This Time, It's Personal

In what is an exciting era in the evolution of oncology treatment, this special feature by **Deborah J. Ausman** explores how Next-Generation Sequencing and Convergent Informatics are enabling personalized cancer medicine.

Humanity's fight against cancer has always been personal. Few of us haven't lost a loved one to the disease. Yet cancer treatment is decidedly impersonal. For decades, all cancer patients, regardless of the specific nature of their disease, have generally had the same three treatment options: surgery, radiation therapy, and chemotherapy. These therapies are often very effective, but they constitute a broad and imprecise attack that can damage both cancer cells and healthy tissue.

Personalized cancer medicine offers the chance to confront cancer by the same route that it attacks us — at the genomic level based on identifying and targeting the molecular alterations associated with cancerous cells. Using the same technology developed a decade ago to decode the human genome, scientists today are sequencing the genomes of cancer cells and tumors to describe the molecular subtypes of this complex disease and understand why some patients respond to certain therapies and others do not. Knowledge obtained from this research is ushering

in a true revolution in cancer care. But battling cancer in this way will require changes to cancer's diagnostic paradigm as well as new systems to manage how diagnostic data generated by clinical cancer sequencing is collected and shared among providers, physicians, and patients.

Two companies are tackling these challenges head on: Foundation Medicine, a cancer diagnostics company that is using a next-generation sequencing (NGS) platform to bring comprehensive cancer genome analysis to routine clinical care, and Thermo Fisher Scientific, a market-leading provider of scientific instrumentation and software, including a full range of solutions for clinical diagnostic labs. Thermo Fisher has developed a new clinical Laboratory Information Management System (LIMS) that combines the research-centered functionality of a traditional LIMS with capabilities typically found in Laboratory Information Systems (LIS), which manage patient records, administrative functions, and privacy compliance in hospitals and clinical settings.

"To make personalized cancer medicine a reality, life science technology and information technology have to evolve in tandem. Routine clinical sequencing of cancer requires a convergence of the up-to-now separate systems that have managed work in the lab and the clinic — the industry is asking for and the science is requiring a single lab-centric solution that delivers patient-centric results," said Dave Champagne, Vice President and General Manager of Informatics at Thermo Fisher.

Advantages of routine clinical sequencing

"The concept of personalized cancer care is simple," said Michael J. Pellini, M.D., President and Chief Executive Officer of Foundation Medicine. "Get the right therapy to the right patient at the right time." Comprehensive genomic assessment of cancer applies tools originally developed to sequence the human genome to the discovery of tumor-specific genome alterations that are associated with and may ultimately cause most cancers.

The implications are enormous. While current chemotherapy or radiation treatments target cellular mechanisms present in healthy cells as well as cancerous ones, therapies based on somatic genomic alterations can direct treatment specifically to tumors based on their genomic map.

Management of cancer patients is changing rapidly as comprehensive genomic assessment of cancer reveals novel therapeutic targets and opportunities for new clinical treatments. Several cancer therapies already exist that target specific alterations in cancer-related genes; trastuzumab (marketed as Herceptin), which targets breast tumors that overexpress the HER2/neu protein, is perhaps the best known, and other approved therapies or those in late stage development target various alterations in major cancer genes including EGFR (lung, colorectal and pancreatic cancers), KRAS (leukemia, pancreatic, colorectal, and lung cancer), and BRAF (melanoma and potentially several other cancers).

In addition to opening up avenues for exploring new therapies, routine clinical sequencing can also aid pharmaceutical companies in designing and recruiting patients for clinical trials and can provide insights into molecular drivers of response and resistance when testing potential therapies. Massachusetts General Hospital and the MD Anderson Cancer Center are two prominent institutions that have begun placing patients in trials based on the molecular profiles of their tumors, and several institutions released studies at the 2011 American Society of Clinical Oncology (ASCO) meeting in June demonstrating the efficacy of matching patients to trials based on their tumor profiles.

"Every day a drug spends in development drains resources a pharma company could put back into new R&D — more importantly, it's another day that a new therapy isn't available to benefit physicians or patients," explained Maureen Cronin, senior vice president, research and product development at Foundation Medicine.

"Routine clinical sequencing of cancer means we'll need fewer patients to prove the efficacy of new drugs. And we'll get better information from the populations we do test by correlating the

results with accumulated profiles to find molecular explanations to determine why certain patient populations don't respond — or respond better than others — to potential treatments," Cronin said.

