Current State and Barriers to Broader Implementation

Genevieve Wojcik, PhD MHS

On behalf of:

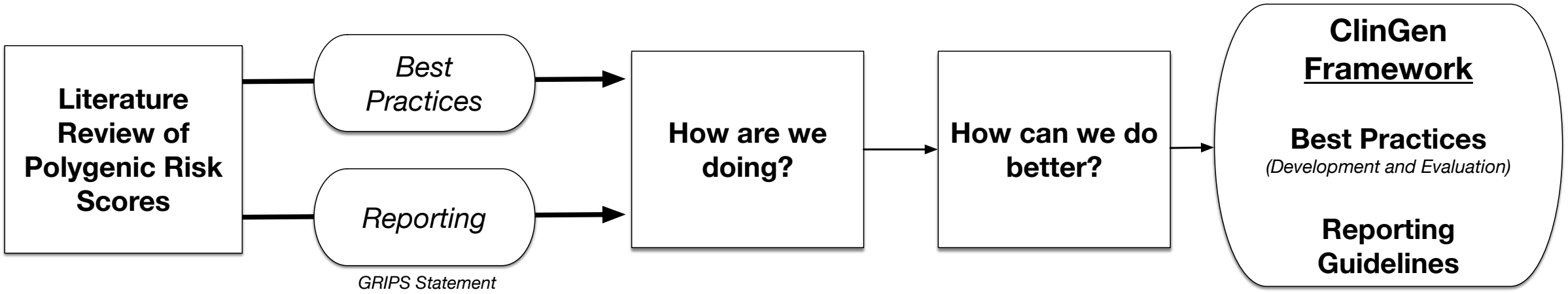
ClinGen Complex Disease Working Group *Hannah Wand, Carlos Bustamante, Kelly Ormond, Kim Ann Kinnear, Kate Rose Vlessis, Katrina Goddard, many others*

NHGRI *Robb Rowley, Catherine Sillari, Cecelia Tamburro*

ClinGen Complex Disease Working Group

Co-chairs: Katrina Goddard, Genevieve Wojcik

GOAL: Create a framework for evaluating and developing genetic risk scores



Collaboration with NHGRI

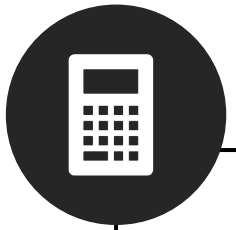
Preliminary Literature Review

- To assess the current state of the field, as well as the knowledge base of previous work

- Starting with 34 representative papers of from the field
  - Span numerous outcomes: Alzheimer’s disease, asthma, autism, breast cancer, cerebral vascular event, colon cancer, coronary artery disease, depression, fracture risk, Parkinson’s disease, prostate cancer, and schizophrenia

- The following summary based on preliminary results

Areas of Focus



Definition

- Review **heterogeneity in PRS definitions**, usage, outcomes, and subcomponents
- These often vary, even when applied to the same condition/outcome

Evaluation

- Adapt previously established GWAS evaluation criteria to assess **model development and performance**
- For example, how were SNPs selected and weighted?

Impact

- Select PRS publications that highlight potential **impact that PRS may have upon clinical care**, despite limitations.

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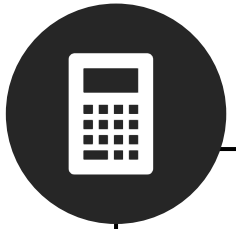

