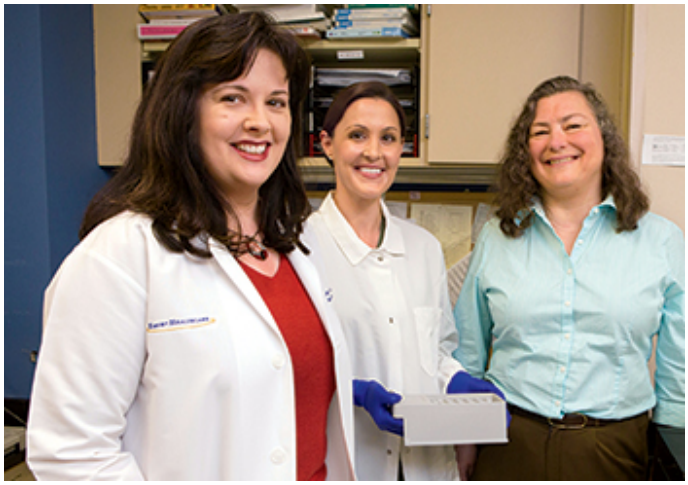
Workflow, regulatory unknowns tax molecular IT

Anne Paxton

April 2015—Alexis Carter, MD, immediate past president of the Association for Pathology Informatics, isn't under any illusion about how well information technology is meeting the needs of molecular diagnostics. "Laboratory information systems right now do a fairly decent job of getting samples to the right lab, tracking the sample, and reporting results," Dr. Carter says. But when it comes to molecular diagnostics laboratories, "LISs are really not where they should be. They're kind of moving at a turtle's pace to keep up."



For molecular diagnostics laboratories, "LISs are really not where they should be," says Dr. Alexis Carter (left), at Emory with Jordan Magee Owens, MLS (center), and molecular diagnostics supervisor Heather Jones, MB, CHS.

Even Dr. Carter was somewhat surprised, however, by the results of a survey she recently conducted, which found that molecular diagnostic labs are heavy users of manual processes and paper. "The vast majority of them have no electronic communication of data between the LIS and the actual instrument that's doing the testing. They're literally manually typing data into these instruments and using paper logs to track work and paper printouts to evaluate test results. Which is completely the opposite of our general chemistry lab."

While knowledge of the genome and demand for molecular diagnostics continue to expand, IT in molecular diagnostics is lagging behind, Dr. Carter and other informatics experts agree. They suggest that the complexities of molecular data, along with big regulatory uncertainties, are among the factors holding back innovation and progress.

In molecular diagnostics, the bioinformatics pipeline is the generation and interpretation of data, particularly for next-generation sequencing or microarrays. Clinical informatics "really wraps over all of that," says Dr. Carter, who is director of pathology informatics at Emory University School of Medicine. "It's how we validate in the laboratory, how we make sure we're doing the right tests for the right patients with the specimen we're looking at, how we automate the workflow process in the lab, how we retrieve data later. Clinical informaticists deal with all of that plus the human-computer interface."

LIS manufacturers like Cerner, Sunquest, and Soft Computer have developed software modules geared to handling molecular diagnostics data, including Millennium Helix, Sunquest Molecular, and SoftMolecular. "Often, the way worksheets are created is not how the molecular lab does testing," Dr. Carter says. "So people end up manually typing in data anyway, and it's kind of a point and click thing. It's not totally automated and electronic."

Moreover, molecular laboratories are rarely flush with cash. “Molecular testing is increasing at a far higher rate than general laboratory testing, but molecular is still not the big moneymaker in the laboratory.” Even at a large institution like Emory, she says, molecular makes up a small part of the budget. “When you are trying to purchase a specialized information system that will help support your workflow, that becomes a real challenge.”

In a large molecular laboratory, it can cost $1 million to $2.5 million just to implement a specialized molecular diagnostics system, Dr. Carter says, plus hundreds of thousands more each year in maintenance. “So your molecular lab has to be quite sizable for you to be able to afford doing this.” This reality, in turn, places the vendors in a difficult position. “In order to put resources into developing their systems to better accommodate molecular testing, they have to have people wanting to buy them, and there are not a lot of laboratories with that kind of funding.”

Her laboratory is in the process of issuing a request for proposals from multiple companies to support its molecular workflow. However, among her colleagues, Dr. Carter says, “Nobody is really telling me they have massive automation in their molecular labs, and the few that are more highly automated have very homegrown systems that have not been purchased from a commercial vendor.”

But the biggest factor stalling sales in molecular IT, in her view, is the threat of serious regulation, as the Food and Drug Administration readies a final rule on laboratory-developed tests—expected to be issued at some point in the next year or so, but possibly later. The FDA issued a draft guidance document on LDTs last October, and public comments were accepted until Feb. 2.

“If the oversight framework for LDTs that the FDA has proposed goes through,” Dr. Carter says, “there are going to be even fewer molecular labs out there that can purchase such systems.” Vendors would naturally want to be cautious about putting a lot of resources into developing molecular lab systems, she says, “because there may not be very many, if any, clients to buy it at the end of the day.”