Technologically, labs today have the capability to rapidly and cheaply analyze tumors. Current next-generation sequencing instrumentation and protocols can generate a significant amount of data on cancerous tissue for a few thousand dollars, and the time and cost of sequencing continues to drop twice as fast as Moore's Law predictions for processor speed versus cost. But, applying cancer sequencing to patient care is significantly more challenging.

The inherent heterogeneity, aneuploidy, and variation in cancer genomes, combined with the small amount of tissue typically available for analysis, require a level of sensitivity and specificity in sequencing that's significantly higher than standard sequencing methods to achieve utility in a clinical setting. That's because any test has to be actionable — performed so that results can be available in the short amount of time physicians have between treatment decisions.

Furthermore, to capitalize on therapies suggested by advancements in cancer sequencing, labs and physicians must overcome additional hurdles in diagnostic methods and data management.

Wanted: Paradigmatic shifts in diagnosis and data management

Currently available molecular tests are limited in scope and put a high demand on physicians and patients. While cancer diagnosis is trending toward using less invasive procedures that require less tissue, increased use of molecular testing in general is putting higher demands on the amount of tissue required. Multiple tests are often needed to fully characterize a tumor, which can mean obtaining large or multiple tissue samples from a single patient. The amount of time, resources, and tissue required for multiple tests is often prohibitive and can cause inconvenience and discomfort to patients already burdened with managing their illnesses.

Foundation Medicine's approach directly tackles these issues. The company's clinical diagnostic test utilizes next-generation sequencing and can be performed on a very small amount of tumor genomic material typically obtained from routine clinical formalin-fixed paraffin embedded (FFPE) specimens extracted through surgical resection, core needle biopsy, or fine needle aspiration (FNA) "We can start with as little at 50 ng of DNA. "And that 50 ng goes a long way, comprehensively assessing all of the somatic genomic alterations in a tumor rather than looking for a single point mutation," said Pellini.

A recent study announced at the June 2011 ASCO meeting reported that Foundation Medicine's test on DNA extracted from 75 cancer tissue samples achieved an average of 200x coverage depth and 100 percent concordance with conventional single-gene analysis for BRAF, KRAS, and EGFR mutations performed by commercial reference laboratories. The test identified 214 driver mutations, of which only 37 could have been detected by conventional hot spot analysis. "Any test's clinical relevance depends entirely on its accuracy and precision," Pellini said.

"Our test can report alterations within all relevant cancer-related genes with greater than 99 percent sensitivity and specificity. This study confirms that comprehensive cancer genomic testing identifies many more mutations than traditional methods — mutations that should open up new therapeutic opportunities for oncologists and their patients," Pellini added.

Foundation Medicine's approach is a promising development in cancer therapy, and the company plans to commercially launch its comprehensive test in 2012. Developing the technology, though, has revealed some unique information technology challenges. In particular, the IT infrastructure needed to deliver

this test in volumes sufficient for a fully operational clinical lab requires the convergence of lab sample tracking data, protected personal information, and a custom high-performance analysis pipeline aligned to the company's product offering.

In working with Foundation Medicine, Thermo Fisher saw that the challenges associated with collecting and communicating diagnostic data are perpetuated by an alphabet soup of well-established software systems that silo data according to the preferences of different user communities.

"LIMS predominates in laboratory settings, managing and tracking samples from when they are received by a lab to when results are reported back to physicians. On the other hand, many clinical labs, clinics, and hospitals use LIS to handle the business side of diagnostic transactions, including requisition management and reporting," Champagne said.

A clinical LIS also ensures that patient data is managed securely and with the appropriate privacy settings to keep a facility in compliance with HIPAA and CLIA regulations. Patient management also occurs in electronic medical record systems (EMRs), which record and store all information associated with a patient — from a physician's notes about a medical visit to medication history to results from all medical tests ordered in the course of treatment. EMRs, in fact, often serve as the primary interface for physicians into an LIS.

Champagne said it became clear to Thermo Fisher that the work Foundation Medicine is doing required a single informatics solution that could bring together these currently disparate tools.

LIMS, LIS, and EMR are critical, workhorse applications with long histories of use. LIMS, for instance, was first introduced to industrial and research labs in the 1980s, but has evolved to be purpose-built for specific applications and needs. Unfortunately, the same functionality that makes these systems so vital to the experts who use them also serves to lock data away and reinforce the traditional and increasingly artificial boundaries between researchers, diagnostic and clinical staff, and physicians. Plus, these systems often fail to play well with each other, forcing organizations operating in the interconnected environment of translational and personalized medicine to cobble together mechanisms to share data between systems.