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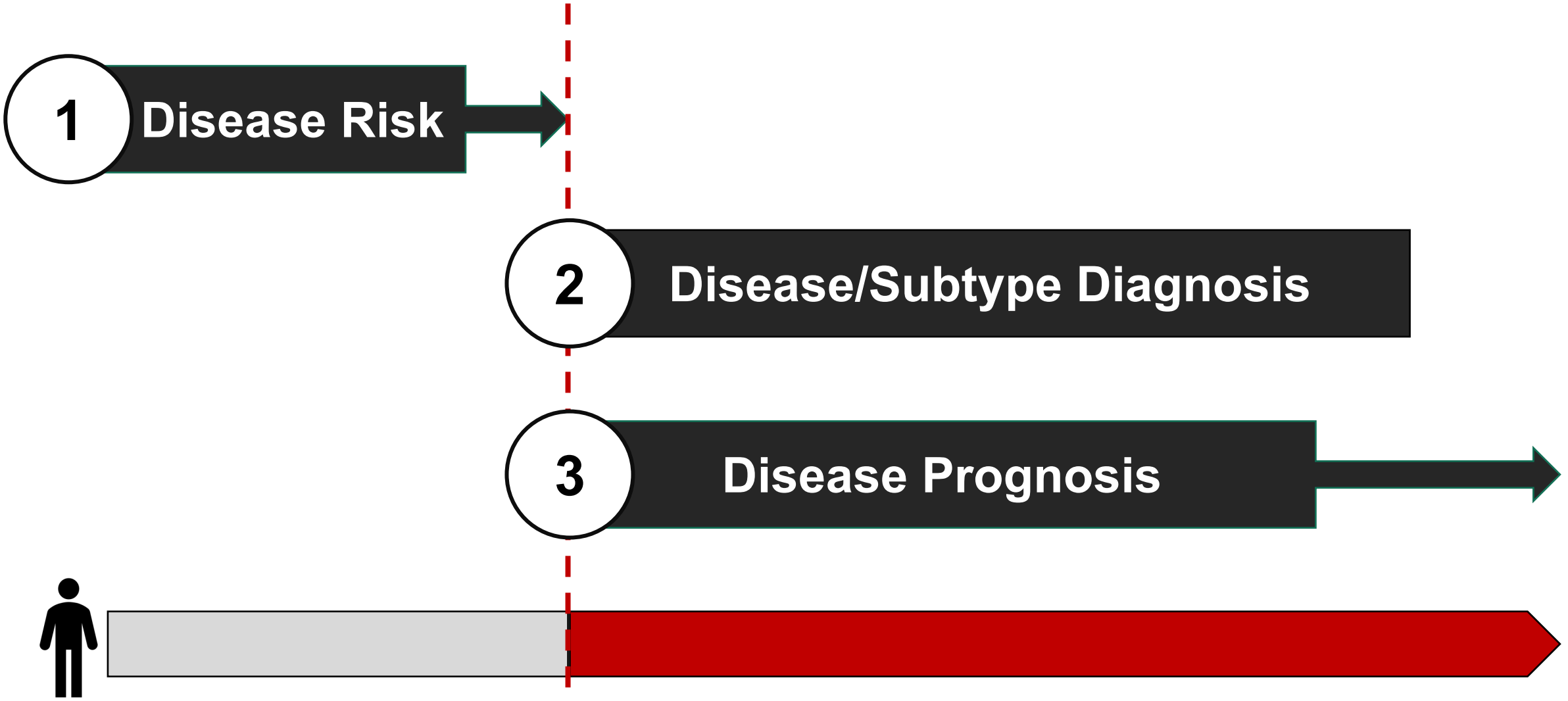
Main Uses of Polygenic Risk Scores



