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Reducing Cardiovascular Risk Using Genomic Information in the Era of Precision Medicine

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Overview

With the pace of current advances in genomics technologies, we are fast approaching an era when patients will have complete genome sequence information on which clinicians will need to act when making routine clinical decisions. Precision medicine is "an approach to disease treatment and prevention that seeks to maximize effectiveness by taking into account individual variability in genes, environment and lifestyle" (PMI Working Group report to the Advisory Committee to the Director, NIH, 2015). One central aim of the recently launched US Precision Medicine Initiative is the return of genetic results for clinical utility. Atherosclerotic cardiovascular disease (CVD), the leading cause of death in men and women, is a chronic disease influenced by lifelong exposure to inherited and environmental risk factors. The major clinical and biochemical atherosclerosis risk factors for coronary heart disease (CHD) and other forms of CVD have been well defined over the past fifty years by prospective population cohorts like the Framingham Heart Study and resulting randomized controlled treatment trials (RCTs). Genetics for CVD risk prediction provides the opportunity to more precisely identify individuals at high risk for developing disease for whom preventive therapy can be directed.

Our initial understanding regarding genetic risk for myocardial infarction (MI) and other forms of CHD has focused on rare (<1:100 carrier rate) monogenic etiologies conferring exceptional risk, such as mutations in genes for the low-density lipoprotein (LDL) receptor (*LDLR*), *PCSK9* or *APOB* underlying the predisposition for familial

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hypercholesterolemia.[1-4] However, due to the efforts of international consortia of investigators over the past decade, genome wide association studies (GWAS) of hundreds of thousands of research participants have led to the discovery of well over fifty common (>1:20 carrier rate) gene variants with strong evidence for modest increases in CHD risk[5] as well as over one hundred and fifty common genetic variants with strong evidence for modest alterations of levels of key lipid fractions.[6]

Genetic risk scores for CHD

Despite many novel discoveries, translation of this rapidly growing catalogue of associated genetic variants into clinical application has lagged behind the pace of discovery. While some variants associated with CHD risk proximally influence traditional risk factors, the molecular mechanisms conferring CHD risk for a large proportion of these variants currently remains limited. Nevertheless, even without an understanding of the causal etiology for the many novel genetic variants, current investigation includes a focus on how the information can be used to predict and prevent disease. An individual's CHD genetic risk score (GRS) is an additive score of the burden of discovered CHD risk alleles that is often weighted by the estimated disease effect of each allele. From available studies in older adults, an aggregate of CHD risk alleles can predict future risk of MI and other forms of CHD independently of conventional risk factors, although the incremental predictive benefit of current models appears modest.[7-11] Nevertheless, in a recent *post-hoc* analysis of RCTs of statin therapy for primary and secondary prevention of CHD, persons with the highest burden of CHD risk alleles were not only at increased risk for CHD events but also, surprisingly, experienced enhanced absolute and relative clinical benefit despite similar LDL-cholesterol lowering.[12] These data suggest that a CHD GRS may identify persons at increased risk who may be more likely to benefit from preventive interventions.

GRS for CHD risk reduction using lipid lowering in the MIGENES Trial

In a study published in in this issue of *Circulation*, Kullo et al have added to our understanding of the potential utility of a CHD GRS for lipid lowering in the MIGENES Clinical Trial[13]. In MIGENES, 203 participants without clinical CHD were randomized to receive a 10-year CHD risk estimation based upon a conventional risk factor score (CRS) alone or also with a CHD GRS. Participants randomized to CRS+GRS received risk information by a genetic counselor in addition to "shared decision-making regarding statin therapy" with a physician. Participants randomized to GRS + CRS were more likely to receive statins (39% vs 22%) and had 9.4 mg/dL lower LDL-cholesterol level than the CRS group. There was no evidence of adverse levels of anxiety in those randomized to GRS but there were also no beneficial changes in lifestyle behaviors, such as lower dietary fat intake or improved levels of physical activity. Within the CRS + GRS participants, participants with a high GRS did not have a significantly lower LDL-cholesterol than those with an average/low GRS.

MIGENES Trial strengths

Kullo et al are to be commended for an ambitious design and meticulous training program for use of genetic information by implementation of GRS based algorithm within the real world context of a health system with an electronic health record (EHR). The conceptualization of genetic risk by both providers and patients can be highly varied, and Kullo et al provide initial insights about applying common, complex genetics in the clinic. Kullo et al have provided an important initial step demonstrating that trials integrating genomics-based decision-making for the prevention and treatment of CHD and other forms of CVD can be successfully conducted. A careful review of this important trial warrants careful interpretation of its results and of the implications for future precision medicine trials.

