Differential performance of polygenic risk scores across groups: real-world experience of the eMERGE Network

Malia Fullerton (University of Washington)

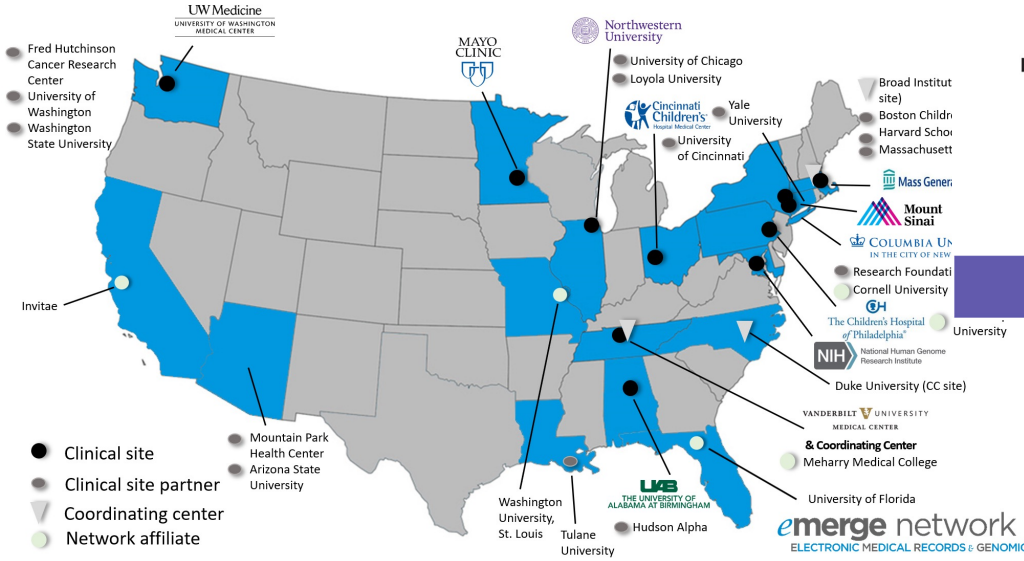
On Behalf of Co-Authors: **Anna C F Lewis**, Rex L Chisholm, John J Connolly, Edward D Esplin, Joe Glessner, Adam Gordon, Robert C Green, Hakon Hakonarson, Margaret Harr, Ingrid A Holm, Gail P Jarvik, Beth Karlson, Eimear Kenny, Leah Kottyan, Niall Lennon, Jodell E. Linder, Yuan Luo, Lisa Martin, Emma Perez, Megan J Puckelwartz, Laura J. Rasmussen-Torvik, Maya Sabatello, Richard R Sharp, Jordan W Smoller, Rene Sterling, Shannon Terek, Wei-Qi Wei

