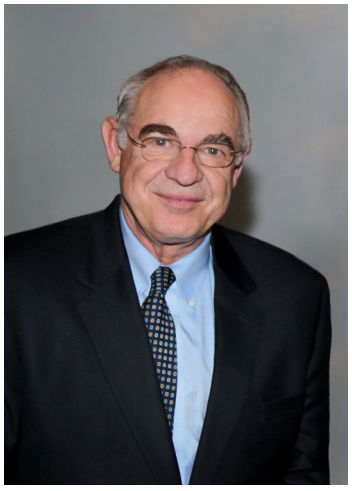
CUSTOMER SPOTLIGHT
DR ERNST J. SCHAEFER, MD

The power and promise of polygenic risk scores

The Polygenic Risk Map from Boston Heart Diagnostics empowers clinicians to take a personalized approach to preventive medicine



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Cardiovascular disease is the leading cause of death and disability globally.[1] Despite an increased understanding of various environmental factors, including smoking, stress, and diet, that contribute to cardiovascular disease, overall risk prediction remains imprecise.[2-5] Over the past decade, large genome-wide association studies have confirmed the polygenic basis of cardiovascular disease and associated metabolic disorders,[6] with multiple variants linked to cardiometabolic disease found scattered throughout the genome. Each single nucleotide polymorphism (SNP) individually accounts for only a small portion of disease risk. However, collectively, they contribute significantly to the overall risk of cardiometabolic disease. Polygenic risk scores (PRSs) are the weighted sum of the risk conferred by multiple disease-associated SNPs across the genome. PRSs are independently associated with multiple cardiovascular diseases[7] and, when taken together with environmental risk factors, are a powerful tool to refine and mitigate disease risk.

Dr Ernst J. Schaefer, the Chief Medical Officer at Boston Heart Diagnostics, is an internationally recognized leader in the field of lipoprotein metabolism, and the diagnosis and management of lipoprotein disorders for the prevention of coronary heart disease. Dr Schaefer co-founded Boston Heart Diagnostics in 2007 with a focus on heart disease prevention. We spoke with Dr Schaefer about the value of PRS testing in cardiovascular disease and their new offering, the Boston Heart Polygenic Risk Map test. This genetic test applies PRS to determine an individual's absolute genetic risk of complex disease, enabling early, personalized intervention strategies.

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Q: Can you tell me about Boston Heart Diagnostics?

Ernst Schaefer (ES): Boston Heart Diagnostics, a subsidiary of Eurofins Scientific, is focused on the treatment and prevention of disease by offering novel diagnostics that drive a personalized approach to improve patient health. Our goal is to provide testing for the prevention of heart disease and related conditions, thereby improving overall health and longevity. At Boston Heart Diagnostics, we offer a comprehensive and integrated approach to enhance care management. In addition to test results, our reports include interpretations and clinical treatment considerations that help characterize risk, develop insight, and communicate more effectively with patients. Providing test reports in the form of actionable, individualized, and easy-to-understand steps ultimately improves patient engagement, health literacy, and adherence to treatment plans.

Q: What services do you offer?

ES: At Boston Heart Diagnostics, we provide clinical testing for heart health and cardiovascular disease risk factors. We specialize in a wide range of laboratory techniques, including gas chromatography, gel electrophoresis, genetic testing, general chemistry, immunoassay, and high-performance liquid chromatography (HPLC). The most important assays for heart disease quantify low-density and high-density lipoprotein (LDL and HDL, respectively) particles, as well as lipoprotein (a). Our laboratory tests can distinguish between various kinds of lipoprotein particles, as well as identify various genetic factors that predispose to cardiovascular disease. We can also perform testing for kidney, thyroid, and liver function. Inflammation markers, like C-reactive protein, are other tests that we use along with a history of high blood pressure and diabetes, smoking, and diet to assess overall heart disease risk. We also now offer the Boston Heart Polygenic Map, which is a PRS test for coronary artery disease.

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Q: Why is PRS testing important in cardiovascular disease?

ES: Cardiovascular disease has a strong genetic component. Many genetic variants together influence an individual's risk of heart disease, that is, the disease is polygenic in nature. PRS tests measure disease risk of these variants spread throughout the genome. By comparing an individual's PRS to that of a reference population, we can calculate their lifetime risk of coronary artery disease. With PRS, we're not looking for rare variants. Instead, we

test for common variants that occur in more than 1% of the population, across the genome, that contribute to the overall risk. Large twin studies done in Denmark indicate that, like many diseases, premature coronary artery disease is about half genetic and half environmental. So, in addition to genetics, what you do in your life is also very important. Smoking status and atherogenic diets can both contribute to risk. But overall, genetics and understanding genetic risk are important factors, which is why PRS testing is recommended.

Q: When did Boston Heart Diagnostics start using PRS in patient evaluations?

ES: We've been doing individual genotyping at the *APOE* and other genetic loci for over 15 years. Since we're in the lipoprotein and the lipid space, we also offer a 23-gene sequencing panel for our customers for rare but severe lipoprotein disorders. However, we've only been offering microarray-based PRS tests for about a year. The power of polygenic risk testing is that you're putting together very large numbers of genetic variants that are much more common in the population—over 1%.

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Q: What challenges do laboratories face with PRS testing?

ES: The major hurdle that we face is getting insurance coverage for any new test that can be considered a lab-developed test. So, our Polygenic Risk Map becomes a cash pay test. With a cash pay test, even if it is not that expensive, and is a one-time test, the patient ultimately has to pay to get tested. Depending on the individual's financial means, it does skew towards those people who are able to afford testing. With that said, these tests provide valuable information and are a good investment for understanding lifelong risks for polygenic diseases.

