For genomic testing, a homegrown software solution

NGS and PGx workflows get big assist from bioinformatics platform

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November 2021—At NorthShore University HealthSystem in suburban Chicago, a homegrown bioinformatics solution is the "secret sauce" that powers the health system's personalized medicine program, says Kamalakar Gulukota, PhD, MBA, director of NorthShore's Center for Bioinformatics and Computational Biology.

Dr. Gulukota and the small group of bioinformaticians who developed Flype, as the solution is known, describe the software's architecture and its diverse set of functions in an article published recently in the *American Journal of Medical Genetics* (Helseth DL, et al. 2021;187[1]:37–47). With genomic testing has come informatics challenges, he and his coauthors write, including managing the data, interpreting the results, and providing clinical decision support.

"Genomics is a rapidly evolving field in terms of the types of data that come through, the types of tests that are run, and how that data is packaged. So the field is immature," Dr. Gulukota says, noting he's seen at least six data formats come through in the five years he and his colleagues have worked on Flype. "On the other side you have the EMR systems, and those are by necessity stable, mature systems," updated infrequently. "So you need something of a middleware to take the data coming through rapidly evolving systems on the one side and package it for the more stable systems on the other side. That's where Flype comes in."

Flype is a web-based platform written with open-source software that has been in operation at NorthShore for more than five years. Broadly, it supports clinical reporting of in-house next-generation sequencing and pharmacogenomic testing to NorthShore's Epic EHR and sends orders to and receives results from NorthShore's commercial NGS laboratory partners. It performs a variety of additional functions: acting as a central repository for all genomic variants identified in patient specimens, allowing population frequency analysis of such variants, and performing secondary and tertiary analysis of NGS data, among others. And it does all this while remaining agile enough to support novel assays and new integrations with commercial NGS laboratories.

Until the full length and breadth of genomic data is defined and "as stable as medical records," Dr. Gulukota says, "the middleware role is not going to go away." EHR companies are having "a tough time growing into integrating all this data," he says, because EHR systems are large to begin with and incorporating additional data and clinical decision support rules is difficult.

Dr. Gulukota

Filtering the results down to the clinically actionable is another challenge, especially for genetic tests performed in-house. Dr. Gulukota estimates that only five to 10 of the thousands of variants detected by NorthShore's somatic mutation testing panel, for instance, are typically signed out and reported. "It becomes difficult for the EMR [companies] to decide how much of that data should be incorporated into the patient record. Generally speaking, they've come to the conclusion that only the signed-out variants will go into the EMR, and I think that's a wise decision. But then who does the filtering? Who handles the sign-out process? That requires a system, so after you sign out, you need to talk to your EMR. So the need for the middleware isn't going to go away, not only because the speed at which the two technologies are evolving is very different, but also because of the analysis, secondary

and tertiary, that needs to happen before the data is ready for the EMR."

Integrating genomic data from external labs into patient management can be difficult because the results are often in the form of a PDF or a scanned image and clinicians have to find those results before they can take action, Dr. Gulukota says. With in-house NGS testing, additional results have to be incorporated into the EHR. "With Flype, we've found different ways to integrate those results into the EHR so they're available not only to someone who looks for them but also as best-practice advisories and other pop-ups needed by our partners." They've integrated in-house and vendor testing, he says, and keep the data in discrete element form and share and analyze it using various knowledge bases.

On Flype's front end is a web interface in which authenticated users can upload and interpret NGS or pharmacogenomic data, sign out test results, and perform audits of test performance. On the back end is a relational database that keeps track of patient samples and the genomic variants identified within them, a custom code base of bioinformatics pipelines, and a connection framework that employs open-source standards to connect to NorthShore's internal systems, as well as commercial NGS labs, other external partners such as consumer genomics companies, and external knowledge bases.

