Background: Glaucoma is the primary contributor to irreversible blindness globally. Given its high heritability, polygenic risk scores (PRS) have emerged as a useful tool for glaucoma risk stratification. The latest multi-ancestry glaucoma PRS demonstrated good performance across major ancestries and has entered clinical use. However, the training and validation data of the glaucoma PRS primarily consist of Northwest Europeans, Chinese, and Indians, leaving its effect and utility uncertain in underrepresented populations. This study aimed to calibrate the multi-ancestry glaucoma PRS in seven underrepresented populations (Vietnamese, Filipino, Sri Lankan, Middle Eastern, Italian, Greek, and Hispanic) that form large communities in Australia.

Methods: We recruited participants from Australian hospitals and clinics, supplemented by established projects including the Genetics of Glaucoma, the Australian and New Zealand Registry of Advanced Glaucoma, the QSkin Sun and Health Study, and CARTaGENE. We leveraged birth country and ethnic background data from the UK Biobank (UKB) and 1000 Genomes as reference panels for genetic similarity clustering to infer genetic ancestries for underrepresented groups in our study. We calibrated the multi-ancestry glaucoma PRS, developed using data from over six million individuals across multiple cohorts, including the UKB. We employed logistic regression to assess PRS contribution to glaucoma risk, quantified as odds ratios (OR) per standard deviation (SD), while adjusting for sex and age. We compared these findings with those from well-represented populations, including Northwest Europeans, Indians, and Chinese. Additionally, we used our estimated PRS effects to calculate population-specific absolute risk, with baseline prevalences and age estimates derived from meta-analyses of previous population-based studies.

Results: The glaucoma PRS was significantly associated with glaucoma risk across seven targeted populations. ORs per SD of PRS ranged from 1.76 for Filipinos to 3.46 for Sri Lankans. The predictive performance showed moderate discrimination, with AUC values from 0.70 to 0.79. Comparative analysis showed that performance metrics were not statistically different for most studied populations compared to their respective most genetically similar, overrepresented counterparts. Notable variations in absolute risk were observed across ancestries, attributed to differences in PRS effects, baseline prevalences, and age effects.

Conclusions: Our findings confirm that glaucoma PRS effectively stratified high-risk individuals in underrepresented populations and could support absolute risk estimation. We observed variations in absolute risk in some ancestries, and larger diverse ancestry cohorts are required to optimise population-specific calibration; this will help ensure equitable access to personalised glaucoma risk prediction.