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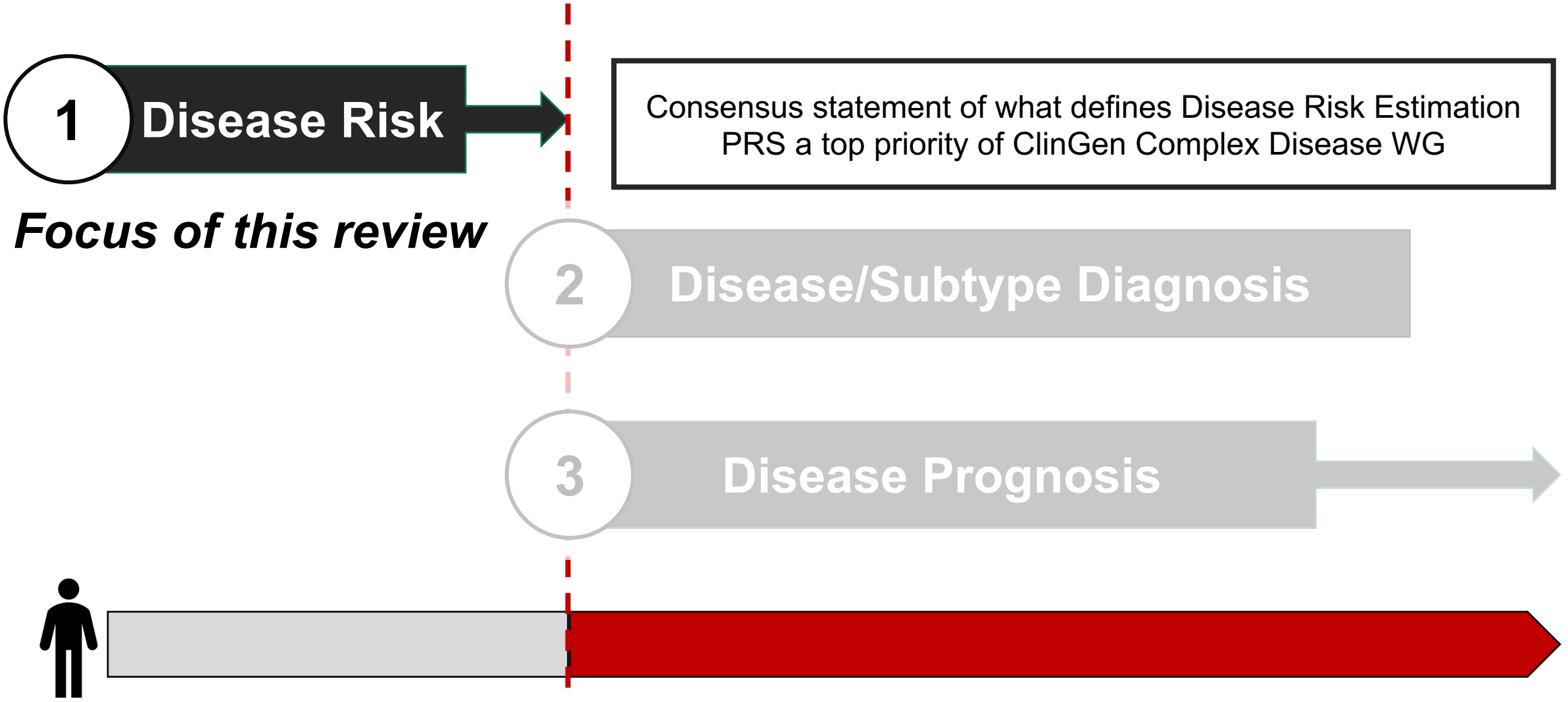
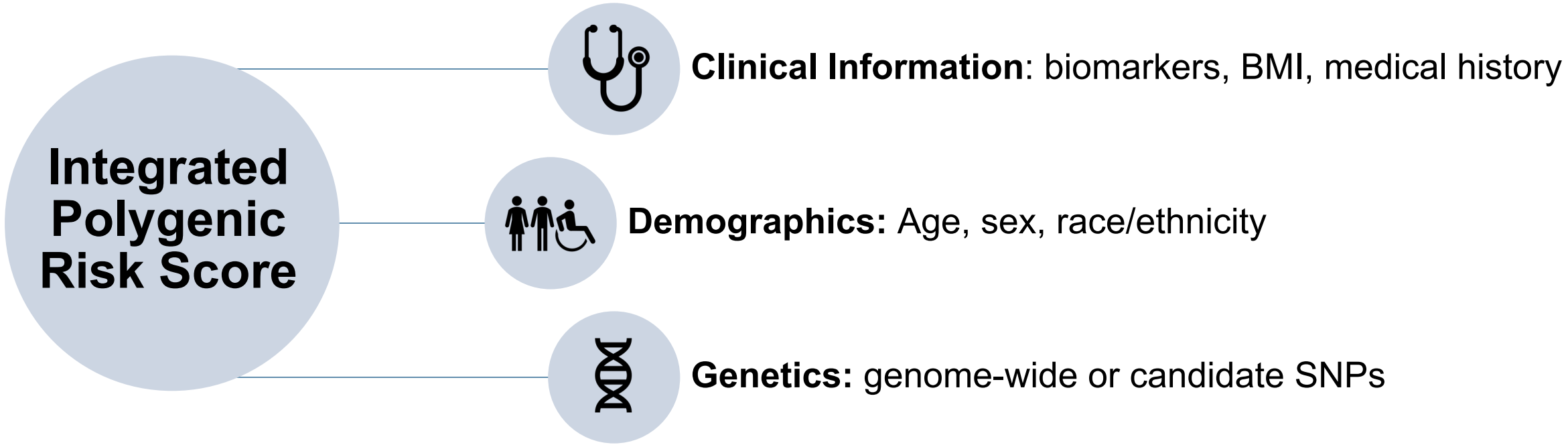


What goes into a polygenic risk score?



