Sequencing as a Tool for Identifying At-Risk Patients for Breast Cancer

"It's easy to get excited about the power of technology, but it has to be for clinical benefit. We're here for the patients. That's why we do what we do."—Prof. Graham Taylor, Leeds University

Introduction

Everyone is at risk. Breast cancer affects men and women, young and old, any race. With early detection, the five-year survival rate is 98%[1]. Clearly, a method for quick, affordable, sensitive, and accurate breast cancer screening needs to be made available to everyone. But how? Answering this question led Prof. Graham Taylor, PhD FRCPath and his team at Leeds University to the Illumina Genome Analyzer.

Sequencing to Diagnose

Disease risk for inherited breast cancer has been linked to mutations in breast cancer susceptibility genes 1 and 2 (BRCA1 and BRCA2)[2,3]. Knowing that there tends to be a genetic predisposition towards breast cancer and that earlier detection is the key to successful treatment, Prof. Taylor chose to venture beyond traditional screening by film mammography for identifying breast cancer. By looking at a person's DNA, at-risk patients can be identified and encouraged to take preventative measures, including seeking out additional medical consultations. With the rising costs of health care, this identification can justify the need for additional, sometimes costly, tests that may make a difference when it comes to patient survival. Developing a DNA test that would enable people to detect breast cancer earlier, before signs could be evidenced in a mammogram, is directly in line with the mission of the Molecular Genetics Development Translation Facility (MGDTF) at Leeds.

The primary goal of the MGDTF is to move next-generation technologies into a diagnostic framework. With its high accuracy, fast turnaround time, and lower cost per sample, next-generation sequencing on the Genome Analyzer was an ideal candidate methodology for the MGDTF. Working with an accredited diagnostic service lab, Prof. Graham Taylor and his team demonstrated that the Genome Analyzer could be used as a reliable, cost-effective diagnostic tool for BRCA1 and BRCA2 in the United Kingdom. Clearly, detection tests for BRCA1 and BRCA2 have been around for at least 15 years. What makes this test unique? "Illumina sequencing allows us to deliver the same information a bit more quickly and for a lot less money," states Prof. Taylor.

Diagnostic Development

When Prof. Taylor first acquired the Illumina Genome Analyzer, it was purely for research purposes. He hadn't started out to set a new standard in diagnostics, but one of his earliest projects with the instrument convinced him that the Genome Analyzer had the ease of use, data quality, and low-cost capabilities that could greatly benefit a diagnostics lab.

Prof. Graham Taylor is a Professor in Molecular Medicine and Diagnostics at Leeds University. His group's mission is to move next-generation technologies into a diagnostic framework. His first success was the using next-generation sequencing for breast cancer screening and is now being delivered throughout the United Kingdom.

His first project in the diagnostic direction involved working with Joanne Morgan to develop a test for tumor protein p53. But Prof. Taylor's intention was always to develop a test for BRCA1 and BRCA2. This is where he saw an opportunity to really make a difference in improving patient outcome. "We deliver this service [sequencing to identify patients at-risk for breast cancer] for a population of about eight million, and it involves about 500 tests a year. It's not a huge number, but that's quite a bit for a genetics lab, and it's only going to get bigger as more [genetic markers] are discovered. We saw that as a pressure point in the lab for capacity. It's very difficult to get more staff, but the Illumina technology is very high tech and advanced, you can do a lot more with the same resources. That's what people want to hear."

The Challenge Fund

To start development for the use of the Genome Analyzer as a diagnostic tool, Prof. Taylor and his team needed funding. This came in the form of the Challenge Fund, a grant developed by Leeds Hospital to specifically support development of new technologies for use in the hospital or clinical setting. It was perfectly suited for Prof. Taylor's group. "Our research is really translating information right into clinical

practice. I can keep going back to this in all of our grant applications. That's what we are doing now," he states. They applied, and were granted the money to begin development.

Led by Joanne Morgan and working in close collaboration with clinical and academic groups, the development team successfully produced a genetic test for BRCA1 and BRCA2 using the Genome Analyzer. True to the "do more with less" mantra, this team consisted of only three full-time staff in a small laboratory. Even more astonishing was the time in which this diagnostic service was developed—from grant to use was less than one year.

Achieving Accreditation

Clinical Pathology Accreditation (CPA), which maps to the ISO 15189/2007 standard for medical diagnostics, is recognized throughout the UK and the rest of Europe as the standard to achieve for delivering diagnostic services for patients and clinicians. By partnering with a service lab that had already achieved this accreditation, Taylor's lab was able to move forward with using sequencing as a diagnostic tool. The introduction of this workflow into an accredited service environment was led by Helen Lindsay and Nick Camm.

Today, what at first had seemed like a risky approach has been proven successful[4,5]. The Illumina Genome Analyzer has been in use as a diagnostic service in the United Kingdom for over a year. "In that time our lab retest rates have fallen 10-fold, costs have been dramatically reduced and so have reporting turnaround times. At the same time the data quality has been consistently very high and the service successfully achieved top marks on external quality assessment," notes Prof. Taylor.

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Data Analysis

For a diagnostic test, sequencing isn't enough. You've got to have the ability to accurately and quickly process the information. With the amount of coverage supplied by the Genome Analyzer, that can be a challenge. To overcome this, Prof. Taylor worked with a group of bioinformaticians from Cancer Research, UK led by Aengus Stewart, based at the London Research Institute. Prof. Taylor was fortunate enough to begin working with this group early on in his diagnostic service development process, so he was well aware of the informatics requirements. He admits that, "the bulk of the work we do now is processing the information. The lab work has become somewhat trivial really—to prepare the sample and do the preliminary analysis is easy." Now, information processing in his lab has evolved to the point where they can swiftly handle all of it. "Once you get used to it, it's really quite straightforward because everything is done informatically. The process you need for a diagnostic pathway is almost done for you in the informatics pipeline, almost automatically. It makes a lot of the quality control going through the process more straightforward and quicker."

The clinicians using the service are excited at the prospect of increasing the ranges of tests available and the development of "one-stop" tests for many genes at the same time.

What's next?

Now that the BRCA sequencing test is in use, Prof. Taylor is exploring new opportunities for using the Genome Analyzer to improve health care. Developing diagnostic methods for cardiomyopathy and colorectal cancer are next on his list. "We're really very much scratching the surface of what's available now."

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