"One of the major goals of the translational research movement has been to bridge the gap from bench to bedside and any initiative to blend the LIS with the LIMS can be understood as an extension of this quest," said Bruce A. Friedman, M.D., active emeritus professor of pathology at the University of Michigan Medical School and a vocal commentator on the role informatics plays in medicine.

He also said the lesson from all of this is obvious. "We now need to make an effort to understand the relative strengths of LIS and LIMS, looking to develop new systems that capture the best features of both."

The best of all information technology worlds

Ultimately, according to Champagne, the various systems needed to drive advancements in cancer clinical sequencing distill into two categories. Research labs require software that can manage samples, integrate with internal applications and laboratory instrumentation, track research processes, and support analysis and reporting. Clinics, on the other hand, need logical, patient-

centered ways to request tests and view results in context with an organization's administrative and business rules and in ways that comply with regulations about data security and patient privacy.

"For personalized medicine to realize its goal of matching the right therapy to the right patient at the right time, the software used by those developing and delivering next-generation therapies must bring the right data to the right people at the right time. Discipline-centered boxes are still vital to ensuring that data is appropriately captured and stored, but it's important to think outside those boxes if we are to empower all the players in therapeutic decision chain and achieve the efficiencies that will drive faster diagnoses and better patient outcomes," Champagne said.

Thermo Fisher Scientific has developed and introduced at Foundation Medicine the first system that combines the functionality of a secure, compliant patient management system with tools to drive complex and changeable lab workflows. The Thermo Scientific Clinical LIMS delivers several capabilities that Foundation Medicine identified as critical to helping them maximize their investment in analytical instrumentation, optimize lab workflows, and streamline communication with physicians. For instance, the system provides a sample-centric orientation.

"Many traditional LIMS focus on processes or workflows. But to make comprehensive cancer genome analysis a part of routine clinical practice, our workflows are anything but routine," Pellini said.

He also pointed out that scientists at Foundation Medicine will often select different library construction or DNA processing steps based on real-time analysis of samples. A sample-oriented system ensures that Foundation Medicine can track everything that has happened to each biospecimen it receives from the moment samples arrive at the lab to when the results are reported back to physicians.

Additionally, the Thermo Scientific Clinical LIMS is built with a hierarchical structure that simplifies and tracks chain-of-custody for laboratories. No matter what path a sample takes in the laboratory, the Clinical LIMS stores history and identifies each user involved in the process. And along the way, patient demographics and required chain-of-custody information remain associated with samples. This enables clinical labs to track the genomic and phenotypic data associated with biospecimens while remaining in compliance with HIPAA and other privacy laws. Furthermore, the software provides contextualized, actionable information on the molecular forces underlying a patient's disease — information that empowers physicians to devise specific, personalized treatment plans for patients.

Champagne said Thermo Fisher has supported the clinical diagnostics field for years, with a comprehensive portfolio of instruments, reagents, biomarkers, analyzers and consumables.

"We saw a real market need. The disparate systems traditionally used by labs and clinics have obstructed the absolutely necessary, unbroken information stream that simply must exist if we are to revolutionize patient care. It was a natural extension of our commitment to the clinical diagnostics market to provide a streamlined end-to-end informatics solution that follows the patient from the point of disease testing through results analysis, diagnosis, and treatment so that physicians can use the latest molecular diagnostic tests, like those being developed at Foundation Medicine, to deliver advanced, personalized care," he elaborated.

Driving innovation in personalized cancer medicine

According to Champagne, as life science organizations continue to search for ways to innovate, the informatics tools that support them must evolve symbiotically.

"Increasingly, our customers are asking for better ways to access, share, and leverage the data they generate so that it has a direct business impact," he said. "It's not just about making the lab run better and faster — it's about finding entirely new ways of approaching a scientific question or tackling a therapeutic problem." Foundation Medicine's Pellini concurred.

"The more cancers we sequence, the more information we'll have to mine — and the more information we'll need to *find a way* to mine," noted Pellini.

To truly personalize cancer treatment and change the diagnostic paradigm from one-size-fits-all therapies to disease-specific treatment plans, labs and clinics must first change the way they capture, store, access, and communicate this information.

"The advances taking place with our informatics partners create enormous possibilities for our company and for our work. Rather than empirically drilling down to find a specific genetic sequence like we do today, we'll be able to comb cancer's genetic landscape for trends, scanning for alterations associated with a given cancer subtype or exploring possible pathways associated with drug resistance," said Pellini. "There's no telling what we'll find." ■

For more information on Thermo Scientific Clinical LIMS or on the work of Foundation Medicine, please visit:
www.thermoscientific.com/clinicallims
www.foundationmedicine.com

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