All the molecular tests and FISH tests done at Emory, for example, are LDTs, she points out. “Even though the FISH tests themselves were FDA approved, because we’re such a big lab and we do so much FISH testing, we have to use automated wash steps, which means we have to revalidate as an LDT because we’ve made modifications to the FDA-approved test.”

With FDA charges for premarketing approval of a test being in excess of $250,000 per test per indicated use, Dr. Carter says chances are not high that Emory or other similar labs would continue performing LDTs if they had to put them all through the FDA. While she can’t predict what Emory would do, she suspects that in such a case, many laboratories will start sending their molecular testing out.

When the FDA draft guidance will be finalized, and in what form, is unknown. “It could change very little or it could change a huge amount between now and when they decide to finalize it. But the very fact that the draft guidance is out there is probably going to stifle innovation and investors willing to invest in IT, because of the threat of regulation,” Dr. Carter says.

Nevertheless, demand for new molecular tests remains high. “The threat of regulation can scare investors off, but every day there are more discoveries about various genes and their potential significance for cancer therapeutics, for inherited diseases, for what drugs can be given to patients that won’t be toxic to them. There’s a huge amount of demand out there, and practically every day we’re getting messages from our oncologists asking ‘when are we going to develop this next test?’” Manual data entry is one of the things diverting resources, she adds, so the lack of safe automation is hobbling progress in making new tests available.

The FDA confronted serious issues when it took up regulation of LDTs, Dr. Carter says. “They were actually trying to protect patients from some very unscrupulous people who develop some very poor tests. Some patients had ovaries removed that didn’t need to be; some patients got chemotherapy who didn’t need chemotherapy.” But while she understands where the FDA standards are coming from, “I think making us all go through FDA approval probably is not going to be as helpful as they think it is. And until we figure out exactly what the FDA is going to do,

there may be even less innovation in this area."

There is a big gap between employing information technology in molecular and its use in the clinical lab, says Federico A. Monzon, MD, former medical director of molecular diagnostics at Houston Methodist Hospital. "We're starting to see instruments that are more geared toward the clinical testing environment, but still there's no specific requirement for molecular instruments to be able to communicate with LISs or produce information specific to laboratories," he points out.

Dr. Monzon

Still, Dr. Monzon, who is now medical director of oncology for the reference laboratory Invitae in San Francisco, does not believe molecular IT necessarily has to stay behind the curve. It's true that the great majority of molecular diagnostic laboratories continue to rely on a lot of paper. But at Invitae, "We believe we're closing the gap."

Even though the average molecular diagnostic laboratory has not reduced its level of manual input very much, "In our lab we've made an effort to automate as much as possible so that any steps after accessioning are all electronic. We are probably one of the most automated labs in that regard."

Forty percent of the personnel at Invitae are involved in IT and informatics, and "we can leverage those resources," Dr. Monzon says. "All our instruments are basically online in communicating with the LIS and creating a record of each step as it happens." Invitae's informatics also include the use of custom algorithms that whittle down data from millions of nucleotides to just the most relevant ones in human disease.

Still, he notes, such capabilities are easier to accomplish at a reference laboratory like Invitae. "Today it would be difficult for a small or medium hospital lab to implement a focused bioinformatics structure for NGS-based molecular assays. But as this technology becomes more widely adopted, we expect development of solutions for all types of labs."

In general, the traditional LIS can provide a good solution for billing and reporting, but it won't handle the workflow of molecular lab testing—identifying the paraffin block, doing nucleic acid extraction on the sample, quantitating DNA/RNA, and handling complex bench workflow, with quality control parameter integration, says Mark J. Routbort, MD, PhD, director of computational and integrational pathology and medical director of laboratory informatics for the University of Texas MD Anderson Cancer Center.

The paper worksheet solution that molecular labs frequently resort to has the failing of interrupting the chain of identifiers on the sample. But it's difficult to translate the general laboratory information system for use in a molecular lab, Dr. Routbort contends. "In the general laboratory, the lab devices themselves receive orders, conduct all the operational steps, and spit out results to the LIS. So a lot of workflow is transparent to the LIS—but automated."

By contrast, instruments doing flow cytometry, cytogenetics, or molecular diagnostics have more complex workflows with steps involving review in third-party software systems dedicated to complex analytic review. "The LIS is not designed to interface with instruments like that." In a sense, Dr. Routbort says, if you consider the logic of the operational analysis that happens inside self-contained automated clinical analyzers, "I would say the guts of that analysis are generally much more exposed for molecular testing." The data files are translated into multiple

workstations for technologists to work with software systems that interpret and analyze the data.

With their molecular modules, the big vendors have tried to refashion the LIS to accommodate the unique workflow of molecular testing, but for the most part the penetrance of those modules in molecular labs is not very high, Dr. Routbort says. He points out that many of his colleagues in molecular labs are still using non-LIS solutions to laboratory workflow.

