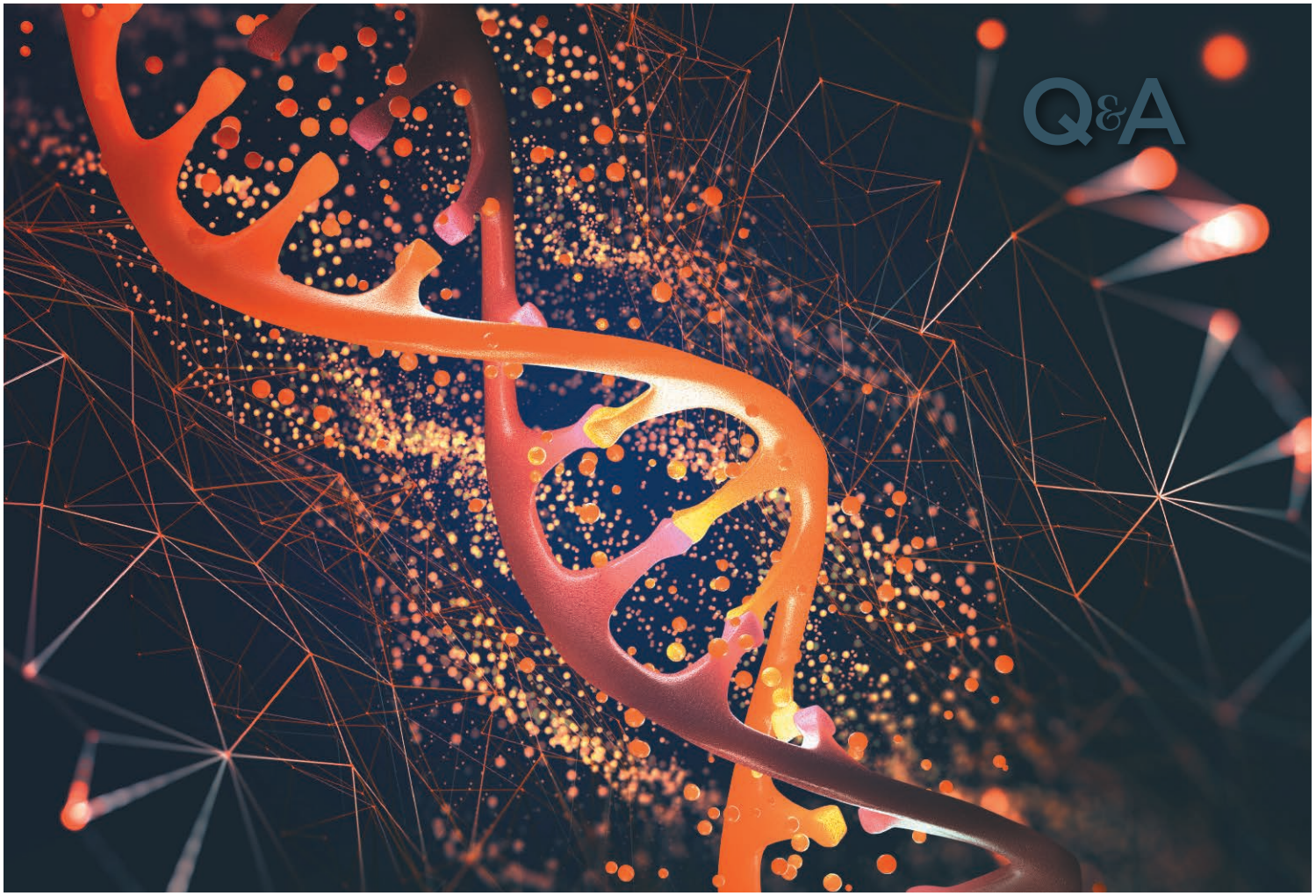


The Rise of Predictive Genomics

An interview with Chad Carter, MBA, VP/GM, Thermo Fisher Scientific, and Richard Pither, PhD, CEO, Cytox

WHAT WE KNOW as precision medicine today dates back at least 40 years to when companies such as Thermo Fisher Scientific first introduced new technologies to help the scientific community better understand how genomics influence health and disease. Over the last several decades, there have been many advances that have helped to democratize these solutions so more scientists, clinicians and pharmacists – and through them, patients – can access genomic insights to improve health. Of note, the 2015 launch of the Precision Medicine Initiative broadened access to data and provided needed funding to accelerate the uptake of results from the Human Genome Project and related medical advances.

