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Genomic Medicine for Improved Prediction and Primordial Prevention of Cardiovascular Disease

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Over the last 10 years, large-scale genetic studies have identified hundreds of novel genetic variants for heart disease and other forms of cardiovascular (CV) disease and their risk factors[1]. Although highly successful in identifying novel genomic loci, genomic research has been criticized for its high costs, slow translation to clinical care and many unfulfilled promises. It is now clear that the promised timeline to reap the genomic benefits for medicine was too short and the benefits themselves, to some degree, were exaggerated[2]. But, major progress continues to be made on several fronts in translating genomics to medicine. In this issue of ATVB, three papers demonstrate one way by which the CV genomics community is using genomic discoveries to further our understanding of fundamental issues in the prediction and prevention of CV disease.

Isaacs et al. using lipid genetic scores, add to the mounting evidence that life-long alterations of both total cholesterol and low-density lipoprotein cholesterol, but not high-density lipoprotein-cholesterol, promote atherosclerosis and vascular plaque, leading to a higher rate of CV events. Since these natural "Mendelian randomization" experiments take advantage of the life-long nature of the genetic exposure[3, 4] and are devoid of confounding and reverse-causality, they provide important confirmatory evidence for the critical causal role of the cumulative effect of modifiable risk factors such as LDL-C in atherosclerosis, vascular disease and CV events while furthering the case against HDL-C as an important cause of vascular disease[5]. Indeed, these genetic studies contribute to the growing evidence base that indicate that the lifelong effect of LDL-C lowering is significantly greater than that seen in short-term pharmacologic trials, suggesting that lowering cholesterol earlier in life (e.g., in early or mid-adulthood) may be substantially more effective in reducing CV disease[6, 7] than current strategies that target lipid-lowering interventions to older adults.

In 2 other papers appearing in this issue of ATVB, Ganna et al and Tikkanen et al. provide new data that genetic information can be used to identify individuals who are at high risk for CV disease beyond traditional risk factors. In both studies, a genomic profile constructed of highly validated genetic variants from GWAS studies was created and in both cases, the genetic risk score (GRS) was highly associated with incident CV disease even after adjustment for traditional risk factors over 10-20 years of follow-up. The authors used rigorous criteria[8] for the evaluation of the performance of the GRS over and above traditional risk factor algorithms (e.g., Framingham Risk Score), including examination of

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discrimination and reclassification. While prior studies reported small to modest[9, 10] or limited[11] incremental benefit for improved CV risk prediction over and above traditional risk factor algorithms, both of the currently reported large studies, impressively demonstrate potentially clinically important changes in risk classification (NRI = 4-5%) by addition of a GRS, suggesting that a GRS may be a useful adjunct for risk prediction.

To illustrate the potential benefit of applying a GRS for risk prediction, both studies provided estimates of the potential public health impact of adding GRS scoring in persons at intermediate risk based on conventional risk algorithms. Ganna et al estimate 318 individuals would need to be screened with 83 treated to avoid 1 CV event. Using a slightly longer time horizon of 14 years (and a larger sample size), Tikkanen et al., provide slightly more encouraging data showing that for every 135 intermediate risk individuals screened with a GRS, 16 more individuals would be eligible for statin treatment, and 1 additional CV event would be prevented over 14 years of treatment.

While not yet ready for application in the clinical setting, these data are encouraging and appear to suggest that a GRS may be superior to other recently suggested biomarkers (e.g. C-reactive protein, fibrinogen)[12] for screening intermediate risk individuals. A major advantage of a GRS is that because genetics are immutable through life, this risk information is available (and potentially actionable) starting at birth, in contrast to many other biomarkers that vary significantly through life or only become predictive at later ages. Even more encouraging is the fact that current GRS capture only a fraction of the total genetic risk and future iterations of a GRS based on larger discovery samples are expected to better discriminate risk[13]. In addition, as current contemporary cohorts with genetic data age, we will soon be able to relate future GRS, not only to 10 or 20 year risks of disease, but to lifetime risks which will also help inform future preventive strategies.

Genomics have provided some of the most compelling data for the importance of earlier lipid lowering while also giving us the tools to predict at an early age the individuals at highest risk for heart disease. These insights suggest that it may be conceivable to target earlier preventive treatments to young genetically predisposed individuals with a propensity for accelerated atherosclerosis and premature heart disease (e.g. based on a high GRS) before they develop any or little vascular disease to maintain vascular health – a form of genomic primordial prevention. By targeting this type of patient population early in the disease process, such a prevention strategy would be expected to be highly effective. However, carefully-designed innovative randomized trials will be needed to confirm the expected benefits of such strategies before they can be applied clinically. To do so efficiently without resorting to extremely large sample sizes, may require use of direct measures of reduced atherosclerosis progression, using vascular imaging or other surrogate outcomes, as valid trial outcomes, instead of “hard” CV events or mortality with the understanding that by preventing atherosclerosis, CV events will be reduced[14, 15]. In addition, we will need to carefully consider the risks and benefits of interventions to be offered to young, predisposed patients. Will lifestyle modifications alone be sufficient to prevent disease in the young or will prolonged lipid-lowering therapy be required? More importantly, we are only beginning to understand how people handle genomic information[16]

and whether such information in itself leads to meaningful changes in preventive behaviours[17, 18].

Although genomics may have been oversold for its immediate impact on medicine, we have without a doubt, learned a great deal from genomics, as highlighted in this issue of ATVB, with important implications for the prevention of heart disease. The time to translate these discoveries and develop the evidence base for genomic medicine is now.

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