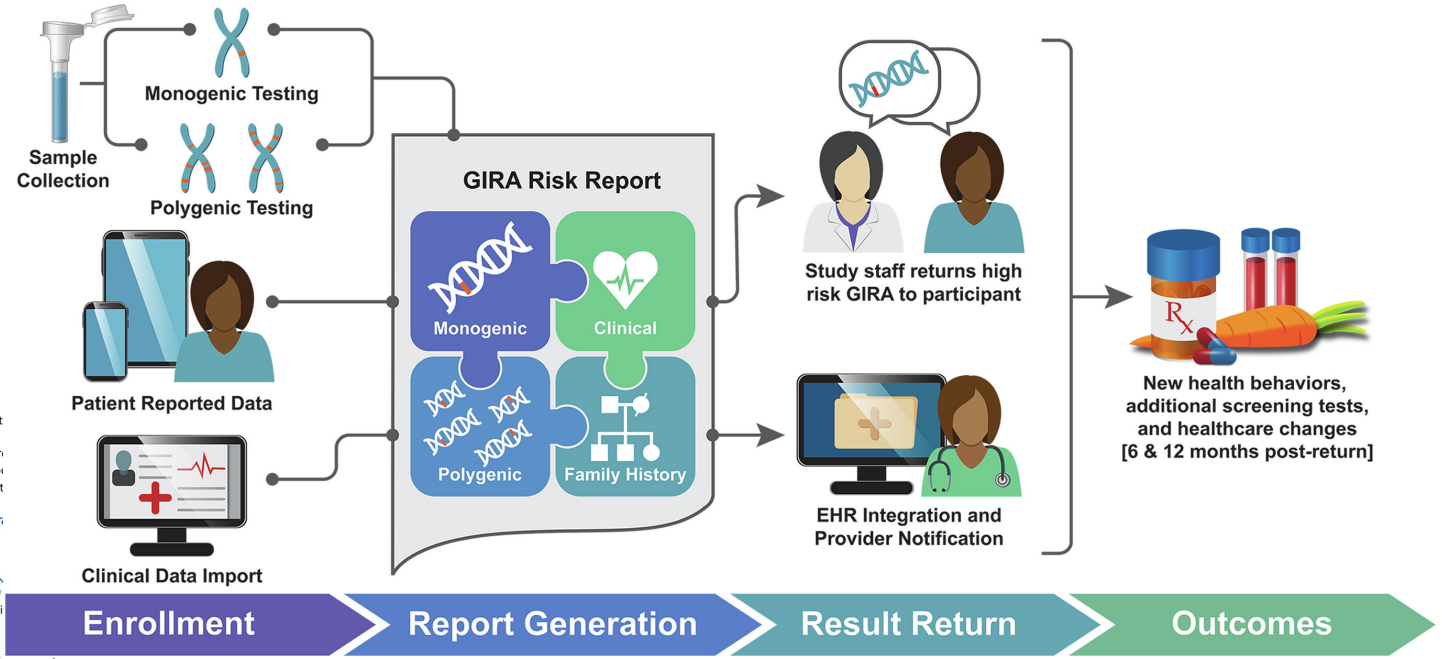
Disclosures

- I have no financial (or related) conflicts of interests to disclose

Electronic Medical Records & Genomics (eMERGE) Network

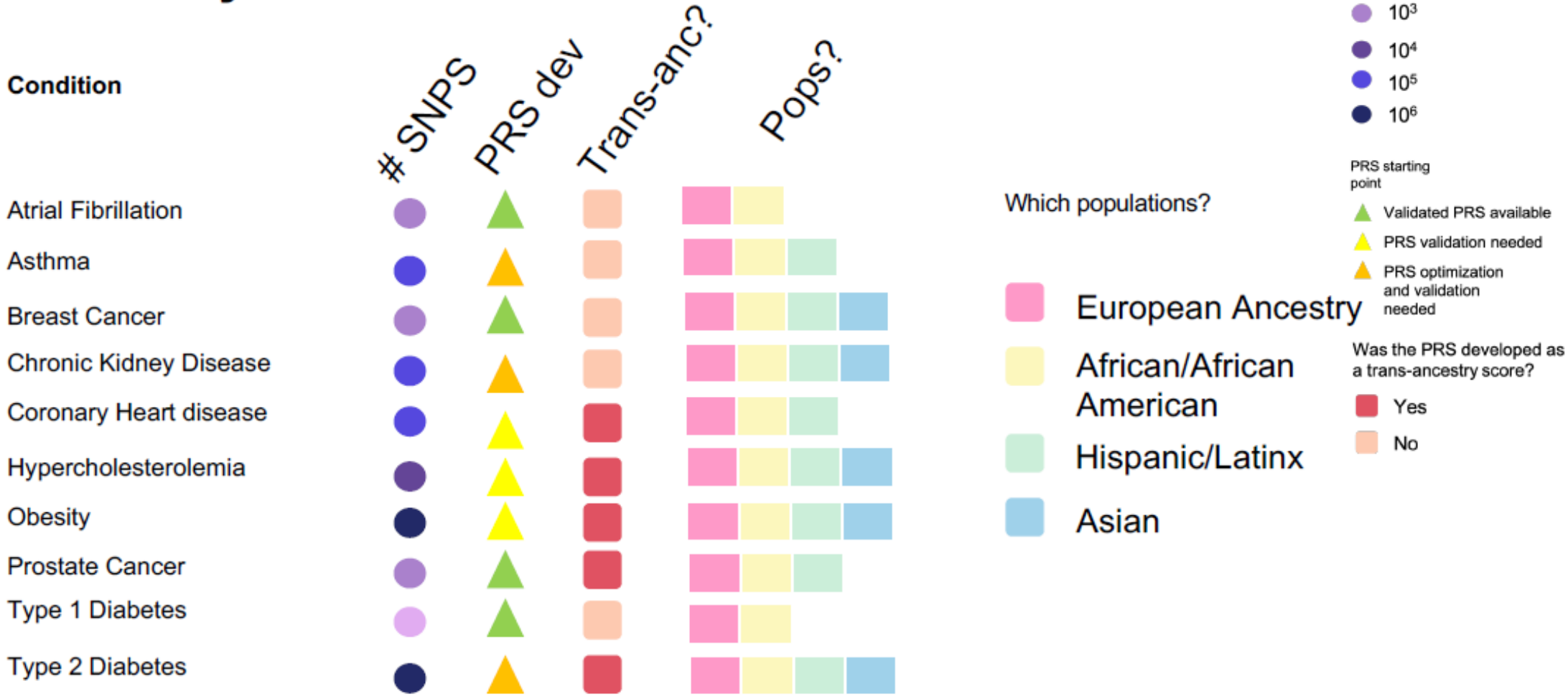
25,000 diverse individuals (3-75 yrs)
PRS for 10 conditions