Example of inconsistency:
Race, Ethnicity, and Ancestry

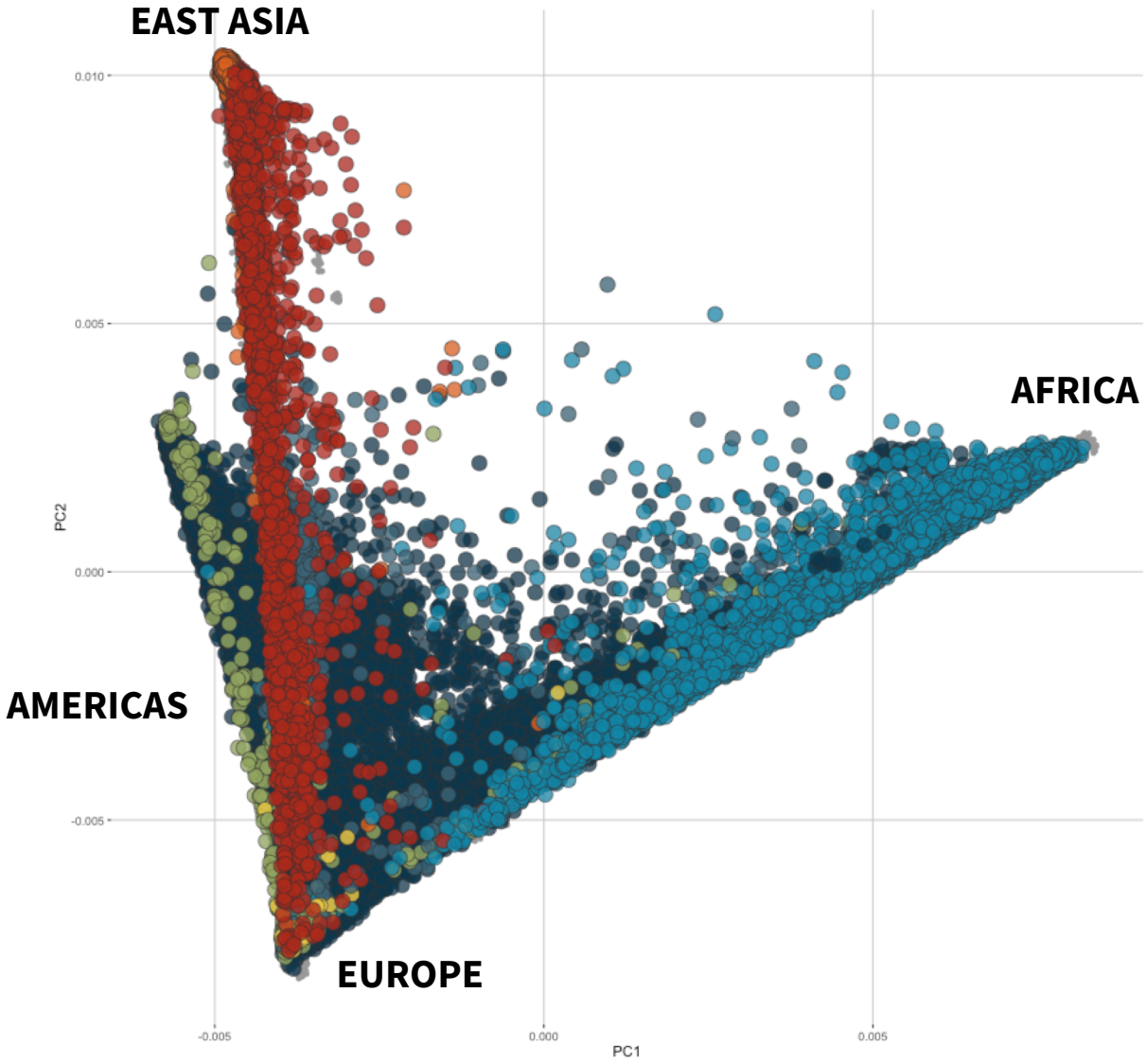
How do we define different groups (self-report, genetic components, etc.)?

