Current State and Barriers to Broader Implementation

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On behalf of:

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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 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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Main Uses of Polygenic Risk Scores

1. Disease Risk
2. Disease/Subtype Diagnosis
3. Disease Prognosis
Main Uses of Polygenic Risk Scores

**Focus of this review**

1. **Disease Risk**
   - Consensus statement of what defines Disease Risk Estimation
   - PRS a top priority of ClinGen Complex Disease WG

2. **Disease/Subtype Diagnosis**

3. **Disease Prognosis**
What goes into a polygenic risk score?

**Integrated Polygenic Risk Score**

**Clinical Information**: biomarkers, BMI, medical history

**Demographics**: Age, sex, race/ethnicity

**Genetics**: genome-wide or candidate SNPs
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

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title and Abstract</strong></td>
<td>Identify, use keywords: genetic/genomic, risk, prediction</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td>Study objectives, specific models investigated</td>
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<tr>
<td><strong>Methods</strong></td>
<td>Study design: Full description of study design and temporality, locations</td>
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<td>Participants: Eligibility criteria, sources/methods of selection</td>
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<td></td>
<td>Variables: Population, measurement, coding/inclusion</td>
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<td></td>
<td>Analysis: Risk model construction, validation, missing data, statistical methods</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>Participants: Sample size, inclusion/exclusion criteria</td>
</tr>
<tr>
<td></td>
<td>Descriptives: Population (demographic and clinical characteristics), model estimates (unadjusted and adjusted)</td>
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<td>Assessment: Model fit, predictive ability, other performance measures</td>
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<td>Validation: Validation of risk model(s)</td>
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<tr>
<td><strong>Discussion</strong></td>
<td>Limitations: Those concerning study design, participant selection, measurement and analyses, with their impact on results of study</td>
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<td>Interpretations: Overall interpretation with other relevant evidence</td>
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<td></td>
<td>Generalizability: Discuss generalizability and, if pertinent, health care relevance of results</td>
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Integrate standards and best practices from other fields such as biometrics, statistics, epidemiology, etc.
BEST PRACTICES
Model Development and Evaluation

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 reach 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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Ongoing Work
Results expected this summer
Acknowledgements

**NHGRI**
Robb Rowley
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Cecelia Tamburro

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Hannah Wand
Kelly Ormond
Carlos Bustamante
Katrina Goddard
Complex Disease Working Group

**Stanford**
Kim Ann Kinnear
Kate Rose Vlessis

Interested in joining or being part of ongoing work? Please let us know!
Contact me (gwojcik@stanford.edu) or Hannah Wand (Hwand@stanfordhealthcare.org)
Some questions for you:

1. Concerns about PRS reporting?

2. What are priorities when assessing a published score?

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