Linder et al. (2023) *Genet Med*

Summary of PRS for 10 conditions selected



Decision Points and Ethical Considerations

How to define the groups used for validating PRS performance?	Use group-specific scores or the same score for everyone?	Include PRS for which it was not possible to validate in all the defined validation groups?	Communicate the differential performance between validation groups?	What terminology to use to describe the different validation groups?	How to explain the differential performance of the PRS reported?

How to define the groups used for validating PRS performance?

Use group-specific scores or the same score for everyone?

Include PRS for which it was not possible to validate in all the defined validation groups?

Communicate the differential performance between validation groups?

What terminology to use to describe the different validation groups?

How to explain the differential performance of the PRS reported?

Practical Problem:

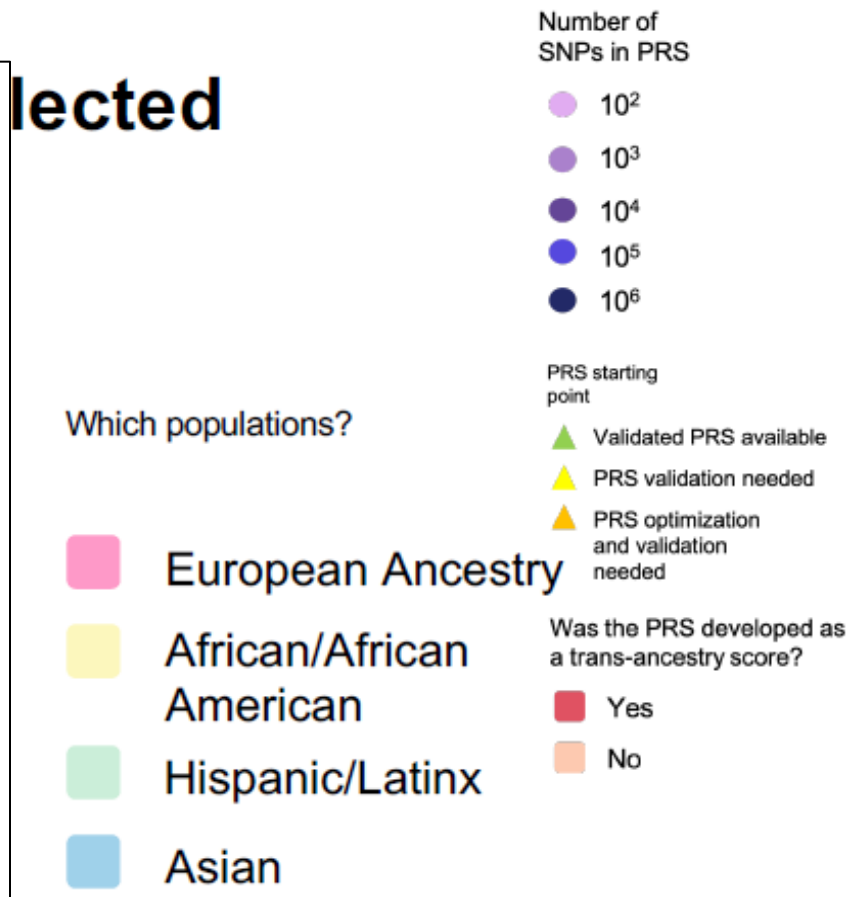
- Validation cohorts relied on different ways of measuring group membership, and used different population labels