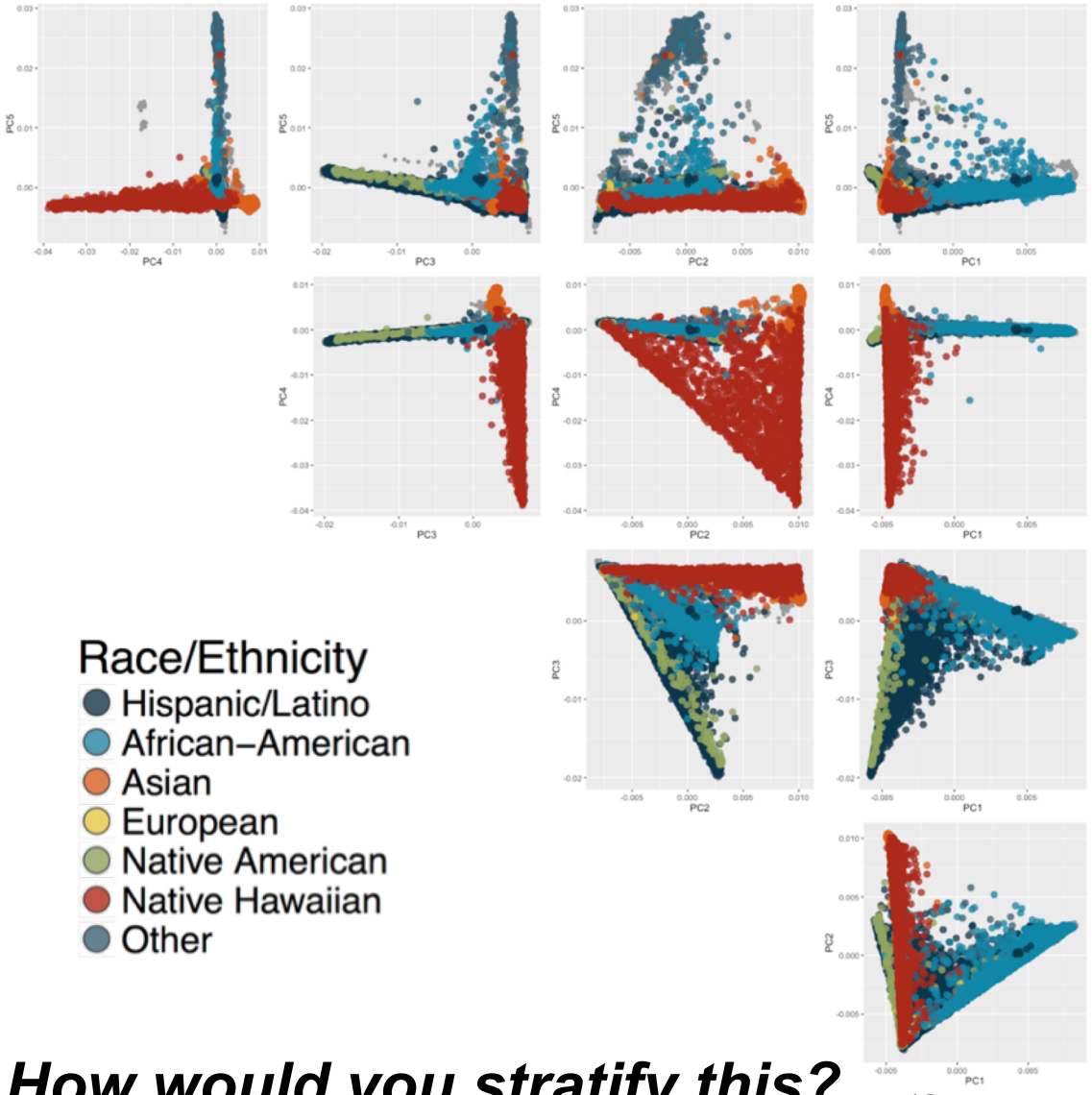
- Do we rely on self-reported race/ethnicity?
- Huo et al (2017)
  - African American: >50% African ancestry
  - European American: >90% European ancestry

- Many studies restricted to only those of European descent

- How do we stratify with admixed populations?

PAGE groups are not discrete.





How would you stratify this?

Example of inconsistency: **Race, Ethnicity, and Ancestry**

What effect does ancestry have on prediction?

