Adjusted Polygenic Risk Score Enables Personalized Cardiovascular Disease Prevention and Clinical Management

EE77

Nikolaos Panagiotou[1], Fragkiskos Bersimis[2], Thanos Fotis[3], Eleni Ntoumou[1], Effie Salata[1], Evi Chatziandreou[4]

[1]iDNA Genomics, Kifisia, Greece
[2]University of Piraeus, Department of Statistics and Insurance Science, Greece
[3]Covariance, Kifisia, Greece
[4]Theracell Advanced Biotechnology, Kifisia, Greece

Introduction

Assessing the risk of cardiovascular disease is central to early detection, prevention, and clinical decision-making. To date, clinical risk prediction relies on demographic characteristics, lifestyle, health parameters and family history. Routine genetic testing, however, is absent from this list. Yet, genetics are the earliest measurable contributor to common adult-onset disease risk. Novel genetic profiling methods have been developed to estimate the probabilistic susceptibility (i.e., predisposition) of an individual to disease, based on their Polygenic Risk Score (PRS). That is a weighted sum of the number of risk alleles carried by an individual, where the risk alleles and their weights are defined by their measured effects as detected by Genome Wide Association Studies (GWAS). The aim of this study was to develop a PRS and an adjusted PRS, which estimates a combined risk by incorporating lifestyle and phenotypic characteristics, for use in medical practice to personalize and enhance cardiovascular disease prevention.

Methods

We developed a novel PRS to estimate comprehensive risk for six common cardiovascular conditions, comprising coronary artery disease, dilated cardiomyopathy, hypertrophic cardiomyopathy, atrial fibrillation, ischemic stroke, and heart failure. Specifically, we designed three unique algorithms to i) search for statistically significant Single Nucleotide Polymorphisms (SNPs) associated with disease predisposition in major databases with published GWAS, ii) detect the appropriate SNPs by assessing p-value, beta coefficient, odds ratio, and linkage disequilibrium metrics, and iii) calculate PRS for each cardiovascular condition under investigation. We then examined risk categorization on a population level (n=447). Finally, we employed the American Heart Association's Life's Simple 7 (LS7) lifestyle and phenotypic characteristics scoring system to assess an individual's cardiovascular health status. Using LS7 categorization, we were capable to generate an adjusted PRS that can dynamically fine-tune risk prediction based on current health status and age.

Results

We developed and employed a PRS methodology, termed iDNA Cardio Health, that allowed us to estimate and stratify genetic risk for a series of cardiovascular diseases, following genotyping of DNA that was isolated from buccal swab samples. Based on published disease prevalence data [**1,2**], the PRS was then divided in three categories: i) low risk (PRS < 20%), ii) intermediate risk (PRS 20-80%), and iii) high risk (PRS > 80%) (**Figure 1**).

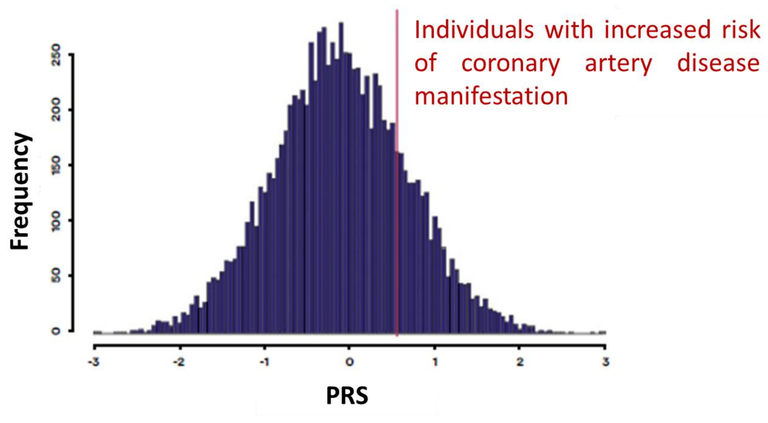

Figure 1: Example of Polygenic Risk Score (PRS) distribution in a population and high-risk categorization (PRS > 80%) for coronary artery disease.

The PRS data that were calculated for a Greek population (n=447), were further analyzed, and risk stratification was specifically examined for a series of cardiovascular diseases, including coronary artery disease, dilated cardiomyopathy, hypertrophic cardiomyopathy, atrial fibrillation, ischemic stroke, and heart failure (**Figure 2**).