Solution:

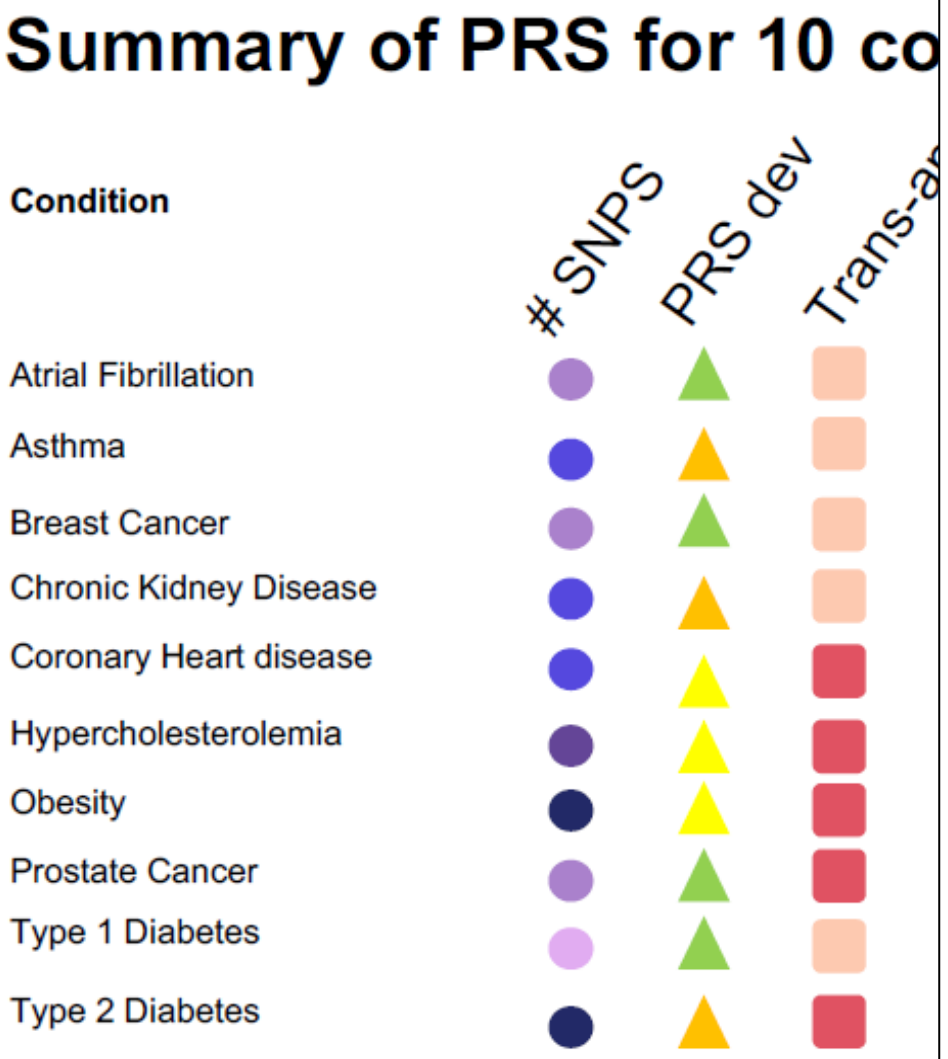
- Decided to validate PRS performance in as many as possible of four groups, designated *by the network* as European, African, Hispanic, or Asian

Implications/Limitations:

- Contributes to the conflation of genetically-inferred categories with social identities
- Fails to account for other human genetic variation known to exist, leaving many not represented



How to define the groups used for validating PRS performance?	**Use group-specific scores or the same score for everyone?**	Include PRS for which it was not possible to validate in all the defined validation groups?	Communicate the differential performance between validation groups?	What terminology to use to describe the different validation groups?	How to explain the differential performance of the PRS reported?