"Flip-flopping" possible where non-European groups predicted to have lower risk. (Amanda Toland, 2019; Jennifer Litton, 2019)

It could have no effect at all. (Khera et al, 2016)

Overall may have reduced prediction accuracy given different genetic backgrounds. (Martin et al, 2019)

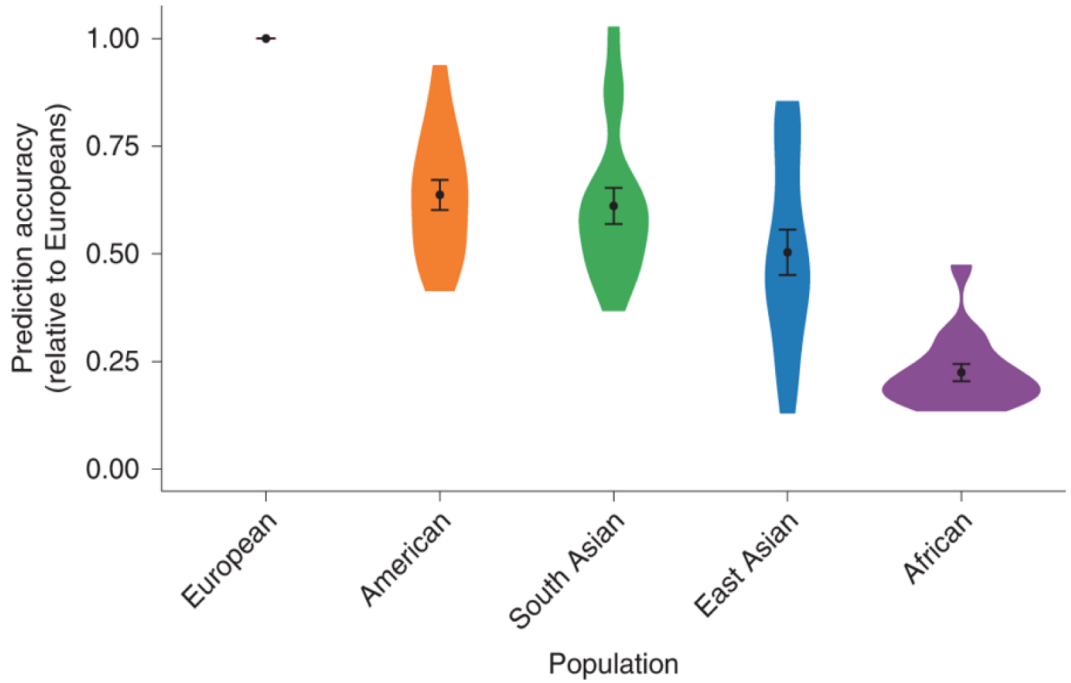


Figure 3 from Martin et al (Nature Genetics, 2019)

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EGAPP Analytical Framework (2009)

Evaluation of Genomic Applications in Practice and Prevention

1. Is it useful to do this in your population?
2. What is known about analytic validity of the test?
   - Assay sensitivity, specificity, robustness, etc.
3. What is the clinical validity of the test?
   - Clinical sensitivity, specificity, positive/negative predictive value, etc.
4. What are potential issues and what is the real impact on changing patient/consumer outcomes?
5. What are potential harms/issues in this population?
   - ELSI to be considered

The GRIPS Statement (2011)
Recommendations for reporting

Title and Abstract	Identify, use keywords: genetic/genomic, risk, prediction	
Introduction	Study objectives, specific models investigated	
Methods	*Study design*	Full description of study design and temporality, locations
	Participants	Eligibility criteria, sources/methods of selection
	Variables	Population, measurement, coding/inclusion
	Analysis	Risk model construction, validation, missing data, statistical methods
Results	*Participants*	Sample size, inclusion/exclusion criteria
	Descriptives	Population (demographic and clinical characteristics), model estimates (unadjusted and adjusted)
	Assessment	Model fit, predictive ability, other performance measures
	Validation	Validation of risk model(s)
Discussion	*Limitations*	Those concerning study design, participant selection, measurement and analyses, with their impact on results of study
	Interpretations	Overall interpretation with other relevant evidence
	Generalizability	Discuss generalizability and, if pertinent, health care relevance of results

Integrate standards and best practices from other fields such as biometrics, statistics, epidemiology, etc.