One of the advancements that has revolutionized medicine is the broader use of genome wide association studies (GWAS). These studies, which are increasingly available globally, have enabled discoveries of thousands of associations between common genetic variants and complex diseases.

Advances in sequencing have made it possible to measure and analyze rare variants in populations. Often, diseases occur because an individual has a rare variation that is not found in a normal single nucleotide polymorphism but rather may

be the result of a combination of variants on multiple genes. The introduction of simplified, targeted next-generation sequencing has also made identification of disease-causing genes more accessible globally by reducing the cost and time it takes to analyze biomarkers of interest that may influence disease progression or help identify therapeutic targets.

Today, advances in technology are enabling increased clinical use of genomics at the point of care to guide treatments for diseases such as cancer. The new frontier is the use of genomics to prevent disease. Insights from predictive genomic testing can compel lifestyle changes or provide an impetus for additional screening. In addition, preemptive pharmacogenomic testing can inform the best treatment and medication dosage for individuals based on their genetics. With the availability of proven, accessible, cost-effective microarray technology, wide-scale predictive genomic testing could realistically be implemented in any healthcare setting in the near future.

As understanding of genomics has evolved, researchers have identified multiple biomarkers associated with a number of complex diseases, such as coronary artery disease, type 2 diabetes and Alzheimer's disease (AD), and combined them into easy to interpret polygenic risk scores (PRSs). In AD, UK-based Cytox is leading the way in bringing PRS into clinical use. In collaboration with Thermo Fisher, the company developed one of the first CE-marked PRS tests, *geno*SCORE, to assess patients for the risk of developing AD before symptoms arise.

We recently interviewed Dr. Richard Pither, CEO of Cytox, and Chad Carter, vice president and general manager of microarray genetic solutions at Thermo Fisher, to learn how polygenic risk scoring on microarrays can help shift the healthcare paradigm to preventative care.

There are a growing number of diseases with associated polygenic risk scores:

1. Hypertension
2. Cardiovascular disease
3. Asthma
4. Type 2 diabetes
5. Prostate cancer
6. Atrial fibrillation
7. Coronary artery disease (CAD)
8. Breast cancer
9. Osteoporosis
10. Age-related macular degeneration (AMD)
11. Primary open-angle glaucoma (POAG)
12. Venous thromboembolism (VTE)
13. Alzheimer's disease
14. Psoriasis
15. Rheumatoid arthritis
16. Coeliac disease
17. Bowel cancer
18. Ischaemic stroke
19. Melanoma
20. Ulcerative colitis
21. Bipolar disorder
22. Crohn's disease
23. Parkinson's disease
24. Multiple sclerosis
25. Type 1 diabetes
26. Schizophrenia
27. Systemic lupus erythematosus (SLE)
28. Ovarian cancer

"Today, advances in technology are enabling increased clinical use of genomics at the point of care to guide treatments for diseases such as cancer. The new frontier is the use of genomics to prevent disease."

Q. Chad, can you start by summarizing microarray-based polygenic risk scoring and its importance?

A. PRS is a fundamental component of predictive genomics. For many complex diseases such as cancer, heart disease, diabetes, psychiatric conditions and Alzheimer's disease, a large number of genes may be at play and would need to be assayed to predict a patient's risk (see inset listing diseases now associated with associated polygenic risk scores). PRS algorithms assess and combine risk across millions of genetic markers to calculate the probability of a genetic disease trait emerging. With a risk score, healthcare providers and patients have a new statistical tool for assessing GWAS data in a way that may contribute to early diagnosis and personalized therapeutic strategies.

Q. Staying with you, Chad, how is microarray technology uniquely suited to enable risk assessment and identify preventative treatment for Alzheimer's and other diseases?

