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Amid Rapid Progress and Uncertainties, NorthShore Brings Personalized Medicine to Chicago Community

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NEW YORK (GenomeWeb) – When Karen Kaul joined the NorthShore University HealthSystem in 1992 to establish a molecular diagnostics lab, she brought with her two lab technicians. She can count the conditions she tested for that first year on one hand: tuberculosis, cytomegalovirus infections, and T-cell and B-cell gene rearrangements for diagnosing lymphomas and leukemias.

That molecular diagnostic lab located in the tree-lined north Chicago suburbs has gone from testing several hundred patients each year on a handful of assays to now running dozens of tests for 100,000 patients a year for a range of infectious diseases, inherited conditions, and cancers. "We've gone from the dark ages of having to run gels with radioactive probes … to now looking at next-gen sequencing," said Kaul, who spent her post-doctoral years at the National Cancer Institute studying the MET oncogene at a time when researchers were just starting to clone genes. "It's exciting to see some of these genes, such as MET, are now reaching the clinic."

For Kaul, who now chairs NorthShore's pathology department, the molecular diagnostics lab is the heart of the system's personalized medicine ambitions. In launching the Center of Personalized Medicine this past spring, NorthShore aims to expend between $4 million and $5 million per year to integrate genetic testing and counseling into various aspects of patient care.

For several years the healthcare facility has operated a Center for Medical Genetics that has implemented programs to identify patients at risk for breast and ovarian cancer, for example. But under the new program, patients and doctors have access to clinics that specialize in individualizing care for cancer and heart conditions, as well as a pharmacogenomics clinic that provides testing and educates people on how biomarkers influence their ability to respond to drugs. Clinicians are working on long-term research studies to improve understanding of how genomics contributes to health risks and developing diagnostics that one day may help doctors prevent illness.

Although many of these efforts are just getting started, personalized medicine has already piqued the curiosity of the community that NorthShore's four-hospital system serves. Around the country, systems like NorthShore's noted an uptick in public interest after President Obama's $215 million Precision Medicine Initiative turned "precision" into a buzzword in healthcare.

On the heels of the announcement that the government will collect and analyze a variety of deidentified data points, including genomic information, from 1 million volunteers, major research centers around the country, drug and diagnostics firms, and hospitals all highlighted their efforts to make healthcare more precise — so much so, HHS felt the need

to service mark the moniker "precision medicine initiative." Meanwhile, the field has face criticism for letting runaway hype overshadow the significant scientific and systemic challenges that still need to be sorted out before personalized medicine can become a reality.

But the experts at NorthShore don't see themselves as being swept up in a trend. The institution, which fields more than 1 million office visits per year, has been laying the groundwork for years. More than two decades earlier, the MDx lab Kaul started at NorthShore was the first for Chicago and one of the first in the US. More than a decade ago, NorthShore became the first in the nation to implement an Epic electronic medical records (EMR) system. Two years ago, NorthShore launched Health Heritage, an online application through which patients can track their medical and family history, generate individualized health risk reports, and share that information with their families and doctors.

All these pieces are critical for implementing personalized medicine. But making the parts work together within a system like NorthShore's requires not just a shift in thinking, but a reimagining of process. Programming the EMR system to alert a doctor that a patient has a gene variant that makes them unlikely to respond to their depression meds, is perhaps the easy part. Parsing out what to do next, based on what could happen due to a patient's health risks, can get pretty convoluted once genomics and a myriad other data points come into play.

A study from Vanderbilt University, which has implemented EMR alerts for a handful of PGx indications, found little agreement among clinicians as to who is responsible for acting on the genetic test results to direct patient care. What happens, for example, when there are two specialists treating a patient and both could act on test results? Once the patient stops getting care within its system, is it still Vanderbilt's responsibility to alert the patient when new, potentially useful genetic information comes to light?

There's a lot of noise out there.

NorthShore has hired and retained experts to figure out these on-the-ground process conundrums raised by precision medicine. Earlier this year, NorthShore brought in pharmacogenomics expert Mark Dunnenberger to run a clinic where patients are screened for variations in 15 genes associated with response to a variety of drugs. Renowned oncologist Janardan Khandekar, a fixture at NorthShore since 1976 and director of the Center for Molecular Medicine, is spearheading programs similar to the National Cancer Institute’s MATCH trial, where cancer patients are prescribed drugs based on the molecular abnormalities driving their disease.