Annals of Internal Medicine

RESEARCH AND REPORTING METHODS

Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): The TRIPOD Statement

Gary S. Collins, PhD; Johannes B. Reitsma, MD, PhD; Douglas G. Altman, DSc; and Karel G.M. Moons, PhD

Biometrical Journal

Invited Review Article | Free Access

The Performance of Risk Prediction Models

Thomas A. Gerds, Tianxi Cai, Martin Schumacher

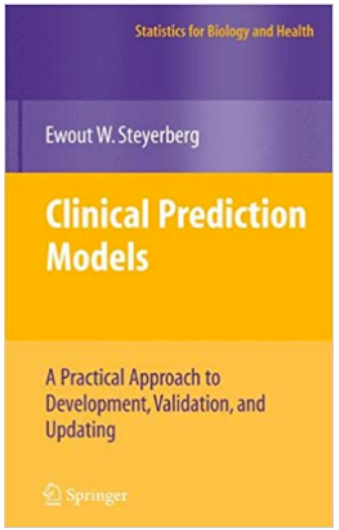
First published: 29 July 2008 | https://doi.org/10.1002/bimj.200810443 | Cited by: 104

ORIGINAL ARTICLE

Assessing the Performance of Prediction Models

A Framework for Traditional and Novel Measures

Ewout W. Steyerberg,[a] Andrew J. Vickers,[b] Nancy R. Cook,[c] Thomas Gerds,[d] Mithat Gonen,[b] Nancy Obuchowski,[e] Michael J. Pencina,[f] and Michael W. Kattan[e]



Special Report

Use and Misuse of the Receiver Operating Characteristic Curve in Risk Prediction

Nancy R. Cook, ScD

CLINICAL/NARRATIVE REVIEW

A Primer on Predictive Models

Akbar K. Waljee, MD, MS[1,2], Peter D. R. Higgins, MD, PhD[1] and Amit G. Singal, MD, MS[3,4]

Prediction research is becoming increasing popular; however, the differences between traditional explanatory research and prediction research are often poorly understood, resulting in a wide variation in the methodologic quality of prediction research. This primer describes the basic methods for conducting prediction research in gastroenterology and highlights differences between traditional explanatory research and predictive research.

Clinical and Translational Gastroenterology (2013) **4**, e44; doi:10.1038/ctg.2013.19; published online 26 December 2013
Subject Category: Clinical Review

Statistics in Medicine

Research Article

Evaluating the added predictive ability of a new marker: From area under the ROC curve to reclassification and beyond

Michael J. Pencina, Ralph B. D' Agostino Sr, Ralph B. D' Agostino Jr, Ramachandran S. Vasan

First published: 13 June 2007 | https://doi.org/10.1002/sim.2929 | Cited by: 2936

BEST PRACTICES

Model Development and Evaluation

nature REVIEWS GENETICS

Opinion | Published: 18 June 2013

Pitfalls of predicting complex traits from SNPs

Naomi R. Wray, Jian Yang, Ben J. Hayes, Alkes L. Price, Michael E. Goddard & Peter M. Visscher

Nature Reviews Genetics **14**, 507–515 (2013) | Download Citation

nature genetics

Analysis | Published: 03 March 2013

Projecting the performance of risk prediction based on polygenic analyses of genome-wide association studies

Nilanjan Chatterjee, Bill Wheeler, Joshua Sampson, Patricia Hartge, Stephen J Chanock & Ju-Hyun Park

Nature Genetics **45**, 400–405 (2013) | Download Citation

Cold Spring Harbor Laboratory

bioRxiv

THE PREPRINT SERVER FOR BIOLOGY

New Results

A guide to performing Polygenic Risk Score analyses

Shing Wan Choi, Timothy Shin Heng Mak, Paul O'Reilly

doi: https://doi.org/10.1101/416545

This article is a preprint and has not been peer-reviewed [what does this mean?].