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Clinical adoption is another challenge. Even though we are in the heart disease prevention space, a lot of our customers are general practitioners or internists. For them, it is a learning curve to use this tool effectively. For example, if their patient's risk for coronary heart disease is high, then they should be aggressive in looking for risk factors and treating them. If the risk for prostate cancer is high, then prostate-specific antigen should be monitored more carefully. The goal is to prevent disease. If a person ends up having an angioplasty or cardiac bypass surgery, that means the high risk was not diagnosed and the disease was not prevented.

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"PRS testing gives us a very good picture of risk of these polygenic diseases and is most valuable in younger people... PRS for coronary artery disease is most useful for people who are under 50 years old."

Q: What led you to develop the Polygenic Risk Map test?

ES: We are primarily in the heart disease prevention space. That's our bread and butter. We are interested in the risk factors for heart disease, like diabetes, high blood pressure, LDL and HDL, triglycerides, lipoprotein (a), and others. So, our focus was to have a PRS for coronary artery disease and these other risk factors. For people over 40 years of age, if you include diabetes and kidney disease, which can lead to death due to coronary disease, then the combination of coronary heart disease and stroke accounts for almost 50% of all deaths in this age group. Right behind cardiovascular disease are various forms of cancer, with lung, prostate, breast, and colon cancers being the most common causes of death in adults over 40 years of age. PRS testing gives us a very good picture of risk of these polygenic diseases and is most valuable in younger people. In fact, a recent publication indicated that the PRS for coronary artery disease is most useful for people who are under 50 years old.[8]

"The Polygenic Risk Map is built on a commercially available microarray. This comprehensive array contains over 650,000 SNPs across the genome."

Q: How did you build the Polygenic Risk Map test? What markers does this test include?

ES: The Polygenic Risk Map test is built on a commercially available microarray. This comprehensive array contains over 650,000 SNPs across the genome. However, a lot of these variants are interrelated due to linkage disequilibrium. So, if one variant is present, you can impute the presence of other variants, which brings the total number of SNPs assessed to over 1.9M for heart disease.
For atrial fibrillation, we use 445K markers, for type 2 diabetes, we use 620K markers, and for hypertension, we look at 247K markers. For HDL, we assess 332K markers, while for LDL only 3K markers are assessed, indicating that the number of genes involved in regulating LDL seems to be lower, or that one or two of them, like the LDL receptor, are more important. For lipoprotein (a), which is known to be highly genetically determined, we use only 39 markers. This is because lipoprotein levels are known to be heavily influenced by isoforms. We also test for other polygenic diseases like dementia and prostate cancer by assessing 136K and 682K markers, respectively. However, we don't report on the individual variants. The data obtained from the array is analyzed to provide personalized polygenic scores and risk assessment.

Q: How do you perform data analysis and reporting?

ES: We take data collected from the microarray and send it to our partner, Allelica, for data analysis and reporting. Allelica leverages data from large data sets, like the UK Biobank and other population-wide studies with data from thousands of individuals who have been followed over several years. Also, PRSs are ancestry dependent. The Allelica analysis pipeline considers an individual's ancestry background while computing PRSs and disease risk. The report generated includes risk scores for coronary artery disease, atrial fibrillation, type 2 diabetes, obesity, and hypertension. The report also has PRS for high triglycerides, lipoprotein (a), and LDL cholesterol, and low HDL cholesterol. We measure all these parameters biochemically, but these risk scores explain the relative contribution of genetic and environmental factors. The report from Allelica also includes information about risk for other polygenic conditions, such as Alzheimer's disease and dementia, inflammatory bowel disease, and breast and prostate cancers.

"The Allelica analysis pipeline considers an individual's ancestry background while computing PRSs and disease risk."

Q: What are the benefits of using a comprehensive microarray for PRS testing?

ES: The microarray we use has excellent coverage, is validated, and is the array of choice for PRS studies. It is cost-effective, which not only benefits the lab performing the test, but also patients who typically pay out-of-pocket for this assessment. One of the challenges with PRS is that there has been an over-representation of the research in European populations, while other ethnicities are often under-represented. The array used for the Polygenic Risk Map test includes 26 global populations to account for ancestry-dependent genetic variation. In addition, data generated from the array can be integrated into Allelica data analysis modules easily. The comprehensive content of this microarray combined with ancestry-informed PRS reporting means that patients get a complete picture of their disease risk.

"The microarray we use has excellent coverage, is validated, and is the array of choice for PRS studies. It is cost-effective...includes 26 global populations to account for ancestry-dependent genetic variation."

Q: What is the future of clinical PRS testing? How will it impact healthcare?

ES: We believe that polygenic risk scoring is beneficial for everyone, especially younger individuals. Companies offering direct-to-customer ancestry testing have generated a lot of interest with consumers and are making genetic testing more accessible.

"...polygenic risk scoring for various disease states is helpful for everybody and has the power to change the way healthcare providers and patients understand health and communicate about disease risk."

We expect that individuals with a strong family history of coronary artery disease, Alzheimer's disease, breast or prostate cancers, and other diseases, can approach their doctors to gain a better understanding of their risk of developing disease in their lifetime. PRS and risk assessments, in turn, can help people make more informed decisions about their health. Now, PRS testing isn't perfect because it does not pick up rare disease-causing variants, but the common variants are overall more important on a population level. With that said, polygenic risk scoring for various disease states is helpful for everybody and has the power to change the way healthcare providers and patients understand health and communicate about disease risk.

Learn more

Polygenic risk scores

Boston Heart Diagnostics

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