The platform is integrated with NorthShore's Ion Torrent sequencing machines. It supports the import and sign-out of a 50-gene cancer hotspot panel, a 40-gene myeloid panel, an expanded gene panel based on the NCI-MATCH trial assay, additional NGS assays to detect cell-free DNA, and an inherited cancer syndrome panel. Flype filters the variants output from the Torrent Suite software to remove known germline polymorphisms based on population databases and any variants that are on a lab-maintained list of frequently seen artifacts. The software provides the sign-out pathologist with a dashboard that lists the relevant results of each sample, along with custom links that contain information about the gene and variant from knowledge bases like OncoKB and BRCA Exchange, as well as a NorthShore-specific knowledge base. From the dashboard, pathologists can enter their interpretation of the variant, assign a variant to be included on the front page of the report, include a variant in the report but label it of unknown significance, or choose not to include a variant in the report. Upon sign-out, the platform generates a PDF of the report and sends it to the EHR.

Flype also retains interpretive information from sample to sample. The software notifies the sign-out pathologist when a mutation identified in a patient sample was previously interpreted and provides a drop-down menu with a list of the tumors in which it was identified. "And you can choose the one closest to your diagnosis, make edits as necessary, and sign it out," Dr. Gulukota says. "You're building on an interpretation someone else already has completed." And sometimes a variant of unknown significance is upgraded to pathogenic in one of the knowledge bases with which Flype is integrated, such as ClinVar. In NorthShore's patient population, such reclassifications happen to at least some variants monthly or even weekly, Dr. Gulukota notes. The platform's built-in reporting tools can identify specific patients who may be impacted, and those patients are informed when clinicians deem it necessary.

When NorthShore began to offer genomic testing, Dr. Gulukota and his colleagues purchased a commercial bioinformatics solution to perform variant annotation and act as a variant repository. But they soon realized the commercial solution lacked functionalities that were needed to advance NorthShore's personalized medicine offerings. It was unable to connect to the EHR or retain interpretive information from one patient specimen to the next, and it had limited ability to connect to external knowledge bases. The capabilities the software did have were too general to speak to the specific use cases NorthShore required, Dr. Gulukota says. "The commercial solution was extremely comprehensive and therefore almost useless." It was unable to determine the most clinically relevant transcript for a given gene mutation, for instance, and instead would include every possible transcript in the report. "Whereas because we were building our own [solution], we could say, 'We know what transcript we mean, and that's the transcript oncologists are familiar with, in terms of coordinates. In the future we can switch the chosen transcript if needed, but for now, let's choose one transcript and call it that.' And that has reduced 20 to 30 percent of the time our pathologists spend looking through results."

"That's just one example," he continues, "but there are 100 such decisions you have to make. And using

something general purpose is less effective than something agile that is able to speak to each individual use case."

The platform's agility was put to the test at the height of the pandemic, he says, when NorthShore became one of the first hospitals in the Midwest to develop a SARS-CoV-2 RT-PCR test. As with NorthShore's genomic testing, the SARS-CoV-2 test posed an informatics challenge. "There are two aspects to it. One, do you have the test itself and can you produce the data? We had the test, and we could produce the COVID-19 negative or positive result. But then, how do you integrate it into patient care?" With isolation beds at a premium and physicians eager for patient results, the lab's call center was overrun. "And it was actually slowing testing down because people were tending to the phones rather than running the tests."

So Dr. Gulukota's team pulled the SARS-CoV-2 sample tracking information from SoftLab, the lab's internal specimen-tracking system, and developed an interface in Flype through which physicians could view results and track test progress. "It was simply a matter of having the accession numbers uploaded and pulling the patient demographics," Dr. Gulukota says. "SoftLab didn't have such an interface so we built one in Flype, so that clinicians could log in and look up results and when they would be available."

"It had nothing to do with genomics," he adds. "We were helping with logistics. Still, it had a huge impact on the throughput of specimens the lab could handle. When unforeseen emergencies occur and your systems are not prepared, an agile system is very helpful for working through new pipelines and workflows."

Introducing pharmacogenomic testing provided further impetus for developing a homegrown solution. Interpreting PGx data requires combining genotypes at multiple loci in a gene into a single star allele diplotype for that gene, and "even this basic requirement was entirely outside the purview of our installed commercial software," Dr. Gulukota and coauthors write in the *American Journal of Medical Genetics*. "You can go to PharmGKB or another knowledge base and look up an exhaustive list of the possible combinations of variants at each locus," he tells CAP TODAY. "Computationally that's not difficult to do, at least conceptually." The problem is that PGx testing doesn't query every locus. "The public definitions of the star alleles are based on any place in which there might be a variant, and they're including all of those in the determination of the star allele. You are testing only a small subset of that, so how do you determine the star allele? And what do you do with the loci that PharmGKB lists but you're not testing, so you can't say what is in those loci?"