A. For a risk assessment test to have utility for personalized medicine, it must be reliable and cost-effective. For companies like Cytox, microarrays meet these criteria while also being easy to use, customizable, and scalable. Microarray technology is also well suited to risk scoring because of its proven quality and the fact that it's already well-validated. In particular, the arrays are designed to assess many genes simultaneously (unlike single-gene assays) and array analysis is supported by a rigorous statistical foundation over a domain space. In a single run, a patient's full spectrum of possible diagnoses may be considered. (See details in **Designing a custom array** inset.)

This capability is analogous to the power of microarrays in preclinical research to formulate and test hypotheses rapidly. Similarly, in the clinical space, clinicians are able to assess a range of diagnoses before focusing on a specific condition and subsequent treatment protocol. Ultimately, what makes this technology well-suited

Designing a custom array

Microarrays can be tailored for specific research aims, including discovery of new associations, confirmation and refinement of previous discoveries, and monitoring or surveillance of known, important variants. In the past, custom genotyping arrays were expensive, required large sample commitments and took time to design and deliver. Today, custom arrays can be designed quickly and cost-effectively by adding, replacing or removing markers on existing arrays. This flexibility also allows researchers to update their array as new genomic information becomes available.

The number of markers (SNPs and indels) on an array is determined by the number of features required per marker. Variants for Applied Biosystems Axiom myDesign Custom Genotyping Arrays* may be selected from the Applied Biosystems Axiom Genomic Database of more than 9.4 million wet-lab tested markers and markers identified by sequencing.

When selecting markers, there are several elements to take into consideration.

1. **Genome-wide coverage for discovery:** Once sufficient genomes have been sequenced to provide a solid reference panel, a vast number of samples can be genotyped on microarrays containing up to 1,000,000 markers. Imputation then allows the calling of tens of millions more variants.
2. **Direct assay of variants critical to study goals:** Variants are selected from previous research findings, literature or clinical practice, as well as predicted relevance to the phenotypes of interest.
3. **Surveillance of variants of known significance:** A research project aimed at new discoveries will need to assay known variants. Expertly curated modules can provide a basis for a new array design, allowing researchers to focus on new findings.
4. **Confirmation of previous results:** In addition to directly evaluating specific variants, a region may be mapped around previous genetic wide association study findings to pin down a causal variant.

**For research use only. Not for use in diagnostic procedures.*

for risk assessment and preventative intervention is that it can be used early, easily, and broadly.

Q. To Dr. Pither: why did Cytox choose to work with Thermo Fisher?

A. Early on we developed a long list of SNPs that needed coverage and we were able to work closely with the Thermo Fisher team to turn that wish list into a reliable test. At the start of the process, we were not experts in array technology, so that collaboration and access to highly-technical support was hugely important.

Chemistry expertise is also important; Thermo Fisher's Axiom platform more accurately and reliably covers the SNPs we rely on, including the single most influential genetic risk factor for late-onset AD, the E4 allele of apolipoprotein E (APOE e4).[1]

Global availability was another factor, as we work with lab partners around the world and eventually want to offer our test in countries outside of the U.S. and UK. With the quality and supply agreements we have in place with Thermo Fisher, we can ensure we deliver high-quality, reproducible results to provide a consistent supply globally.

Thermo Fisher is a unique partner because its research-related and commercially driven collaborations support the entire diagnostic/prognostic clinical community as well as biopharma. Over the years Thermo Fisher has continued to demonstrate their understanding of the landscape in which we work, their support for our research and partnership, and their commitment to the Axiom platform as the basis for a sustainable business.

The Axiom® Genotyping Solution enables genotyping studies on a single platform quickly, easily, and cost-effectively.

Q. Regarding application of the technology, Dr. Pither, how is Cytox helping patients better assess their risk for Alzheimer's disease? Are patients better able to understand clearly explained PRS and other risk scoring tools or educational materials?