Practical Problem:

- PRS risk estimates may differ by group; if report group-specific scores, must decide what group the participant belongs in

Solution:

- Decided NOT to report group-specific scores
- The odds ratio (and CI) associated with the high-risk threshold was determined separately in each of the four groups for which there was sufficient data

Implications/Limitations:

- Range of ORs reported out, with group-specific differences noted at end of the GIRA
- Not really enough data to understand the broader clinical implications of different relative risks

How to define the groups used for validating PRS performance?

Use group-specific scores or the same score for everyone?

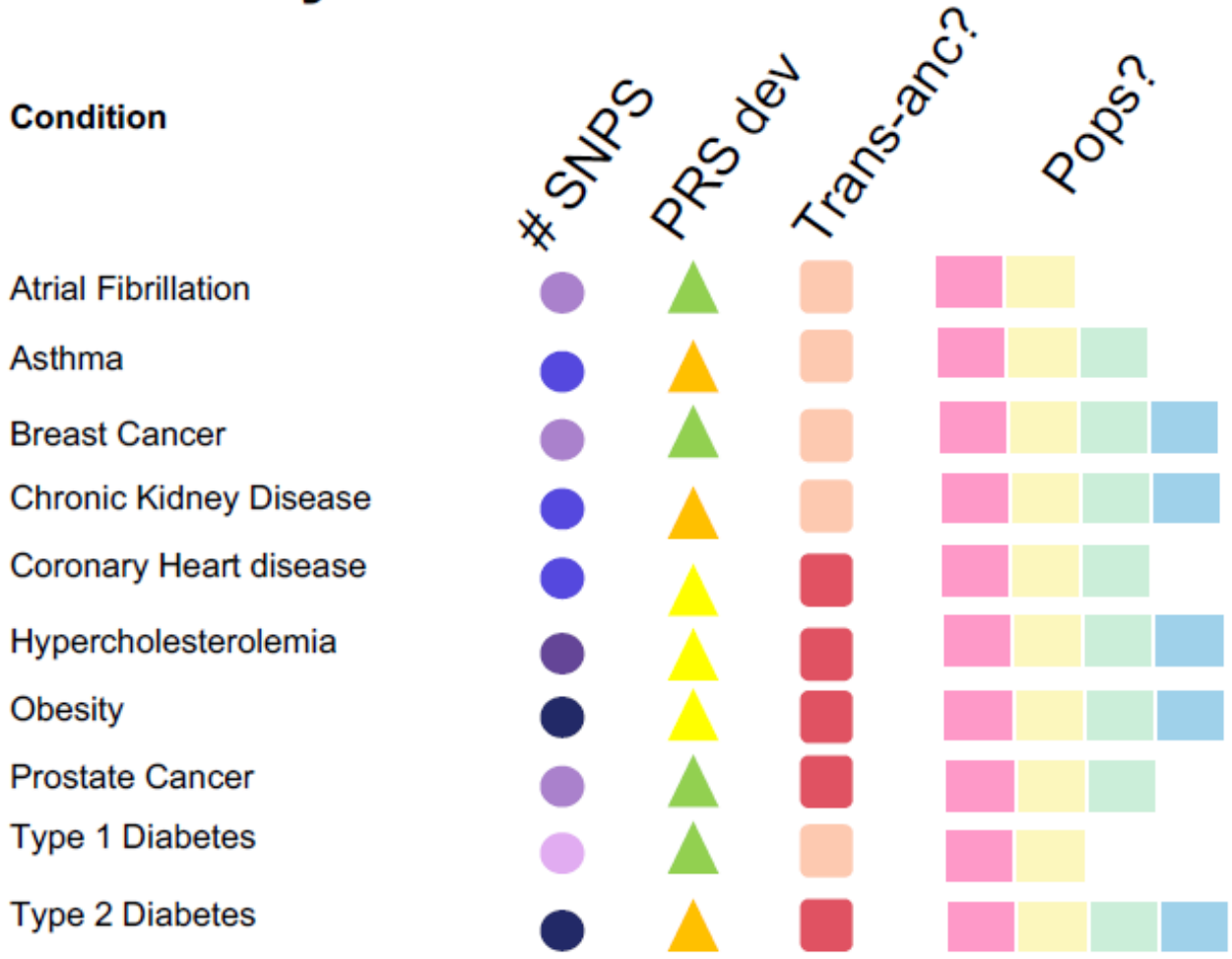
Include PRS for which it was not possible to validate in all the defined validation groups?

