Q&A with Dr. Elaine Lyon, Vice President of Lab Genetics for ACMG's Board of Directors, on Key Issues Affecting Laboratory Genetics in 2020 and Beyond

In a recent interview with *The ACMG Medical Geneticist*, ACMG Vice President of Laboratory Genetics Elaine Lyon, PhD, FACMG, Director of the Clinical Services Laboratory at HudsonAlpha Institute of Biotechnology, explained how the College is advocating on behalf of laboratory geneticist members to improve reimbursement, update the process for developing new tests, and mitigate professional consequences related to SARS-CoV-2.

ACMG Medical Geneticist: Last year ACMG released a statement on *Recognition of Board-Certified Clinical Laboratory Professionals as Qualified Healthcare Professionals*. How would this help improve reimbursement for results interpretations performed by laboratory geneticists and what is needed to make this a reality?

Elaine Lyon (EL): Through a survey a couple of years ago we identified that this is one of the issues that is very important for our members. The PhD members as well as many international MD and DO without state medical licensure are board-certified through the American Board of Medical Genetics and Genomics, and in all aspects they are recognized as healthcare professionals, except for billing purposes. So ACMG started by issuing a statement about how these laboratory geneticists should be recognized, and that started a conversation with other organizations.

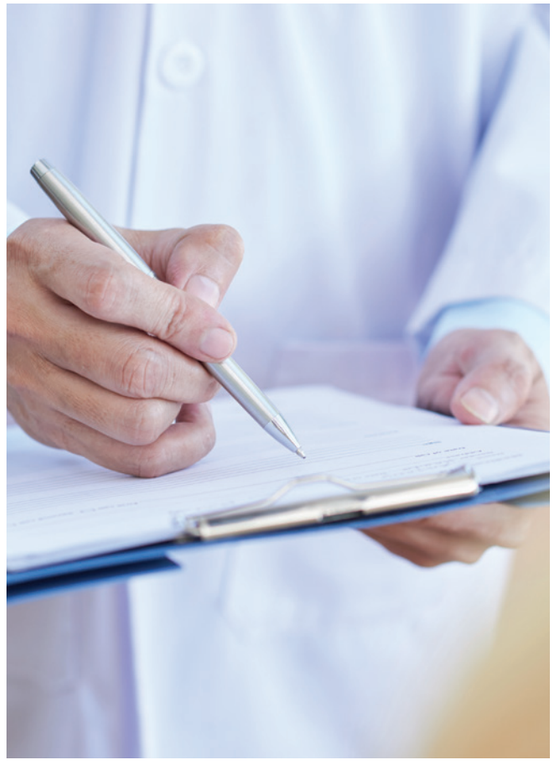
This is the first step, not the end in and of itself. Once board-certified PhDs and MD/DOs are recognized as a healthcare professional by the Centers for Medicare and Medicaid Services (CMS), there is more work to be done. It may require licensing in different states and working with state legislatures, and it may require adjustments in current billing codes or creation of new codes. But it's the right thing to do because in all aspects we are working as healthcare professionals.

ACMG is doing groundwork now with other organizations and working on draft language to take to Congress. It is critical that we have the support from other organizations, such as medical associations whose members rely on interpretive information in reports provided by laboratory professionals, before moving forward with Congress. We were planning to accomplish most of this work during face-to-face meetings, which haven't happened, so it's putting us behind a little bit. But we are still working on it and once we have the support and the language, then we need to take it to Congress to find sponsors both in the House and the Senate who will introduce this bill and champion it. The language will be added to another bill, in all likelihood. And then—you've probably heard the phrase, "It'll take an act of Congress," meaning it will take a long time—in this case it actually will take an act of Congress! But persistence and tenacity will be in our favor, and we'll need to have a lot of persistence to move this along.

After a bill with language has been introduced, ACMG members will be able to help by reaching out to their Congressional leaders. We will be encouraging members to become actively involved in this. COVID-19 has gotten in the way a bit, and this is an election year, so not much is going to happen until after the elections. But as soon as Congress is ready for us, we will be ready for them.

ACMG: Last year the Food and Drug Administration (FDA) made multiple statements and took actions on pharmacogenomic laboratory-developed tests (LDTs), including restricting what information could be included on the reports provided to ordering healthcare providers. How does this affect laboratory professionals' ability to provide clinical information to the ordering healthcare professional, and could it impact the physician's ability to treat their patients?

EL: The FDA's concern was that some labs were providing more information than what they maybe should have, and also that they may have been interpreting some gene-drug associations where the evidence wasn't as strong as what



FDA would have liked. The other concern was that patients might use that information to make changes to their medications without their physician's input.