A. Our patients fall into two main categories: those whose family history creates concerns about their personal future risk of AD – or another family member's risk – and those who have developed early symptoms. PRS provides a single risk score that is easy to interpret but it's still important that we help physicians understand how to best communicate PRS to their patients.

With mounting evidence that lifestyle interventions play a significant role in maintaining cognition and function as well as preventing or delaying the onset of disease,[2] clinicians may use PRSs to recommend behavioral changes to patients. In fact, patient-modifiable factors account for more than 40% of the risk for dementia, making it important that clinicians have appropriate tools to understand the future risk of progression and provide appropriate clinical management.

Q. Going back to PRS, Dr. Pither, what lessons has Cytox learned in using genetic and scoring data to help patients understand their diagnosis and options? Can you provide examples of how clinicians are using these data, how patients are responding to the scoring tool, and how can patients be educated to take advantage of these data?

A. We've learned that PRS data is extremely important in helping physicians and their patients make proactive and meaningful changes. Even a report of relatively high risk certainly isn't all bad news. Physicians working with PRS data have developed novel protocols that take multiple modifiable factors into consideration, and this provides a starting point for diagnostic workups that can ultimately lead to development of personalized treatment and oversight regimens.

"For example, we worked with Sir Peter Donnelly, founder of Genomic PLC, to develop a custom array that physicians in the UK are now piloting as part of the ongoing HEART Study. As another example, medical centers across Taiwan are now using the custom genotyping array we designed with Dr. Pui-Yan Kwok to enroll patients in the large-scale Taiwan Precision Medicine Initiative, which is, in turn, already providing actionable genetic results to individuals to empower their health."

On that last point especially, application of PRS and array technology is critical to enabling patients to be assessed early, easily, and over a domain of possible conditions so that behavior modification

and other interventions can be brought to bear as early as possible.

Q. Back to you, Chad, are physicians adopting polygenic risk scoring in their clinical practices? Are they able to position PRS, clinical laboratory results, and lifestyle in a holistic message to their patients?

A. There is still work to be done to fully integrate the science of PRS into standard of care. I like to describe it as being on mile five of a marathon. It is accepted science that our genes control a significant part of our health, but patients, clinicians, and payers are still trying to work out the actionable end of this knowledge. Many of the global programs ongoing today are aiming to address questions surrounding how to leverage genomic information to improve health and how to earn a return on investment for everyone involved. They are making progress.

Cytox and many of our other partners are enabling the adoption of PRS in clinical practice. For example, we worked with Sir Peter Donnelly, founder of Genomic PLC, to develop a custom array that physicians in the UK are now piloting as part of the ongoing HEART Study. As another example, medical centers across Taiwan are now using the custom genotyping array we designed with Dr. Pui-Yan Kwok to enroll patients in the large-scale Taiwan Precision Medicine Initiative, which is, in turn, already providing actionable genetic results to individuals to empower their health.

It is incumbent on all the stakeholders, including experts within Thermo Fisher, to advocate for and support genetic studies at scale. This will provide the evidence of scoring-intervention-outcome correlation that will ultimately encourage more widespread adoption of PRS and genomic testing in the future. The next five to ten years will be an exciting time as we see the power of genomics emerge in healthcare. At Thermo Fisher, we are very proud to be part of this journey.

Q. So, in follow-up, Chad, what are the barriers to broader integration of PRS-based testing into standards of care?

A. The greatest barrier to broader integration is paucity of evidence (especially outcome-based or real-word evidence). More evidence is what will move physicians to adopt new technologies and change clinical workflows. Evidence will also drive regulatory approval and reimbursement, since agencies are especially driven by data, evidence, and outcomes. So, there is very much a health economic component and business models that need to be worked out. Fortunately, the work Dr. Pither and others around the world are leading is enabling us to gather more evidence each day. Thermo Fisher continues to partner with organizations and governments to ensure that this evidence is generated and accumulated in well-defined databases such that patients and health systems will realize overall benefit.

"Additional economic analysis is needed to quantify the potential savings to healthcare systems that use PRS for earlier risk assessment and mitigation. This research into how healthcare management is impacted by PRS, as well as the result of subsequent interventions, is an important precursor to reimbursement and widespread adoption."