NorthShore further bolstered its genomics expertise by hiring Jianfeng Xu to direct the personalized cancer care program. Xu has developed a test that gauges polymorphisms in 250 genes associated with patients' lifetime risk of 20 common cancers. If validation studies are successful, NorthShore hopes to test patients with a strong family history of certain cancers and use the results to guide preventive measures.

Pablo Gejman, who led a large-scale international research effort that uncovered novel genetic markers associated with schizophrenia a few years ago, is spearheading NorthShore's Genomic Health Initiative. Through this project, the institution plans to genotype thousands of people and explore associations with common diseases.

NorthShore has made these investments with an eye toward a future where the field will have a better understanding of the links between genes and diseases and personalized care will be the norm. But the doctors and researchers guiding these efforts, while enthusiastic about personalized medicine, seem to appreciate that they've signed up for what may be a very long haul. Meanwhile, at the present juncture between actionable science and hype, figuring out what to report back to patients and physicians, and how to present this information, can be tricky.

Peter Hulick, who joined NorthShore as a medical geneticist in 2008 and now heads its Center for Medical Genetics, spends his time thinking about just this. For the most part, he sees the NorthShore patient community as one that wants to get more involved in their care. For example, two-thirds of the approximately 60 patients that NorthShore's PGx clinic has seen since launching came out of their own interest rather than being referred by another physician or healthcare facility.

After the president announced the Precision Medicine Initiative, Hulick noted a spike in calls to the medical genetics division from people wondering what this means for their health. He also has found that the center starts getting more calls every time the press breathlessly reports a new genetic risk factor for cancer. "There's a lot of noise out there," he said.

The 'Aha!' moment

Clinicians at NorthShore are consciously trying to cut through some of the noise within its personalized medicine program. For example, patients who come to the PGx clinic must sit through two days of in-person education. Before they get a test from PGXL Laboratories that depending on insurance coverage patients may have to pay a few hundred dollars for, the first day at the clinic is all about setting realistic expectations about what they can and cannot learn at the end of the process. If they decide to go ahead with testing, the second visit a week later is to receive and discuss results related to 15 genes.

On that second visit to the clinic, not everyone finds answers to their drug-response difficulties, but for some, the results provide that "Aha!" moment, explaining years of trial-and-error prescribing. Dunnenberger recalled one patient who had gotten PGx testing two years ago because the pain management drugs she was on wasn't doing their job. But her doctors didn't know what to do with the test results.

When she came to NorthShore hoping to make sense of things, Dunnenberger was able to explain that the CYP2D6 gene encoded an enzyme that was important for metabolizing certain opioids. But she had a variation in CYP2D6 that made her a "poor metabolizer," meaning she was unable to normally metabolize the drugs. By this time, she was already getting the right treatment through trial and error, but the clinic visit helped explain why she hadn't been responding to all those drugs for so long. "This got her to trust her clinician more, that they were doing right by her," Dunnenberger said.

This patient's experience also shed light on the frustration doctors felt. Previously, physicians would order testing through NorthShore's Center for Medical Genetics, but they didn't know what to do next. "Then, they began questioning the value of pharmacogenomics," said Dunnenberger, who completed a residency at St. Jude Children's Research Hospital in Memphis, Tennessee, one of the few places in the country with a so-called preemptive PGx testing program.

Experts who believe in pharmacogenomic testing as a tool for preventing drug-related adverse events believe this information is most useful if it is already available to doctors when they go to prescribe a drug. This requires testing patients "preemptively," well before the results are needed to guide care, and storing the information in the EMR.

Dunnenberger and other experts at NorthShore are giving a lot of thought to how to incorporate the results garnered in the PGx clinic into patients' EMR and when to alert doctors to something really important. "Clinicians have been prescribing the right medications to the right patients for years through trial and error," he said. "But now we're just trying to add genomics in there to make their picture a little clearer."

Patients who get tested through the PGx clinic receive a report detailing their results for 15 genes related to drug response, and the findings are incorporated in a progress note in the EMR. A few PGx indications have been incorporated into alerts so far. If physicians decide not to follow the recommendation in the alert, they have to indicate why in order to override it.

Crafting these electronic alerts involves some art. Physicians will likely ignore too light a nudge, while too many alerts could have the unintended effect of deterring doctors from prescribing the drugs that trigger the alerts. "One thing that would be bad is if we drove people away from a really good medication that was relatively cheap, to an alternative that was very expensive but also good," said Dunnenberger, whose group is collecting information on what doctors do in response to these pop ups. "We're working methodically to figure out these alerts. We don't want to send a bunch of alerts that no one is paying attention to."

