Genetic testing has become more common in cancer care in recent years. However, nearly all such tests are limited to a few genetic alterations that affect patient responses to targeted agents. Now, several groups are working to expand that approach to more patients and more genes, including many with unknown function or import.

Earlier this fall, researchers launched two programs designed to offer genetic testing to thousands of patients in routine care. Cancer Research UK is running one program, and Dana-Farber Cancer Institute and Brigham and Women’s Hospital in Boston are running the other. Together, the projects will probably speed uptake of genetic testing in regular cancer care, as well as provide the raw data that researchers need for future drug development and improved interventions.

Making the Most of a National Service
In the first phase of Cancer Research UK’s Stratified Medicine Programme, investigators plan to test tumor samples from 9,000 patients who have melanoma, breast, bowel, lung, prostate, and ovarian cancer and who are seen at one of seven National Health Service (NHS) hospitals over the next 2 years. Once patients agree to participate, tumors will be tested for approximately 20 genetic alterations in eight genes. The results of individual tests will be returned to the patients’ physicians, but the data are for research purposes only and not intended to guide therapy. (Traditional NHS programs will continue to administer standard-of-care tests approved for clinical care, such as epidermal growth factor receptor [EGFR] testing in lung cancer.)

The goals of the Stratified Medicine Programme are twofold, according to Director James Peach. The first is to improve service delivery of genetic tests within the NHS. The second is to demonstrate that they can capture useful research data from genetic profiling and routine care data in NHS. “There is a bunch of stuff that the NHS makes more difficult,” Peach said. “But the one thing the NHS makes easier is a unified bioinformatics solution, and that is what we are trying to do.”

The first portion of the work builds on existing systems to improve the quality of genetic tests while reducing their time and cost. “The informatics side—data checking, extraction, and analysis—is a more green field,” he said. “Datasets that have been designed either for payment or to facilitate further care may not be checked or defined in such a way that would enable them to be used for research,” Peach continued. Therefore, the team needs to ensure that the recorded data are accurate and of the right quality for research and are standardized enough for extraction and analysis.

Once those hurdles are overcome, the real power of the project comes from the type of patients most likely to participate. Unlike many clinical trials, which are aimed at patients who do not respond to standard care or who have advanced disease, patients in this project will exhibit all stages of cancer, with many coming in with early-stage, treatable disease. That patient group is relatively untapped as yet, and combining the genetic data with carefully collected patient care data outcomes should lead to new insights about potential drugs or therapeutic approaches.

As an example, Peach points to the EGFR inhibitors gefitinib and erlotinib, which were initially targeted at the lung cancer population as a whole but were later found to be effective only in patients with EGFR mutations. He suspects that with the Stratified Medicine data, investigators might see subpopulations that respond to standard drugs and thus improve patient response rates to existing agents, as well as reveal potential new targets for experimental drugs.

The second and third phases of the program aim to integrate the lessons learned from the first phase into standard care and to expand the program to more patients and more cancer types. “We think what is unique about the project we are doing here is the scale,” Peach said. If it can eventually be applied to the entire NHS population with millions of cancer patients, it would be “transformational.”

Ten Thousand Genotypes in a Year
Meanwhile in Boston, investigators at the Dana-Farber Cancer Institute have established a project called Profile, designed to genetically test tumors from approximately 10,000 patients each year. Patients will be recruited through the institute itself and through Brigham and Women’s surgery departments. As with the British program, patients with disease at any stage, or even suspected cancers, are eligible, although many will have more advanced disease by virtue of Dana-Farber’s status as a tertiary referral center.

The investigators are testing each patient’s tumor by using the OncoMap multiplex test, which probes 471 mutations in 41 genes. Initially, standard-of-care tests will go through normal channels, and the OncoMap results will be for research purposes only. Patients, though, may have their genetic test results returned to their physicians if they choose to and if the tests find information that merits medical intervention.

“The vast majority of these results are neither medically significant nor actionable, because we don’t know what they mean yet,” said Barrett Rollins, M.D., Ph.D., chief scientific officer at Dana-Farber and an architect of the program. “That is the point of the research.”
His team’s view of what is medically actionable, however, goes beyond U.S. Food and Drug Administration–approved drugs and genetic tests and includes mutations that might be relevant for clinical trials with experimental drugs. For example, in a trial testing an inhibitor of PIK3CA in breast cancer, a PIK3CA mutation in a patient is considered actionable. To ensure that the results can be used for clinical decision making when appropriate, all the OncoMap tests are being done in a Clinical Laboratory Improvement Amendments–approved setting.

Rollins says those incidental findings will surely be important for individual patients and their clinicians, but “the real heart of the project is in depositing the results from 10,000 patients per year, year after year, in two enormous data warehouses.”

Creating those databases, and secure means to link them for research queries, was an enormous challenge, according to Rollins. He expects all the effort will pay off. For example, if an investigator wanted to know what the likelihood of response was for a breast cancer patient with a particular mutation who did not respond to trastuzumab, “We’ll be able to answer that question in about 30 seconds by doing these queries,” he said.

**Influx of Data**

In addition to these two recently launched projects, many other groups are working to integrate genomic testing or sequencing into clinical care. For example, Foundation Medicine, in Cambridge, Mass., plans to use next-generation sequencing technology to analyze approximately 200 cancer-related genes in patient tumors. Moreover, René Bernards, Ph.D., head of the Molecular Carcinogenesis group at the Netherlands Cancer Institute in Amsterdam, a non-profit foundation, and colleagues at two other Dutch institutions have set up a pilot trial to sequence a similar number of cancer-related genes in patients as well.

Bernards notes that these relatively unbiased genotyping efforts in cancer patients not only will be crucial for moving the field forward but also will offer patients important opportunities in the short term. “We want to do this—on the one hand to do good translational science and on the other to attract promising drugs to the Dutch population sooner, because pharmaceutical companies would be interested to access our infrastructure to test their biomarker or find their biomarker candidates,” said Bernards.

But for Rollins the most important aspect of these new efforts is going to be the number of patients participating. “I think the key to cancer insights is all in the numbers,” he said. “As you think about mutations that are responsible for 2%, 3%, or 5% of cancers, the only way we are going to find them is by doing a relatively unbiased analysis of large numbers. I think it is doable, and I think these examples show it is.”

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