Q. Back to you, then, Dr. Pither, what do you see as the major barriers to broader adoption of microarray-based PRS-based testing?

A. Before we see widespread acceptance of PRS, we'll need to do a better job of convincing physicians. As Chad said, that will take more clinical evidence.

Today, more than 75 clinics are registered to use our test in North America, and many are already using it on a repeat basis. This uptake and application is helping us understand how PRS is guiding interventions and affecting long-term outcomes. We are also conducting studies with individual investigators to understand how our test has had an impact in particular healthcare settings and how clinical management changes once our test is used. This combination of uptake, evidence, impact, and management adoption is an important step toward justifying reimbursement and making testing as widely available as possible.

Q. To follow up, Dr. Pither, what does it mean for healthcare systems to introduce a risk scoring system? Are there new models emerging to introduce such tools, encourage adoption, and demonstrate long-term value?

A. We'll soon be presenting to a molecular diagnostics expert group at CMS to help make the health system case for PRS. Our hope is to encourage expert input into additional studies and insight that enable wider adoption. Additional economic analysis is needed to quantify the potential savings to healthcare systems that use PRS for earlier risk assessment and mitigation. This research into how healthcare management is impacted by PRS, as well as the result of subsequent interventions, is an important precursor to reimbursement and widespread adoption.

Q. Question for you, Chad, what long-term patient outcomes and economic benefits may come from leveraging microarray-based testing for a prevention-first approach to AD?

A. Alzheimer's disease affects more than 46 million people globally, and, with aging populations in the US, EU, UK and Japan, projections call for that number to reach 75 million in 2030, with an estimated economic impact exceeding $1 trillion per year.[3] PRS, enabled by microarray technology, can guide specific interventions for individuals with AD, including lifestyle changes and access to clinical trials, and track health outcomes over time. PRS-related data being collected now for AD and other diseases are driving healthcare economic studies that will ultimately quantify the costs of prevention versus the cost to cure. The shift in both economic and healthcare management will be based on evidence.

Q. Similar question for you, Dr. Pither, given that no current long-term cure currently exists for Alzheimer's, what's the value of microarray based, PRS testing, both for individual patients and systemwide?

A. In the absence of a cure, the value of PRS testing is significant. First and foremost, PRS can aid with diagnosis, which can be challenging because the onset and progression of clinical manifestations such as memory loss, vision problems, or impaired judgement can be variable, gradual, or mistaken for other conditions.

PRS can provide actionable insights as well. There are groups offering interventions to younger individuals, creating tangible value in understanding your risk and being armed with the information to act early.

And while there is no cure at the moment, treatments are on their way, with more than 150 AD drugs in clinical trials.[4] A patient may learn genetic information today that could match them with a new therapeutic treatment a few years from now. In the meantime, there are a growing number of interventional programs offered by clinics that can provide personalized treatment to patients at all stages of disease, many of which claim very high success rates.

Q. Final question for you, Dr. Pither- today, 99% of clinical trials for Alzheimer's

disease fail. How can the Cytox approach improve those failure rates and why is microarray technology so well suited for making trials more successful compared to other approaches?

A. The recent FDA approval of Biogen's Aduhelm (aducanumab) creates some optimism, but it isn't yet widely reimbursed in the U.S., and it is currently prohibitively expensive. If this drug and others like it – focusing on beta amyloid removal – are to have an impact more broadly, we'll need to target them to individuals who are at greatest risk, and we must do so early.

Nothing is more effective than genetic testing at assessing risk, and a genetic risk-scoring test such as *geno*SCORE can therefore be used for stratification earlier in the clinical trial recruiting process, enriching the study population based on specific genetic signals that link to responsiveness to one drug intervention or another to improve trial outcomes and potentially bring new therapies to market faster.

Q. A couple more for you, Chad: are there other examples outside of Alzheimer's disease where microarray technology is showing evidence of clinical utility and long-term economic benefits – pharmacogenomics, for example?

