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Editorial

Exploring the intersection between genetic risk scores and coronary artery calcium – Mutually exclusive or complementary?

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1. Text

Accurate detection of increased cardiovascular disease (CVD) risk and timely prevention of CVD events remain two central needs in cardiovascular medicine. Over the last three decades, a number of clinical scores combining traditional risk factors have been developed, aimed at estimating a person's risk of CVD events and aiding the allocation of preventive pharmacotherapies.[1–3] However, in the present era of precision medicine, the performance of such scores has been proved to be far from optimal.[4,5]

The limited accuracy of clinical scores has driven the identification of novel risk markers, aimed at improving CVD risk assessment through a more personalized approach. This includes imaging techniques such as the coronary artery calcium (CAC) score,[6] which allows visualization of calcified atherosclerotic plaque burden; and more recently, panels of genes and single nucleotide polymorphisms (SNPs) which might portend increased risk of developing CVD and other conditions[7–9] –so-called genetic risk scores (GRSs).

The expanded availability of these tools has boosted debate within the cardiovascular scientific community, from scientific journals and conferences to social networks, and even in the mass media. Should ideal risk assessment focus on the detection of increased genetic risk? Or, should identification of subclinical atherosclerosis be the priority?

Indeed, each approach has strengths and weaknesses. CAC provides a highly sensitive, direct measure of disease, and its prognostic value is supported by a wealth of epidemiological evidence.[10,11] Nevertheless, CAC involves radiation exposure, and its ability to detect increased risk may be limited in very young adults, in whom plaque may be absent for years, or be non-calcified. Also, as a measure of cumulative lifelong exposure to risk, CAC may arrive late in terms of disease prevention and changing patients' behaviors, its main utility likely being the allocation of pharmacological treatments in patients with detectable subclinical disease.

The opposite is true for GRSs, which allow for very early assessments of CVD risk – even at birth. Nonetheless, how to communicate such information, and whether such information leads to effective, sustained lifestyle change is currently unclear. Also, it is poorly understood who may get the greatest benefit (or potential harm) from early life genetic screening. In addition, epidemiological studies have shown wide cardiovascular risk heterogeneity within genetic risk strata,[9] highlighting the great relevance of lifestyle and environmental features and suggesting that genetic scores alone may explain only about 10% of risk, particularly after childhood. Thus, GRSs are unlikely to be routine clinical tools guiding preventive pharmacotherapy decisions in adult patients.

Importantly, although atherosclerosis imaging and genetic testing may be perceived as mutually exclusive options, strategies combining both may allow maximizing their strengths and open new doors in CVD risk assessment. In this issue of the *Journal*, Severance and colleagues present an interesting analysis of the potential interplay between a GRS and CAC for CVD risk evaluation.[12] In 6660 apparently healthy participants from the Multi-Ethnic Study of Atherosclerosis (MESA), a GRS combining 157 SNPs meta-analytically shown to be associated with CHD[13] was moderately associated with CAC burden, and helped identify the age range at which CAC scoring might be most informative (given a fixed detection rate, i.e. 25% with detectable CAC). For example, among male MESA participants with a GRS 2 standard deviations above the mean, 25% would have detectable CAC at an age of 39, while 25% of male MESA patients with a GRS 2 standard deviations below the mean have detectable CAC at an age of 52 (≈13 years difference). Similar results were observed for a more parsimonious version of the GRS including only 102 SNPs.[12]

Some limitations of the study must be noted, including MESA's age range (45–84 years) which precluded including younger adults in the present analysis, the need for validating the study findings in other cohorts, and the fact that the authors did not compare the GRS to the

Abbreviations: CAC, coronary artery calcium; CVD, cardiovascular disease; GRS(s), genetic risk score(s); MESA, Multi-Ethnic Study of Atherosclerosis; SNP(s), single nucleotide polymorphism(s)

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heritable risk information provided by family history, which is usually more readily available; among others. Despite these, Severance and colleagues should be commended on taking what should be considered important *first steps* in exploring the potential interplay between these two powerful, increasingly available tools.

The study also raises a number of questions, some of which will certainly be at the center of the stage of the CVD prevention debate in the coming years. For example, who should be screened with GRSs early in life – the whole population, or specific subgroups of individuals? Would either approach be cost-effective, and which the ethical implications? Should the focus instead be on widespread, comprehensive recommendations for healthy lifestyles to the entire population at early life, without any genetic profiling?

With regards to CAC, should use be expanded to an almost mammogram-like screening test,[14] recommended systematically for certain age and genetic risk groups – as proposed by the authors? Or, provided the correlation observed between GRS and CAC burden, would simply recommending preventive pharmacotherapies to specific age groups based on their genetic risk at birth (such as those defined in the study) yield better outcomes without need for checking CAC? Finally, if genetic risk scores, age, CAC, and clinical risk scores were all to be used, which would be the optimal combination? Perhaps a strategy based on genetic scoring early in life, followed by tailored (rather than at a fixed age[1–3,11]) use of clinical risk scores and subsequent, selective use of CAC? How will the coming era of low cost, low radiation CT angiography change this calculus?

In 2019, we still have a lot to learn about how to best predict and prevent CVD events while maximizing effectiveness, efficiency, safety, ethics, and patient preferences. In this context, rather than polarized debates on mutually exclusive approaches, collaborative efforts between experts in clinical risk scores, atherosclerosis imaging techniques, GRS development, population health, and medical ethics will yield the synergy necessary to truly move preventive cardiology forward. It took 25 years for CAC scoring to be placed alongside traditional risk factors for clinical risk prediction – with focused efforts by like-minded scientists, hopefully the union of GRSs, atherosclerosis imaging, and traditional scores will occur exponentially faster.

Disclosures

The authors declare that they have no conflicts of interest relevant to the content of this manuscript.

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