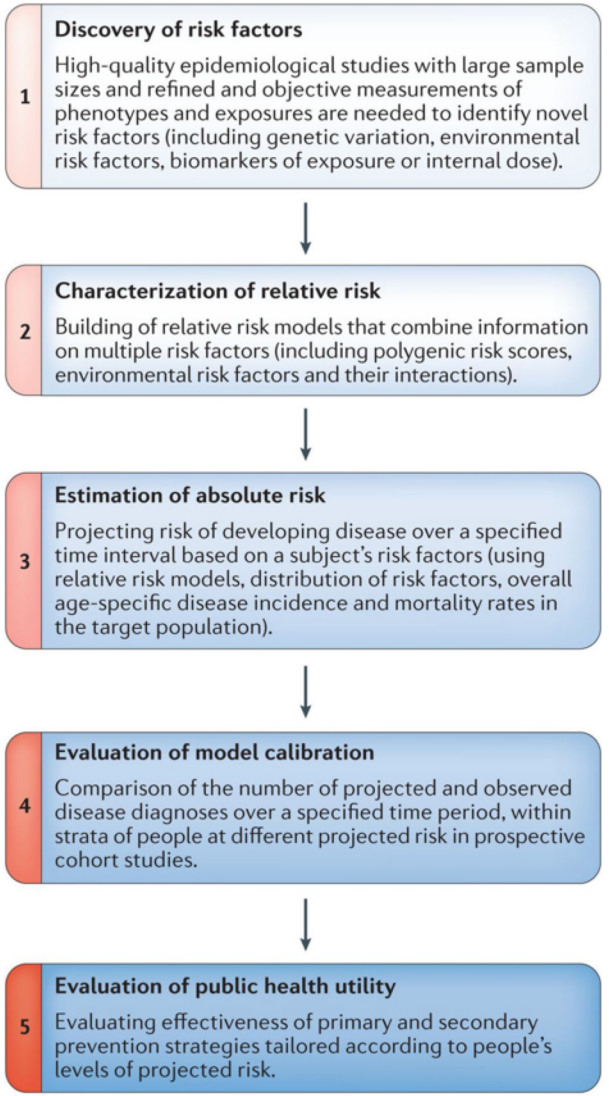
nature genetics

Technical Report | Published: 02 February 2015

LD Score regression distinguishes confounding from polygenicity in genome-wide association studies

Brendan K Bulik-Sullivan, Po-Ru Loh, Hilary K Finucane, Stephan Ripke, Jian Yang, Schizophrenia Working Group of the Psychiatric Genomics Consortium, Nick Patterson, Mark J Daly, Alkes L Price & Benjamin M Neale

Nature Genetics **47**, 291–295 (2015) | Download Citation



Building and evaluating absolute risk models for general population
(Chatterjee et al, 2016)

Variables that determine predictive abilities of PRS dependent on 5 factors.

(Chatterjee et al, 2013)

1. The number of true risk SNPs compared to total number included in model
2. The true effect sizes of risk SNPs
3. The chosen significance level for SNP selection
4. The power of underlying association test to reach that significance level
5. The expected value of the estimated regression coefficients and their squared values for selected SNPs

Preliminary conclusions

- Manuscripts vary widely in reported measures
- Validation practices are inconsistent
  - Internal, external validation
  - Validation absent completely in some
- Overall, reporting is inconsistent and it is difficult to judge the qualify of a score without complete methods details
- We hope to have a full round of reviews completed shortly, followed by expanding our review to get a better view of field.

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Several examples reveal potential of PRS in clinical care

Coronary Artery Disease

Inouye et al (2018)

- metaGRS constructed from 3 different published PRS
- Evaluated independently and integrated with traditional CAD risk clinical covariates
- Resulting model segregates groups into quintiles of risk, outperforming scores from *only* genetics or conventional risk factors.

Breast Cancer

Li et al (2017)

- BOADICEA: Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (family history)
- Combined 24 known breast cancer risk variants into score
- 14% of women would reached 20% lifetime risk with use of BOADICEA alone
- PRS would increase that number to 23%
- Best when both used to increase sensitivity

Future Impact

- PRS offer a method to tailor risk, based on a patient's unique genome, potentially improving risk identification and management.

- This remains to be tested, however, and requires adoption of common standards across studies to define clearly the outcomes and phenotypes the PRS are estimating.

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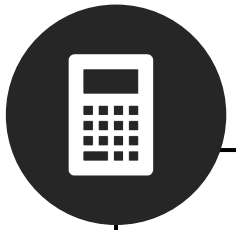

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Ongoing Work

Results expected this summer

Acknowledgements

NHGRI

Robb Rowley

Catherine Sillari

Cecelia Tamburro

ClinGen

Hannah Wand

Kelly Ormond

Carlos Bustamante

Katrina Goddard

Complex Disease Working Group

Stanford

Kim Ann Kinnear

Kate Rose Vlessis

ClinGen
Clinical Genome Resource

Interested in joining or being part of ongoing work?
Please let us know!

Contact me (gwojcik@stanford.edu) or
Hannah Wand (Hwand@stanfordhealthcare.org)

NIH
NHGRI

Some questions for you:

1. Concerns about PRS reporting?

2. What are priorities when assessing a published score?

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