Challenges for clinical trials using GRS information

Evolving Clinical Risk Score Algorithm

Even during the short course of this RCT, CHD clinical risk calculation and statin therapy guidelines have evolved. Framingham 10 year CHD risk factor scores[14] have been updated more recently to assess "global" CVD risk.[15] Recently updated risk scores in multiethnic populations have employed these risk factors in the prediction of global future CVD risk in multiple US populations, and the recent ACC/AHA guideline incorporates information from multiple cohorts to refine baseline risk estimates.[16, 17] Such newer approaches appear to better determine statin eligibility.[18]

Evolving Genetic Risk Score Algorithm

The authors use a CHD GRS for their algorithm that became outdated over the course of the RCT. While the authors cite the 2013 CHD meta-GWAS[19], they were unable to update the RCT for the updated 2015 meta-GWAS with additional novel loci and refined effect estimates at previously discovered loci.[5]

Interpretation of GRS prediction

The authors' clinical-teaching tools provide evidence for patients indicating that GRS can increase the number of patients who will develop CHD events over and above risk factor score. However, only limited data are available for use to derive the teaching tools used to communicate risk/benefits to patients for the modest incremental prediction of risk from a CRS+GRS. Furthermore, it is unclear to what extent providers and patients are influenced by subtler changes in estimated risk using GRS, related to notions of "genetic determinism."

Generalizability of GRS and risk factor algorithms for race/ethnicity

The authors conducted their study in only non-Hispanic whites and they acknowledge the need for further independent study of the generalizability of the risk factor algorithm, GRS and the teaching algorithms used to communicate risk / benefit information. That most research participants in CHD GWAS studies are largely of European ancestry is a major gap in population cardiovascular genomics research.

Interpretation of GRS actionability

The authors provide evidence that randomization to CRS+GRS versus CRS leads to increased statin prescriptions and decreased LDL cholesterol. In the "shared decision making" study design, it is difficult to know whether increased statin prescriptions were due to a lower threshold for statin prescriptions by the physician versus a lower threshold for patient refusal of a statin prescription. Interestingly, despite GRS value, LDL-cholesterol was similarly lowered suggesting that more understanding regarding appropriate interpretation and implementation is required. Furthermore, LDL-cholesterol lowering solely via statin prescription without accompanying alterations in lifestyle factors may not be the optimal approach. While recent analyses suggest that those at high genetic risk may enjoy greater clinical benefit for similar LDL-cholesterol lowering from statins,[12] it is possible that personalized non-pharmacologic LDL-cholesterol lowering may also provide meaningful benefits.

Laying the groundwork for precision medicine

While there are a number of challenges to the conduct of this type of RCT and proper interpretation of its results, the authors have boldly laid the groundwork for implementation of future precision medicine trials using genetic information. Key considerations going forward will include:

Infrastructural challenges

The incorporation of dynamic risk assessment from evolving literature on clinical and genetic risk prediction acknowledges the exponential pace of the field attempting to catch up with the rapid data generation and urgent interest in clinical translation. Furthermore, with routine addition of genome sequence information, EHR systems will need to manage a huge bolus of diagnostic test data conferred by adding over 3 billion base pairs per individual to the EHR and continually updating the clinical annotation of genome sequence.

Educating patients and providers

The field of human genetics has evolved rapidly over the last two decades. Patients and providers typically have limited understanding of human genetics. Accurate representations and education regarding incremental risk and modifiable risk from polygenic risk scores are required to for appropriate interpretation.

Incorporating biology

Recent successful examples of effective novel pharmacotherapy tailored to genetics include new drugs for cystic fibrosis[20-22] as well as the development of PCSK9 inhibitors. Rare genetic mutations in *LDLR*, *PCSK9*, and *APOB* result in high LDL cholesterol and increased risk for premature CHD; approaches to lower LDL-cholesterol reduce CHD risk in such patients. While current GRS approaches use an aggregate of CHD risk alleles, such alleles represent a diverse range of mechanisms influencing atherosclerosis many of which have yet to be characterized. Whether the driving biology from molecularly uncharacterized risk alleles is modifiable through alternative therapeutics is unknown.

Proper design of RCT in the genomic era

An RCT is optimal when included participants are at high risk for disease, the intervention carries a large relative benefit, and adverse events are minimal. A key question is the incremental value of genetics beyond clinical factors. Current approaches have focused on identifying those at highest absolute risk as preventive approaches with statins in clinical subgroups have had similar relative effects.[23] With recent data suggesting that relative risk is increased in those at highest genetic risk,[12] a 2×2 trial of statin vs placebo and high vs low genetic test may be needed to test whether there is an absolute risk difference between the two genetic groups and whether there is a relative risk difference with similar LDL-cholesterol lowering. In a "genotype-first" approach, eligible patients may be selected for lower risk for developing statin-related complications.[24]

Opportunities for the large precision medicine cohorts

We are now entering an exciting time in cardiovascular medicine with the advent of new health care associated cohorts orders of magnitude larger than traditional epidemiological cohorts, such as the planned Precision Medicine Initiative Cohort and related mega-cohorts including the Veterans Administration Million Veteran Program,. Such efforts will allow us to study the role of genetics on common diseases, such as atherosclerotic cardiovascular disease, in the real world at an unprecedented scale. Building on the lessons of the Framingham Heart Study and related cohorts, these 21st century precision medicine cohorts will provide key insights into cardiovascular biology CVD prevention and treatment.

Conclusion

Kullo et al show that when patients and providers are presented with an interpretation of polygenic CHD risk in an RCT of 203 participants, LDL-cholesterol is lowered largely via statin medications. There are several uncertainties and challenges about the role of genetics in the management and prevention of chronic disease. The national focus on precision medicine aims to catalyze an effort to better understand human disease biology, and optimize disease treatment and prevention using a combination of clinical, biochemical, and genetic factors.

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