ACMG strongly supports that adjustments only be made with a physician's order, and that the physicians will be the ones to make the judgments because they have personal interaction with the patient and have information the laboratory may not have. However, clinicians and patients do rely on the laboratory to provide an interpretation. For example, what does it mean if you're a poor metabolizer? And the idea of restricting the information we provide actually runs counter to some regulations. In addition, CMS recently came out with a decision to cover reimbursement for certain pharmacogenomic tests and indicates that laboratories need to provide interpretation with those reports.

Right now there may be a fine line between what a "genetics lab report" may be and what qualifies as "clinical decision support," meaning a situation where information from a patient, such as what medications the patient may be on, can be used to personalize the report and make it more useful. That qualifies as clinical decision support, and we perhaps should separate those two out to allow the labs to do the interpretation that is needed. But if the labs are providing clinical decision support, the situation may require more input from pharmacy professionals.

ACMG has a Laboratory Quality Assurance Committee workgroup that is updating their standards from 2012 for the gene *CYP2D6*, and while *CYP2D6* is a good example, I hope it can be applied more broadly. I'm very enthusiastic about what ACMG will come out with as a professional society.

The other good news is that FDA wants to work with the pharmacogenomics community, and they put in a table of gene-drug interactions that they feel have enough evidence, including drugs with FDA labeling that require testing before the drugs are prescribed. As the laboratories and other professional societies provide their input, the FDA's list will grow. We'll be able to continue pharmacogenomic testing with appropriate genetic interpretation.

ACMG: For more than a decade there have been attempts by the FDA and Congress to reform regulatory oversight for LDTs so that FDA plays a bigger role. Is there a need for FDA oversight in development of any LDTs? If so, which ones? And what should that oversight look like?

EL: I support ACMG's recently issued statement, published June 2020 in *Genetics in Medicine*, which describes a role for third-party assessment. The statement proposes three risk categories—low, medium, and high—where for low-risk tests, labs can continue doing what they're doing, for moderate-risk tests, laboratories can bring the test on and have it reviewed by a third party, and the high-risk test will require a third-party review before its offered to the public. ("High-risk" is defined as a test that could predict risk of a disease associated with progression of a disease that carries significant morbidity or mortality, and test methodology based on a unique algorithm or proprietary method that makes it difficult to accomplish inter-laboratory comparison.)

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I think everyone acknowledges that some reform or CLIA modernization needs to be done, but whether it needs to involve the FDA is another question that requires further discussions. CLIA was developed in 1988, when there wasn't even a hint of the type of genomic testing we are doing now in 2020. So, modernizing it to provide clarity would be good, but without imposing additional burdens for labs.

ACMG: The introduction of the Verifying Accurate, Leading-edge IVCT Development Act, or the VALID Act (H.R.6102 and S.3404), this year has renewed attention to FDA regulation of LDTs. If passed, how would the VALID Act impact laboratories?

EL: This is a major issue for ACMG members. To give a little background, Congress currently gives CMS authority over clinical laboratories and LDTs, and the FDA has authority over manufacturers. FDA currently assumes the authority to regulate labs because they consider labs to be test manufacturers, but to date they have exercised enforcement discretion, meaning they haven't required labs to submit LDTs for FDA review for the most part. The VALID Act of 2020 would change that by giving FDA legislative authority over LDTs, under the claim that developing LDTs in CLIA-certified labs recategorizes those labs as manufacturers.

The 245-page VALID Act proposes a system most CLIA labs are not prepared for because they simply don't have processes in place to perform what it describes, including premarket approval, adverse event reporting, and postmarket surveillance. Currently, labs can take FDA-cleared products and modify them to expand their use and fit specific niche testing, working collaboratively as customers of manufacturers, but with VALID the CLIA labs would be responsible for taking these modifications to the FDA. Yet the principles are the same as what clinical labs currently follow through CLIA (clinical and analytical validation, pre- and post-processes, indications and claims for the test, and appropriate testing). One positive is that it would allow grandfathering in existing CLIA tests under certain conditions.

The language of the VALID Act could be beneficial for true manufacturers because right now it's incredibly expensive for them to get a test through FDA with the number and type of studies that are required, and the goal of this act, according to what I've heard, is to "level the playing field" between manufacturers and clinical labs, since it's easier for labs to develop, validate, and implement an LDT than it is for a manufacturer to take a test kit through the FDA. But the VALID Act will also put clinical labs under dual regulation with CMS and FDA, which is not really leveling the playing field. Instead, dual regulation will most likely make it more difficult for clinical laboratories to bring on new tests.