A. There are a number of groups around the world using microarray technology to advance precision medicine. For example, through a collaboration with Thermo Fisher the Qatar Genome Program is studying genetic alterations that increase individuals' risk of both prevalent and rare diseases with the first microarray designed specifically for the Qatari population. We are also working together to refine algorithms and assess PRSs and clinically relevant variants, including those related to pharmacogenomics.

Here in the U.S., Dr. Philip Empey and his team at the Pharmacogenomics Center of Excellence, an academic-industry partnership between the University of Pittsburgh Medical Center and Thermo Fisher,[5] are using microarray technology to deploy pharmacogenomic testing approaches as a clinical standard of care for patients who receive stents to treat clogged arteries.

Predictive genomics is also showing great promise for improving prognosis in the mental health field beyond AD.

"Healthcare has primarily focused on treating patients once they're ill. We need to shift the healthcare model from reactive to preemptive. Earlier intervention than currently practiced could save lives and reduce healthcare costs."

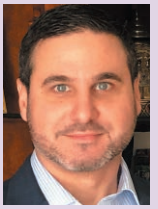
Q. And finally, Chad, how might PRS testing with microarray technology shift the paradigm from investing disproportionally in cures to investing in prevention instead?

A. Healthcare has primarily focused on treating patients once they're ill. We need to shift the healthcare model from reactive to preemptive. Earlier intervention than currently practiced could save lives and reduce healthcare costs. Mounting evidence suggests that predictive genomics can provide individuals and health systems with information on who is at risk of a wide range of diseases. Until recently, however, it seemed the costs of assessing risk through genetic testing would outweigh the benefits of having greater risk knowledge and interventional capability. Microarray technology now makes precision genomics more cost-effective and scalable, and data will show definitively whether prevention costs less than the cure.

With the widely accepted science that genes and genetics control a significant part of our health, we must raise the question: why are we ignoring half of the puzzle? It's time to make predictive genomics part of the standard of care. JoPM

Summary Points

- Advances in technology are enabling increased clinical use of genomics at the point of care to guide treatments for diseases. The new frontier is the use of genomics to prevent disease.
- Polygenic risk scores (PRSs) are a fundamental component of predictive genomics. They assess and combine risk across millions of genetic markers to calculate the probability of a disease trait emerging.
- In collaboration with Thermo Fisher Scientific, Cytox developed one of the first CE-marked PRS tests, genoSCORE, to assess patients for the risk of developing Alzheimer's disease (AD) before symptoms arise.
- For companies like Cytox, microarray technology provides a customizable, scalable and cost-effective tool for risk scoring. PRS using array technology enables risk assessment to guide behavior modification and other interventions as early as possible.
- Mounting evidence suggests predictive genomics can provide individuals and health systems with information on who is at risk for a wide range of diseases but there is still work to be done to fully integrate PRS into standard of care.
- As Cytox and other organizations provide evidence of the clinical utility and economic value of PRS we'll see increased clinician adoption, regulatory approvals and reimbursement.



Chad Carter

Chad serves as the Vice President & General Manager of microarray genetic solutions at Thermo Fisher Scientific where he is focused on bringing the power of microarray genetic analysis to research, clinical, and agriculture applications around the world. Chad has also managed laboratory consumable and equipment businesses for Thermo Fisher. Prior to joining Thermo Fisher, Chad worked for both 3M and Ecolab in various roles focused on healthcare products. He has a B.S. in Mechanical Engineering from Michigan Technological University and a MBA from University of Minnesota.

Richard Pither

At Cytox, Richard has led the team through the development of novel genetic tests for assessing Alzheimer's Disease risk. The marketed genoSCORETM products in US and Europe, developed in partnership with Thermo Fisher Scientific, Sampled and Yourgene Health, are aimed at clinicians assessing patients at risk of cognitive decline due to Alzheimer's disease, in addition to Pharma companies seeking high risk patients for recruitment into clinical trials. Over the past 30 years, Richard has been involved with the development of diagnostic and therapeutic products for GE Healthcare (Medical Diagnostics), UCB-Celltech, Lorantis and Amersham plc. Richard's academic training is from Bristol University and Harvard Medical School.

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