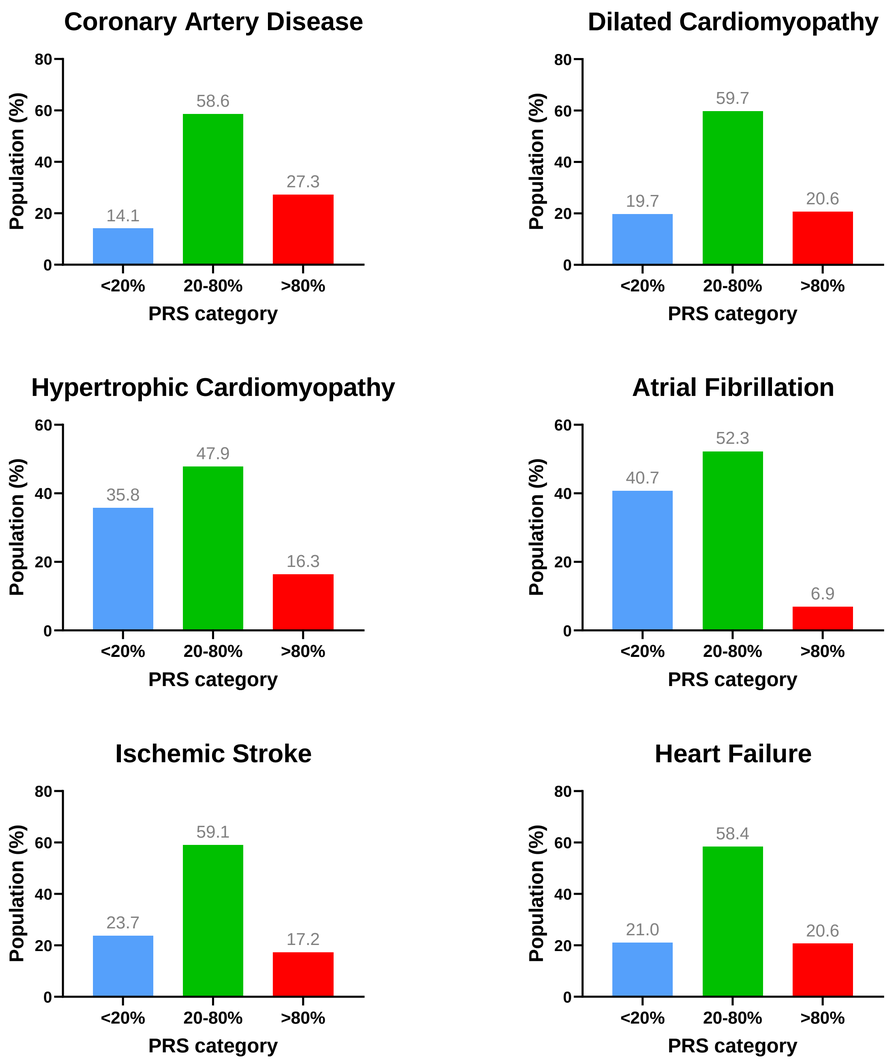

Figure 2: Percentage of the population (n=447) classified per Polygenic Risk Score (PRS) category [Low risk (<20%), intermediate risk (20-80%), high risk (>80%)] for coronary artery disease, dilated cardiomyopathy, hypertrophic cardiomyopathy, atrial fibrillation, ischemic stroke, and heart failure.

Our PRS stratification data suggest that we can identify a percentage of the population that is at high risk and could thus benefit from lifestyle changes and a preventive medicine approach [**3**]. Nevertheless, to further improve risk prediction with the use of PRS, we aimed to incorporate commonly examined cardiovascular disease clinical risk factors. Specifically, we employed the Life's Simple 7 (LS7) (**Figure 3**) questionnaire and scoring system to produce a PRS that combines lifestyle and phenotypic parameters [**4**], termed adjusted PRS.

Figure 3: American Heart Association's (AHA) Life's Simple 7 (LS7). Using the best available evidence, the AHA developed the LS7, which comprises the seven most important predictors of heart health to define and highlight a pathway for achieving ideal cardiovascular health. It includes four modifiable behaviors (not smoking, healthy weight, eating healthy and being physically active) and three biometric measures (blood pressure, total cholesterol and blood sugar / glucose).

Employing the LS7 methodology, individuals can also be categorized in three distinct categories of cardiovascular health status: i) poor, ii) intermediate, and iii) ideal. Hence, following LS7 classification, PRS data can be dynamically adjusted, also depending on chronological age, to depict a combined score of genetic, lifestyle, and phenotypic parameters. Therefore, current cardiovascular health can significantly impact upon the existing genetic risk estimated with a PRS and affect the adjusted PRS (**Figure 4**).

