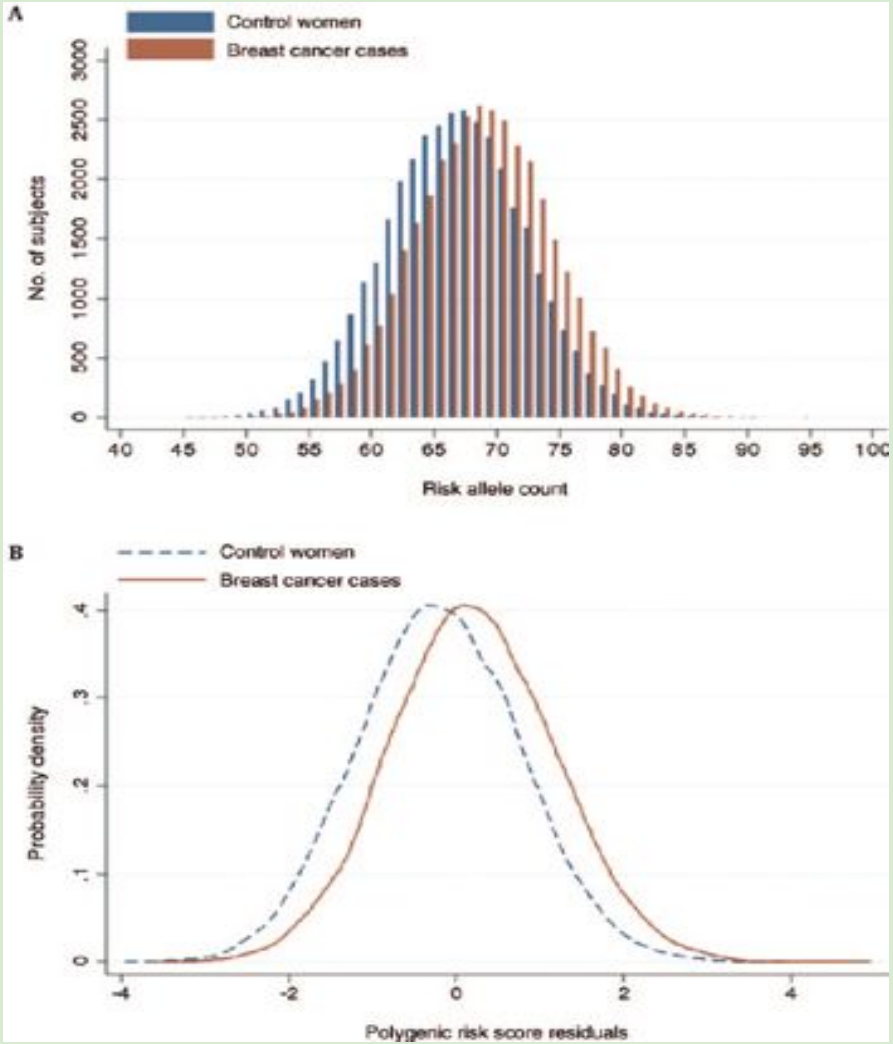
1) **Test Cohort:** Find a cohort to analyse and compute PRS e.g. collected yourself or from a readily available genotype dataset
2) **Summary Statistics / Reference data**: Identify available effect sizes for a phenotype? E.g. effect size derived from depression genetic study
3) **Results (PRS)**: Weigh variants in 1) with effect sizes from 2) and sum the effects up. Every individual will have a unique PRS based on their genotype.

$$PRS = \sum_{i=1}^{m} (Count\ of\ reference\ alleles\ at\ SNP\ i) * (Effect\ size\ SNP\ i)$$

Interpreting PRS in a trait



Fullerton and Nurnberger (2019) *F1000Res*



Mavaddat *et al* (2015) *JNCI*

Computing Limitations of PRS

- Difficulty in predicting outcome in non-Eurocentric populations
- Dependent on quality and genetic variation of summary statistics i.e. size used, ascertainment, medical records, data clean up, SNPs vs large variations
- Not every trait with a summary statistics can be used
- Results of computation are **predictions** and have to be taken with a grain of salt

Kumar warms up container for hands on

Let’s try computing our own PRS for depressed patients who consume antidepressants

workshop.hail.is

Workshop name: `GenSpace2020`

Password: `pgx`

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How do you feel so far?

Advantages and Limitations with PRS?

CAN

- Differentiate between cases and controls
- Inform research on psychiatric or cardiovascular biomarkers for diagnosis or treatment
- Whether a trait is correlated with genetic polygenicity
- Guide genetic counselors to better understand the complex relationships between genetic and environmental risk.

CAN'T

- Individual level for diagnosis of disease
- Does not help with genomic testing for autism and developmental traits
- Cannot be used to substitute for family history in clinical assessment of disease
- Trait correlation for non-eurocentric population

Fullerton and Nurnberger (2019) *F1000Res*

Clinical Utility of PRS

- PRS-informed therapeutic intervention
- PRS-informed disease screening
- PRS-informed life planning

Clinical Applications of PRS

Lewis and Vassos (2020) *Genome Medicine*

What other examples can you think of the application of PRS in medicine especially in pharmacogenomics?

How would this impact you?

Condition	General Population Risk	Hypothetical PRS
Breast Cancer	12.5%	25%
Coronary Artery Disease	7%	12%
Schizophrenia	1%	5%

Additional information

How could this impact care?

	Breast Cancer	Coronary Artery Disease	Schizophrenia
Therapeutic intervention	Preventive surgery Risk reducing medications	Risk reducing medications (statins)	PGX tests or PRS for potential treatment medications
Disease Screening	Earlier and more frequent imaging OR Less frequent	Earlier and more frequent screening Monitoring additional risk factors	Earlier and a more accurate diagnosis
Life Planning	Healthy lifestyle Self-breast exams	Healthy lifestyle Routine physicals	Healthy lifestyle

Ethical Implications

??????????

Ethical Considerations

- Accurate only for individuals with 95% European Ancestry
- Confidence in the data
- Medical Guidelines
- Insurance coverage
- Life insurance coverage
- Exacerbate health inequities
- Stigmatizing or discriminatory

Recap

- What is personalized medicine?
- What did you learn about pharmacogenetics?
- Who is ready to do a direct to consumer genetic test?
- What did you learn about polygenic risk scores?
- What do you want to learn more about?

Notes for updates to Jupyter Notebook from Beth

What are we doing?

This hand-on workshop will allow you to explore a conventional approach to computing PRS using a ubiquitous genetics tool called PLINK.

Add hyperlink to PLINK

Problem statement: Scientifically, we know that approx 53-65% of patients with depression respond well to antidepressants.

(SSRIs).
Add this in case people don't know the abbreviation

Hypothesis: We hypothesize that this variability is potentially caused by genetic risk.

Scientific question/objective: Are individuals with higher depression PRS responsive to SSRI?

Step by step overview

Firstly...

We will obtain a reference data that contains effect sizes needed for calculating PRS.

The effect sizes (or summary statistics) that we will be using were generated from a reference data published by David Howard and co in *Nature Neuroscience* (2019). Their study attempted to understand the genetic risk of major depressive disorder in a very large collection of depressed patients. The reference data from this paper will contain effect sizes that we will need to calculate PRS in our test data which is a modified version of the 1000 Genomes Project.

Add hyperlink to the project