Communicate the differential performance between validation groups?

What terminology to use to describe the different validation groups?

How to explain the differential performance of the PRS reported?

Summary of PRS for 10 conditions



Practical Problem:

- Some PRS risk scores were not validated in all 4 groups

Solution:

- Decided to include PRS for traits that were only validated in 2 or 3 groups (based on empirical work suggesting participants were not concerned about missing/lower performance in non-Euro groups)

Implications/Limitations:

- Such limitations, where relevant, were noted in the GIRA
- As the range of risk estimates can vary by condition, the broader clinical implications remain unclear

How to define the groups used for validating PRS performance?

Use group-specific scores or the same score for everyone?

Include PRS for which it was not possible to validate in all the defined validation groups?

Communicate the differential performance between validation groups?

What terminology to use to describe the different validation groups?

How to explain the differential performance of the PRS reported?

Layered Communication Strategy

This participant is at high risk for the following condition(s)

Type 2 Diabetes	Risk Category: **Polygenic Risk** **Care Recommendations** •Emphasize a healthy lifestyle: –Exercise regularly. –Maintain healthy body weight. –Eat a heart-healthy diet. •For adults and children 12 and older: –Assess for symptoms such as polyuri –Consider a biochemical screen with f fasting glucose. –If elevated hbA1c or fasting glucose: –Consider prescription of metformin. –Consider medical nutrition therapy **References:** American Diabetes Association 2021 Preventionhttps://diabetesjournals.org/ Supplement_1/S34/30895/3-Prevention Diabetes-Standards

Polygenic Risk: High Risk

A high polygenic risk score for type 2 diabetes was found in this individual. A high polygenic risk
associated with 3-7 times increased risk for developing type 2 diabetes relative to a person not i
risk category. The data is based on populations of African, European, East Asian and Hispanic/La
Information is insufficient or not available for populations of other descent.

Results Summary

In this patient the Polygenic Risk Score for the following condition(s) was determined to be **HIGH***:

Type 2 Diabetes

*See detailed results for a description for how this risk was determined.

Detailed Results

This patient met the threshold for HIGH POLYGENIC RISK for the following condition(s):

Condition: Type 2 Diabetes

1. A high polygenic risk score for type 2 diabetes was found in this individual. A high polygenic risk score is associated with 2.6 to 6.9 times increased risk for developing type 2 diabetes relative to a person not in the high risk category. The data is based on populations of African, European, East Asian and Hispanic/Latino descent. Information is insufficient or not available for populations of other descent. Values within the top 2% of this polygenic risk score are associated with a 4.21 OR in European populations at a 95% CI [3.66-4.84], 2.55 OR for African populations at a 95% CI [2.09-3.11], 4.58 OR for Asian populations at a 95% CI [4.00-5.23], and 6.87 OR for Hispanic/Latino populations at a 95% CI [3.11, 15.15]. Information is insufficient or not available for populations of other descent.
2. Factors including monogenic disease risk, family history, and other clinical measures can have an impact on the individuals overall (absolute) risk and should be considered.
3. This participant was tested as part of the Electronic Medical Records and Genomics (eMERGE) Genomic Risk Assessment and Management Study. The participant's integrated Genome Informed Risk Assessment (GIRA) report will be generated which will incorporate the results from this report as well as family history and monogenic risk status, if available.

The PRS report **first** indicates in which conditions the individual is at high risk, and in the **detailed** results section gives both the aggregate range, odds ratio, and confidence interval for each group included in the validation.

To aid the conversation between p
where the patient participant ident
groups, we included the following
participants during recruitment:

*"If you do not identify with one of t
this with the study staff and your c
from groups you most closely iden
make informed decisions about yo*

Practical Problem:

- PRS risk estimates may differ by population group; if report group-specific scores, must decide what group the participant belongs in

Solution:

- Decided NOT to report group-specific scores
- The odds ratio (and CI) associated with the high-risk threshold was determined separately in each of the four groups for which there was sufficient data

Implications/Limitations:

- Range of ORs reported out, with population-specific differences noted at end of the GIRA
- Not really enough data to understand the broader clinical implications of different relative risks

How to define the groups used for validating PRS performance?