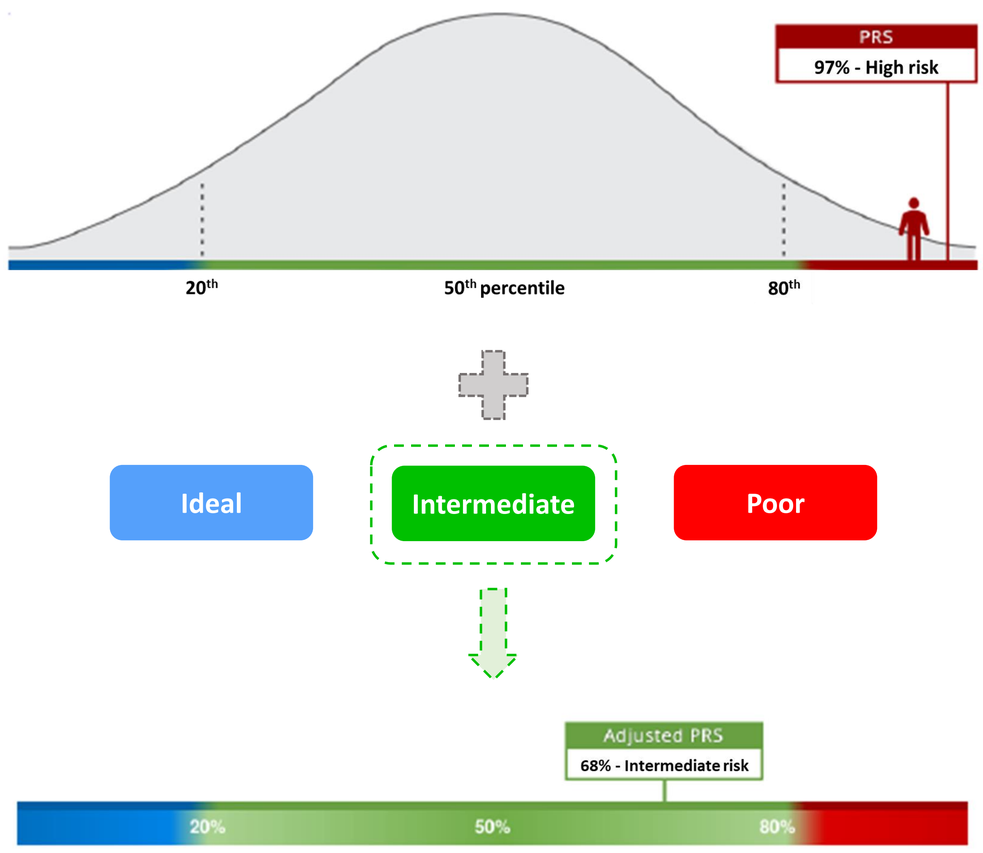

Figure 4: Example of adjusted PRS estimation by combination of a high risk PRS (97%) with an intermediate status of current cardiovascular health assessed following LS7 categorization criteria, for a 50-year-old individual.

Discussion

PRS estimation can significantly improve upon the current issue of cardiovascular disease risk underestimation, enhance compliance and intervention efficiency, and identify high-risk individuals who are expected to experience higher benefits following primary prevention, such as statin therapy [**1-3**]. Moreover, as others have recently indicated [**5**], PRS implementation can reduce the average healthcare costs, improve Quality-Adjusted Life Years (QALYs), and prevent future cardiovascular events, with significant benefits in young individuals with borderline/intermediate risk. Finally, our novel adjusted PRS methodology, that at its core encompasses genetic risk, can then be combined with traditional clinical risk prediction metrics to revolutionize cardiovascular risk detection, monitoring, and disease prevention, thus enabling a personalized medicine approach.

References

1. Torkamani *et al.* The personal and clinical utility of polygenic risk scores. Nature Reviews Genetics, 2018. 19(9): p. 581-590.
2. Khera *et al.* Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nature Genetics, 2018. 50(9): p. 1219-1224.
3. O'Sullivan *et al.* Polygenic Risk Scores for Cardiovascular Disease: A Scientific Statement From the American Heart Association. Circulation, 2022. 146(8): p. e93-e118.
4. Hasbani *et al.* American Heart Association's Life's Simple 7: Lifestyle recommendations, polygenic risk, and lifetime risk of coronary heart disease. Circulation, 2022. 145(11), 808-818.
5. Mujwara *et al.* Integrating a Polygenic Risk Score for Coronary Artery Disease as a Risk-Enhancing Factor in the Pooled Cohort Equation: A Cost-Effectiveness Analysis Study. Journal of the American Heart Association, 2022. 11(12): p. e025236.