Title: Addressing equity in exome sequencing: Proactive reanalysis helps to reduce racial, ethnic, and ancestral disparities

Authors: Andrew Giles, Kimberly Zayhowski, Aidan O'Hara, Maggie Ruderman, Meghan Towne

Objectives: Race, ethnicity, and ancestry (REA) are associated with diagnostic utility of multi-gene panel testing. Specifically, non-European populations are generally less likely to receive a positive result and more likely to receive an uncertain result compared to people of European ancestry. This disparity is contributed to, in part, by a lack of diverse representation in population genomic databases used for variant interpretation. Diagnostic yield by REA has not been comprehensively evaluated for exome sequencing (ES) cohorts, especially in the context of ES reanalysis. This study aims to investigate the associations between REA and ES diagnostic yield and outcomes of ES reanalysis.

Methods: We performed a retrospective review of 10,921 probands sent for clinical ES to a clinical laboratory between 2011 and 2021. Diagnostic yield (original and after reanalysis), reanalysis rates and initiators (provider, laboratory, family studies), and reclassification rates and contributing evidence type (gene, variant, clinical overlap) were analyzed by patient REA, as reported on their test requisition form.

Results: Diagnostic yield for the total cohort had a relative increase of 19% (21% vs. 25%). When accounting for confounding variables of age, sex, and clinical indication, patient REA was found to be significantly associated with diagnostic yield before ($p=0.004$) and after reanalysis ($p<0.001$), reanalysis rates ($p<0.001$) and initiators ($p=0.038$), and reclassification rates ($p=0.030$). The African American and Black cohort was consistently left behind, with among the lowest diagnostic yield, reanalysis rates, and provider-initiated reanalysis rates. While patients in the African American and Black cohort were among the least likely to receive reanalysis ($p<0.001$), when performed, they were among the most likely to result in reclassification ($p=0.04$). Conversely, the White cohort was the most likely to receive reanalysis and among the least likely to result in reclassification.

Conclusions: ES reanalysis provides an increase in diagnostic yield across all REA cohorts. However, the diagnostic yields, uptake, and success of ES reanalysis are significantly impacted by patient REA. This study suggests that laboratory-initiated reanalysis can help reduce disparities in ES utility between REA groups.

These trends were most prominent in the African American and Black cohort. Reanalysis was least likely to be initiated for the African American and Black cohort ($p<0.001$); however, when performed was among the most likely to result in reclassification ($p=0.04$). Conversely, the White cohort was the most likely to receive reanalysis and among the least likely to result in reclassification. The AAB cohort had the highest rates of laboratory-initiated reanalysis and lowest rates of provider initiated reanalysis.