Population Discordance In Economic Evaluations of Polygenic Risk Scores: A Scoping Review

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Objective

- Explore population discordance between reference populations and modeled populations in economic evaluations of polygenic risk scores

Background

- Polygenic risk scores (PRS) calculate the risk of an individual developing a disease by aggregating variants at a variety of genetic loci.
- These scores are developed from databases of individuals who have undergone genetic testing, the majority of which are of European ancestry, which may reduce accuracy in non-European populations.
- Economic models of PRS that do not explore accuracy across diverse populations may inaccurately estimate the value of testing resulting in inappropriate coverage, reimbursement, and clinical implementation decisions.

Methods

- We conducted a scoping review of the literature through November 30th, 2021.
- Papers were included if they were an economic model assessing the impact of PRS testing in influencing screening approaches, published in a peer-reviewed journal or on a pre-print server, and available in English.
- We searched PubMed and EMBASE using terms related to PRS and economic evaluation and identified additional literature through snowballing sampling from reference lists, including preprints.
- Data was abstracted from full manuscripts using a standardized template.

Population discordance was defined as occurring where authors:

Did not state the race or ethnicity of the population modeled in the economic analysis or to derive the PRS

OR

Modeled a population that did not match the population used to derive the PRS

Model Characteristics

Economic Model	PRS Development	Race and Ethnicity of the Population(s) Modeled	Race and Ethnicity of Population(s) Used to Develop the PRS	Population Discordance
Jarmul (29650716)	Mega (25748612)	American	Swedish, White, Other	Yes
Pashayan (29978189)	Michailidou (29059683)	English or Welsh	East Asian, European	Yes
Callender (31860675)	Dadaev (29892050)	British	European	Yes
Naber (32025627)	Dunlop (22490517)	American	American, Australian, British, Canadian, German, Spanish	Yes
Cenin (31748260)	Jenkins (26846999)	Australian	European[3]	Yes
Guinan (33032912)	Tremblay (34226943)	Canadian, White	European, British (White)	Yes
Hendrix (34023874)	Liss (25982801)	American	White (Non-Hispanic), European	Yes
Karlsson (33630863)	Ström (29331214)	Swedish	Swedish	No
Liu[1]	Craig (31959993)	Australian, British	British[4], European	Yes
Thomas (34039685)	Huyghe (30510241)	British	East Asian, European	Yes
Wong (33892705)	Unpublished data[2]	Singaporean	Unknown	Yes

Papers labeled by First Author (PMID)
1: Published as a pre-print, DOI: https://doi.org/10.1101/2021.02.18.21251906
2: Methods for data collection or development not cited or discussed in manuscript
3: Used a simulated model of European patients
4: British population derived from UK Biobank, ~90% White

Results

- 11 papers or preprints met inclusion criteria.
- Ten of these papers exhibited population discordance, with most papers using a PRS developed in a subset of the population and extrapolating the risk to the larger population.
- No model explicitly considered discordance in their methods, results, or discussion.
- No models used adjustments for discordance in their primary analysis.
- One model, Karlsson et al used a Swedish population for their model, and a PRS score developed in a Swedish population, and one model, Naber et al, considered discordance in the sensitivity analysis.

Limitations and Future Work

- Word count limits may have prevented authors from including sensitivity analyses in the main paper or appendices.
- Lack of PRS validation in diverse populations may have prevented authors from explicitly modeling diverse population outcomes in their analysis.
- Future work by this group will include an expansion of this analysis to genetic testing in cancer, as well as germline pharmacogenomic testing for a variety of conditions.

Conclusions

- Future economic models PRS should be explicit about the genetic ancestry of simulated patients in their analysis and those used to develop the PRS.
- These approaches should be transparent about population discordance and consider testing the impact of discordance on the uncertainty of model findings
- Economic analyses may be viewed an alternative to clinical trials for large genetic studies, such as the implementation of PRS into clinical practice. Just as clinical trialists strive to include diverse populations in their analysis, so should modelers.

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