Applying Confidence Intervals to Clinical Polygenic Risk Scores in 60,000 Exome+ Sequenced Individuals

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The Polygenic Risk Score (PRS) is an emerging tool for the clinician to understand an individual's genetic risk of disease by stratifying their score into categories based on many common genetic variants and has been applied to common diseases such as Type 2 Diabetes (T2D), Coronary Artery Disease (CAD), and Prostate Cancer (PCa). The majority of these PRS have been developed thus far using microarray technology but recently this research is shifting towards utilizing sequencing. Applying previously developed PRS to sequenced samples presents a technical challenge of how to leverage low confidence sequencing calls. Conservative PRS methods would no-call these sites, substituting population allele frequency for the low confidence call. However, while these methods maintain high confidence results by restricting the reportable range, ignoring sequencing information potentially leads to erroneous categorization. Utilizing lower confidence calls may improve the accuracy of correctly categorizing an individual's disease risk, but requires capturing potential error to approximate the likelihood of misclassifying an individual's result. The confidence in risk estimation should be utilized to determine when a PRS test is inconclusive.

In this study, we developed a method for reporting PRS confidence in clinical tests by utilizing known sequencing and imputation error rates to provide confidence intervals together with disease risk estimates. We applied this method to T2D, CAD, and PCa tests for 60,000 individuals sequenced using Helix's Exome+. Utilizing this dataset, which targets exons and common variants, we show that an individual's genotype can often score in close proximity to a category boundary with confidence intervals that span different categories, leading to a higher likelihood of an inconclusive result. We also report how altering acceptable risk thresholds affects the tradeoff between sensitivity and accuracy, such that a more restrictive cutoff produces more inconclusive results. Finally, we applied this method to standard coverage whole genome sequencing (WGS) and low coverage WGS, showing that it can be applied across multiple sequencing data types.