Use group-specific scores or the same score for everyone?

Include PRS for which it was not possible to validate in all the defined validation groups?

Communicate the differential performance between validation groups?

What terminology to use to describe the different validation groups?

How to explain the differential performance of the PRS reported?

Summary of PRS for 10 conditions selected

Practical Problem:

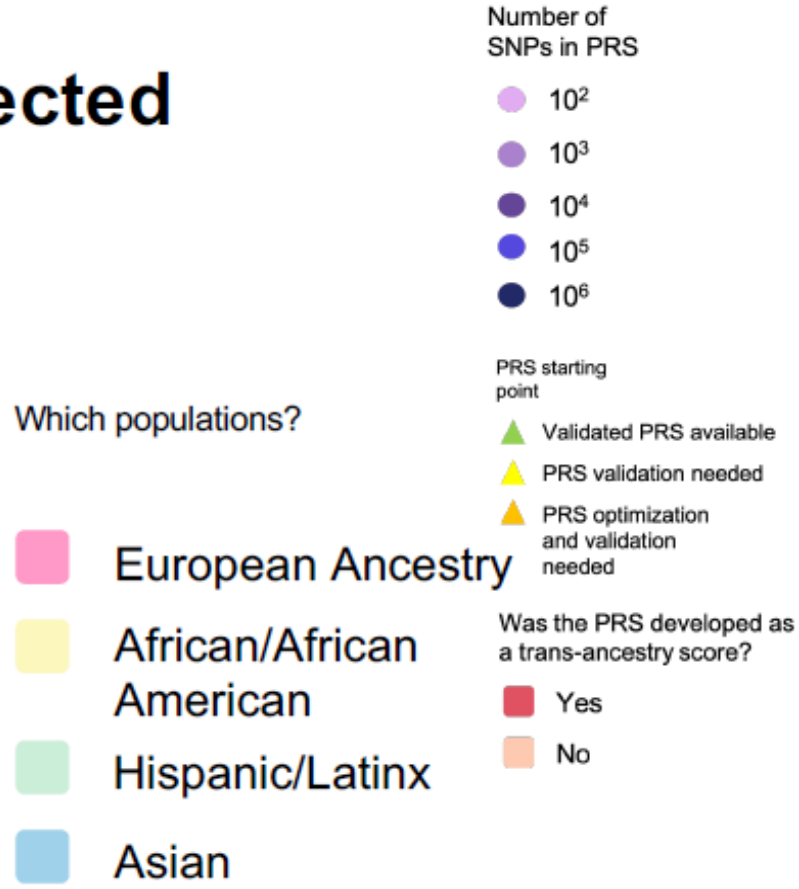
- "Population" as a group descriptor is often ambiguous, understood as people living in one area by the lay public – how best to describe?

Solution:

- Decided to use the term "descent" group, as recommended by a MGB community advisory board

Implications/Limitations:

- Not entirely clear if the substitution avoids conflation of genetically-inferred categories with social identities



How to define the groups used for validating PRS performance?

Use group-specific scores or the same score for everyone?

Include PRS for which it was not possible to validate in all the defined validation groups?

Communicate the differential performance between validation groups?

What terminology to use to describe the different validation groups?

How to explain the differential performance of the PRS reported?

Example language from GIRA limitations (similar in consent):

“Genetic research studies need large numbers of participants to understand how human DNA (or genes) contributes to disease risk. When research studies have low representation of some races, ethnicities, or ancestries (populations of descent), there is less genetic information available to understand risks for people in those groups. The GIRA health risk report has been validated (or confirmed) in up to four populations: Asian descent, African descent, European descent, or Hispanic/Latino descent. The report will name the populations included in the validation process. The estimate of risk may not be as accurate for some conditions if the participant is from a population that was not included in the validation process.”

Not really enough data to understand the broader clinical implications

In Conclusion

- Differential performance of Polygenic Risk Scores by population genetic background poses a number of practical difficulties for clinical genomics translation
- The eMERGE Network, an early attempt at large-scale implementation, relied on ELSI-led deliberation for guidance as it established its protocols and procedures in the face of these challenges; numerous limitations nevertheless still pertain
- The longer-term, clinical, implications of returning potentially inaccurate polygenic risk information remains to be determined