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VALID may hinder laboratory modification of FDA-approved tests—a practice I like to call "continual improvement," since we are able to adjust and improve these tests as more scientific information surfaces. For example, it may delay access to early technologies because clinical labs will be less nimble. It may also limit the number of new tests that clinical labs can bring on because if every test or test method needs to be submitted to the FDA, they won't have the capacity for their current development plans. And, of course, the real concern is what will it do to the cost of developing new tests. The current process for a premarket approval evidently requires millions of dollars for companies to do the studies. The other pathway is the 510(k) clearance process, which is still several hundred thousand dollars. Even with precertification which would allow a "technology certification," the costs may be prohibitive for clinical labs to bring on several new tests with different technologies in a year.

ACMG laboratory geneticists and other ACMG members are "Stepping Up in the Fight against COVID-19." To highlight the work of ACMG members, we have requested stories from all members about the important work they are doing during the pandemic, which were then profiled on ACMG's Facebook, Twitter and Instagram channels. Some of these stories are included in this edition, starting on page 12.

My main concern if this VALID Act goes through is that the smaller laboratories or specialty laboratories won't be able to afford to customize tests, and clinical testing may go into more of a pharmaceutical company model with only several very large clinical laboratories involved with development because it's too much of a financial risk for the small labs with lower test volumes, particularly the academic labs. And unfortunately, it's the academic labs that are training our next generation of laboratory professionals. So, if that component goes away from academic medicine, it will be more difficult for us to have a highly trained workforce. I don't know that all of this will happen, but there's a potential for it to happen.

ACMG: The sponsors of the VALID Act have touted that this legislation could have prevented delays in the rollout of SARS-CoV-2 testing by removing regulatory uncertainty, whereas others have said that FDA involvement with LDTs unnecessarily impedes availability in emergency situations. What do you see as the role of FDA, if any, in implementation of LDTs in public health emergency situations such as this?

EL: I believe that any immediate response to a public health crisis needs to pull in the expertise of laboratory professionals. LDTs may not be the final answer, but LDTs could be a first step to get some testing out for initial management of the situation. In any immediate response, there's so much expertise from the laboratory professionals who have been designing and developing these tests for years that they need to be part of the first responders. So, any emergency response should give the lab professionals freedom to do this.

With the onset of SARS-CoV-2 infections, clinical labs anticipated that the FDA would begin enforcing their oversight of LDTs (as was done previously with Zika), and they knew that FDA was likely to come out with a statement about the emergency regulatory requirements. As I mentioned previously, clinical labs don't have the processes in place to take tests to the FDA quickly. This meant that most had to wait for the manufacturers to develop the needed SARS-CoV-2 test kits. And it wasn't even just that. There also seemed to be a general expectation that the Centers for Disease Control and Prevention (CDC) would manufacture test kits and send them to the public health labs for testing. However, the belief that public health labs could handle these volumes of testing was unrealistic and it was a problem that most of us in the field could see. So, if the FDA would allow the clinical laboratories to perform the LDTs during an emergency, as we are trained and experienced in doing, I think we could respond much more quickly to any pandemic going forward.

ACMG: We have already covered some very important topics, but are there any other concerning issues that are currently impacting laboratory geneticists that you'd like to discuss?

EL: Several other legislative bills have been introduced that I'd like people to be aware of. First is the Verified Innovative Testing in American Laboratories Act, or VITAL Act, of 2020 (S.3512), which simply clarifies that clinical labs aren't manufacturers and therefore not subject to FDA oversight. It's very short and there's not much traction to date, but we're keeping an eye on it.

Two other bills provide incentives for state Medicaid programs to cover genetic and genomic sequencing. One of these bills is the Advancing Access to Precision Medicine Act (H.R.4393), the other is Ending the Diagnostic Odyssey Act of 2019 (H.R.4144 and S.3116), and they're very similar. One is broadly for genetic sequencing, the other specifically covers only whole genome sequencing.

Finally, the Coronavirus Provider Protection Act (H.R.7059) is written to protect physicians from unique liability concerns during this pandemic when they may be called to help with COVID patients even though that's not their specialty, or they've been asked to not see patients because the hospital was closing down nonessential services. Sometimes there may have been significant problems with patients because they were not able to see their physicians. ACMG recognizes that similar challenges apply to the laboratory side, where people were shifting resources to handle COVID, and at the same time the regular testing hasn't been coming through at its usual volume. Both of those circumstances can affect turnaround times the laboratory can meet.

If you have enjoyed reading this Q & A with Dr. Lyon, we invite you to listen to her recent interview with the mendelspod.com podcast. Dr. Lyon discusses the challenges of COVID-19 testing, how regulatory uncertainty has impacted the development of tests, and new draft legislation including the VALID and VITAL Acts.

ACMG recognizes that these issues apply to laboratories, and we are working with Congress to identify opportunities to include language for laboratories and lab professionals. The College recently started a new Advocacy and Government Affairs Committee, and I'm very excited about this new committee because as you can tell, there's so much going on and ACMG is going to be right there. This committee could be another way for members to become involved with our work.