"We built an automated pipeline based on the data coming from our panels," he continues. "Then we say, 'Based on these loci in the genome that we are querying, here are the star alleles that we can determine, and here are those we can't determine.' We have a boilerplate at the end of the report that says, 'These are the ones that we can distinguish,' and given the report we write out the diplotype."

Flype's PGx testing workflow is similar to the platform's NGS workflow. Lab personnel upload PGx data directly into Flype, after which the platform converts the genotype results from the PGx testing panel to the corresponding star allele diplotypes. PGx experts in NorthShore's pharmacy department then review the results, add prescribing recommendations to the report, and sign it out, at which point Flype sends the report to the EHR. At the same time, Flype sends the results to ActX, an external PGx knowledge base partner. When a physician writes a prescription through the EHR, communication with the ActX rules engine is initiated to determine any potential concerns based on the patient's PGx results, some of which trigger interruptive warnings. "The script is evaluated in real time at the point of care and relevant information is sent to the clinician," Dr. Gulukota says. And Flype is involved with every step, he notes, "from creating the data to sending discrete data elements to the patient record."

With Flype, molecular tumor board discussions are easier to arrange, Dr. Gulukota says. When tumor genomes are sequenced, the pathologist's report includes not only the variants found but also all relevant information from NorthShore's internal knowledge base, as well as the external knowledge bases with which Flype is integrated. The report is sent automatically to the molecular tumor board so that "when they arrive, they have all the elements in place."

Flype also helps with quality control. The platform's population frequencies pipeline monitors when a particular

genotype occurs at unusually high or low levels in NorthShore's patient population. "That tells you there may be a problem with your test," Dr. Gulukota says. Flype also has helped the lab identify patients with rare genetic material. "And those patients' DNA becomes very valuable because it can be used to validate new platforms." Dr. Gulukota and his team solicited input from the pathology lab throughout Flype's development, he says, and continue to meet weekly with the lab to discuss new needs or updates. "We're working closely with the folks who are doing the testing, signing out the reports, and analyzing it on the clinical side."

While the field of genomic medicine still is in flux, several trends are apparent, Dr. Gulukota and coauthors write. One is that the dichotomy between clinically actionable findings and all other genomic findings, such as those patients receive from consumer genomics companies, is gradually becoming weaker. The actionable portion will grow over time, they say, and thus it's important to have a clearinghouse, distinct from the EHR, for storing genomic data that is not yet clinically actionable. Future laboratories are likely to report all variants that are reliably detected, they predict, regardless of whether they are actionable at the time of testing. Making this a routine component of clinical practice will help organizations track the status of such variants, they write, and "provide a more robust integration of genomic results into clinical practice."

The second trend they note is that the $1,000 genome still is far away for clinical purposes, and it's unclear how an entire genome would be represented, let alone used, in clinical care. Interfacing with multiple knowledge bases, providing clinical decision support in the EHR, and updating periodically the variant status for all patients would be valuable. These capabilities are bundled into Flype, Dr. Gulukota and coauthors say, and "will be put to the test in the future as more and more genomic data are marked up as clinically relevant."

Third, given the economics of genome sequencing technology, the commercial NGS labs will remain a strong presence, they write, and the need to interface with multiple labs will remain important. In addition, genomic data formats are likely to continue to fluctuate. The modular, extensible code employed by Flype could allow organizations to respond to changing data formats by approaching new formats as additional third-party connections to be brought into the existing framework.

Flype is configurable for use by other health systems, and Dr. Gulukota and colleagues will provide the source code on request. But marketing Flype to other organizations would raise issues of intellectual property and questions about the extent to which NorthShore would be involved in supporting the software. "Obviously we are not in the software business, so the best thing for us to do would be to provide other organizations with the source code" and let them take the lead from there. "But they would need bioinformatics groups strong enough to be able to take the code and run with it and do all the things needed to connect it to their other systems."

"We've had some interest," he says of the discussions that have taken place with a few groups. "It runs into logistical challenges."

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