Contributing to research

By involving the community it serves in research projects, NorthShore also aspires to contribute to the field's evolving understanding of how genomics influences health and disease. The centerpiece of these efforts is the Genomic Health Initiative, in which researchers are studying the prevalence and outcomes associated with known disease-predisposition markers and hoping to discover new associations. Since the project was launched a year-and-a-half earlier, 8,000 people have enrolled at various medical sites or through the NorthShoreConnect patient portal.

Volunteers give a small amount of blood — less than a tablespoon's worth — in addition to the blood they would give when they visit an outpatient clinic or a phlebotomist. Patients give NorthShore researchers consent to analyze their sample, use it to conduct research, and to access their EMR information so their DNA data may be studied alongside medical and family history.

To genotype blood samples, researchers are using a SNP chip that scans for 850,000 SNPs, many of which are linked to pharmacogenomic traits and risks for common disorders. Around 6,000 participants have been genotyped thus far.

This has to be done with great responsibility.

Gejman, who is leading GHI, said there was no hard target as to the number of participants investigators wished to enroll, but a future goal would be to try to encourage all NorthShore customers to volunteer. "We thought this was an opportunity for us to get a lot of samples in a short amount of time," said Michael Caplan, chief scientific officer of NorthShore's

Research Institute. He would eventually like to see GHI project volunteers become part of the 1-million-person cohort that will power the government's Precision Medicine Initiative.

Before agreeing to be genotyped, GHI participants can decide if they want to be contacted should testing uncover actionable markers related to his or her health. Several hundred patients could potentially have actionable results from GHI. So far, more than 90 percent of enrollees have said they want to be recontacted.

This surprised Caplan, who is part of a committee chaired by Hulick to figure out which results to return to study participants. "I kind of thought may be half would [want to know] and the other half would be worried that this was information they didn't want to know," he said.

Because within GHI genotyping will not occur in a lab certified under the Clinical Laboratory Improvement Amendments (CLIA), researchers will only inform patients that a medically important result has been found. If the patient wants to learn the specifics, the results must be confirmed by a CLIA-certified lab and the patient may require genetic counseling, according to Gejman. "The results from GHI aren't incorporated into patients' EMR unless there is a return of clinical data," he explained.

Gejman's team is being very conservative about which results to report, since patients will be tested for SNPs that have unclear links to diseases or confer very small risks for common conditions, as well as rare markers that are more penetrant. "We're very aware that returning genetic results to participants in this kind of a study is a moving target," Gejman said.

The committee in charge of deciding which results to return will take into account recommendations of the American College of Medical Genetics and Genomics. The committee will also consider proposals from individual investigators about returning results on specific markers. "But this will be very strict, because this has to be done with great responsibility," Gejman said.

An example of the type of information patients could learn is whether they have a BRCA mutation associated with heightened risk of hereditary breast and ovarian cancer. Patients with deleterious mutations would get counseling, and based on their medical and family history, could get surgery to reduce their cancer risk.

Whether to report APOE4 carrier status, meanwhile, has been a more difficult decision within GHI. People with one or two copies of APOE4 are at risk of getting late-onset Alzheimer's disease several years earlier than those without these markers. Like BRCA mutation carriers, APOE4 carriers aren't destined to get the disease, but they are limited in the ways they can mitigate their Alzheimer's risk beyond dietary and lifestyle changes. The committee figuring out which results to return to study participants is still mulling what to do about APOE4.

Oncology is another area where genomic research and patient care will connect at NorthShore. Khandekar and his colleagues within the oncology division are working on launching studies similar to NCI's MATCH trial. NorthShore will be partnering with a group in California to rapidly sequence patients' normal and tumor tissue in the hopes of identifying more effective treatment options. Experts at NorthShore wouldn't name the California lab since this deal hasn't been finalized, but said they wanted to fast track this type of analysis for cancer patients.

"Patients are very savvy, in general, so they know genetic testing is available," said Annette Sereika, a nurse at NorthShore's Cancer Center and the Center for Personalized Medicine. But cancer care is expensive, and the science is still evolving. So, not every patient will receive molecularly-guided treatment.