At MD Anderson, "We're using a custom-designed software solution that has a full-fledged, server-based, relational database with a front-end application to handle exports for sample lists to instruments and imports for integrating instrument results." For some tests like BCR/ABL1 fusion percentage—used to track responses to therapy in CML patients—a numeric analytic value can be obtained in a structured way. "But we also have a large number of tests where the data does not fit into a typical lab model. For example, microarray data, and NGS mutation and copy number variation. Neither of those fits very well into a model of 'here's the analyte and here's the number,' because the complexity of results you see is basically unbounded. There's no predefined list of mutations that a patient might have; they may have novel mutations that have never been described before."

As is the case in the molecular labs of other large academic institutions, most of MD Anderson's tests are laboratory developed, Dr. Routbort says, and he considers IT to be part and parcel of each test. "Increasingly, IT systems are recognized as part of the molecular test and subject to the same kinds of validation and change control that would apply to your instruments or reagents."

Dr. Routbort

As a point of reference, he says, "Our main NGS panel, when we run an assay, has about 30 software parameters that are individually settable for just the portion of the system that calls mutations, and changing any one of those can potentially change the characteristics of the data that come out of that assay in profound ways. So you can't just 'tweak the system' by changing one parameter in isolation. You essentially have to revalidate the changed parameter against all your data."

At this time, the major IT project his laboratory is working on is front-end automation. "We're focusing on the steps from receiving a sample in the laboratory to the preanalytic product, which would be DNA, RNA, or cDNA, because those are high-volume steps in our lab and shared by many different workstations. Once those products are generated, we may do Sanger-based sequencing, NGS, microarray—a bunch of different tests. But the generation of those initial samples is something we'd like to have as automated as possible."

By employing automated tube labelers that can map conventional human-readable labels with preprinted matrix identifiers on the bottom of each tube, the lab will be able to deploy rack level scanners throughout the laboratory that can identify and track each sample. "That opens up the road to all kinds of downstream automation for DNA and RNA extraction and the quantitation of those products," Dr. Routbort says. Interestingly, the technology is already widely used in research labs but has been slow to be placed into clinical molecular labs, to a large extent because of the interrelationship of the latter with the LIS, he adds.

Aside from the pending FDA rule on laboratory-developed tests, another gray area that has yet to be charted is whether molecular laboratories can store their data in private servers on the cloud. "It's a very complicated topic," says Dr. Carter. "There's no consensus guideline for how to manage your data in the cloud."

The Health Insurance Portability and Accountability Act was passed in 1996, and its final security regulations were

adopted in 2003, specifying what can and cannot be done with electronic protected health information. “HIPAA describes what identifiers you have to scrub from your data in order to de-identify it under HIPAA, but they had a catchall clause at the end,” Dr. Carter says. “Many people didn’t interpret genetic information in that catchall, as having to be scrubbed from a person’s record, because they considered it to be like a laboratory test result such as a sodium.”

Then along came the 2008 Genetic Information Non-Discrimination Act, or GINA, the goal of which was to protect patients and their genetic information from being discovered by an insurer and used to discriminate against them. Under that act, an extremely broad definition of genetic information was adopted, so that a protein test of a patient that could indicate their native, inherited genetic status was considered genetic information.

Fast forward five more years, and the HIPAA Omnibus Rule of 2013 made more sweeping changes, including specifically adding genetic information, as defined in GINA, as protected health information. “Effectively, the conservative interpretation is that a genetic test now has to be scrubbed from a patient’s record in order to de-identify it,” Dr. Carter says, “although the precise interpretation has not gone to court and we haven’t had anyone like the Supreme Court weigh in on this.”

In her view, conservative interpretation means you cannot use genetic data alone—even without an identifier like the patient’s name or date of birth—because in and of itself the genetic data is an identifier. “If you’re talking about a whole exome or genome sequence, one could reasonably argue that the data could be matched to an individual patient. That would mean for a lot of researchers that they have to get informed consent from patients to use their genetic data. But many labs are still operating as they did previously.”

On the other hand, a short sequencing algorithm like pyrosequencing, for example, looking for a BRAF mutation which is identified in about half of melanoma patients, could reasonably be viewed as not individually identifiable, she points out.

Making sure storage on the cloud is HIPAA-compliant is not going to be a simple task for molecular labs. “This has been identified as a major issue and source of confusion for many labs by the Association for Molecular Pathology,” says Dr. Carter, who is chairing a new informatics subdivision of AMP that is considering developing guidance for laboratories on how to deal with the cloud.

“Many labs have identified that having data managed by professionals is a far better situation than having it on a server or on a personal computer in your lab. But there may be labs that aren’t aware of all the other regulations they have to pay attention to when they do that. Just as we’re struggling to find LISs that can support our workflow, I think we’re also struggling to find software companies that can support storing that data in the cloud in a way that is not going to get us in trouble with HIPAA audits.”

Despite such regulatory challenges, as Dr. Monzon emphasizes, the importance of molecular IT extends beyond the individual molecular diagnostics laboratory. Responsible management of the information is critical, Dr. Monzon says, because sharing of genetic information benefits everyone. “Right now, when we identify a novel mutation, it’s sometimes difficult to find information about its clinical relevance. The biggest challenge for the next few years is going to be how do we share this information to make it as clinically useful as possible by the use of public databases, such as ClinVar and ClinGen.”

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