Some cancer patients are referred to NorthShore's Personalized Oncology Clinic and tumor boards discuss difficult cases in order to decide which patients should receive molecular profiling. These patients get tested on a sequencing panel conducted by firms such as Foundation Medicine or on a panel developed at NorthShore.

In this way, Khandekar and his colleagues have already uncovered new cancer mutations. For example, one prostate cancer patient had a ROS1 rearrangement, usually found in 1 percent of non-small cell lung cancer patients. This prostate cancer patient received the lung cancer drug Xalkori (crizotinib), which targets this marker, and he has responded well so far, according to Khandekar.

Despite these successes, the reality is that not every cancer patient will benefit from molecularly-guided treatment. So, Khandekar is careful in setting patient's expectations. "We try to tell people this is just the beginning of the field and it's going to take time," he said, recognizing that personalized medicine may not be broadly available in his professional lifetime. "We tell them right up front the limitations and that we don't know if we are going to find something. Or that we might find something but there may not be a drug. Ultimately, we don't know if it's going to work out."

Progress in uncertain times

Although its early days, proponents of personalized medicine are encouraged by progress in the field. The US Food and Drug Administration is approving more and more precision drugs every year, and according to the Personalized Medicine Coalition, 20 percent of newly approved drugs last year fit in this category. Still, precision drugs comprise a small slice of the overall drug market, and there are limited molecular treatment strategies for diseases beyond cancer.

Similarly, the molecular diagnostics space is projected to top $8 billion by 2020, but currently comprises around 10 percent of the more than $50 billion in vitro diagnostics market. However, having noted the breakneck expansion in the MDx industry, payors are paying closer attention to the types of testing they consider medically necessary. In recent years molecular diagnostic firms have faced deep payment cuts, and some companies have gone belly up.

We only know the tip of the iceberg. Most of the genome remains a black box.

Kaul feels fortunate to have operated NorthShore's molecular diagnostics lab profitably all these years. "It was always an issue with evolving reimbursement challenges to cover lab costs and continue to grow," she said. "It was advantageous to have a broad menu, especially early on, and not just do cancer testing."

NorthShore's MDx lab currently has two Life Technologies sequencing instruments, has capabilities for conventional sequencing, and several real-time PCR systems. Using these machines, the MDx lab can analyze patient samples for specific analytes or a range of markers at once if needed. Still, she acknowledged that educating physicians and payors on what testing is medically necessary is a constant challenge.

For example, in recent years, insurers deemed PCR testing for whooping cough and flu experimental. One insurer even refused to pay for gene rearrangement testing, saying it's not standard of care. "That's been the standard of care for decades," Kaul said. "We need better communication with insurers to clarify why coverage of such tests is valid."

Another worry for Kaul is the uncertainty around FDA regulation of laboratory-developed tests (LDTs). The FDA issued draft guidelines and held public meetings to discuss its plans with industry, but a large part of the lab community hasn't backed the proposal.

If FDA's LDT guidelines were implemented as proposed, "it would be detrimental to patient care," Kaul said. Many of the LDTs in the MDx lab would have to be revalidated, but in the meantime, there wouldn't be FDA-approved alternatives, she pointed out.

When discussing the havoc FDA regulation would create, lab industry players often cite the example of KRAS mutation testing for metastatic colorectal cancer. Researchers published data in 2007 showing that patients with certain KRAS mutations are unlikely to respond to the drug Erbitux (cetuximab), but it wasn't until 2012 that doctors gained access to an FDA-approved kit. By then, researchers were finding that mutations in the RAS family of genes, not just in KRAS, may be important for personalizing colorectal cancer treatment.

In those intervening years before there was an FDA-approved test, NorthShore's MDx lab, like many others around the country, was performing its own, internally developed and validated KRAS testing under CLIA (the traditional regulatory pathway for labs). Then, as research elucidated the utility of other markers, NorthShore's lab began testing additional RAS genes.

While Kaul acknowledged there is room for improvement in LDT oversight, she wondered what would have happened if her lab couldn't perform KRAS testing all those years before FDA approved a kit. "Would that have been in the best interest of patients?"

Ultimately, its patients and what's in their best interest is guiding NorthShore as it navigates the fast evolving and often experimental nature of precision medicine today. Patients in the NorthShore system currently receive genetic testing or molecularly-guided care in very specific disease contexts, within its clinics, or as part of research, but the majority likely won’t. For now, that's just as well. "We only know the tip of the iceberg," Gejman said. "Most of the genome remains a black box."