Clinical labs worry proposed FDA rules may force tough choices

At ARUP Laboratories in Salt Lake City, pathologists and clinical chemists receive tens of thousands of blood, urine and biopsy samples every day. Some come from the nearby University of Utah, which owns the not-for-profit lab, whereas others come from government agencies, large teaching hospitals or small clinics around the country. All of these clients have one thing in common: they rely on ARUP to perform clinical tests that they rarely use and so don't provide at their own facility. ARUP offers more than 3,000 different tests, and hundreds of them are carried out using protocols that the lab has created itself and then fine-tuned over many years. These lab-developed tests, as they're called—because they don't pass hands between a company that develops them and a lab that purchases and uses them—have never before been regulated by the US Food and Drug Administration (FDA). That's about to change.

In response to the proliferation of lab-developed tests, which are increasingly marketed to consumers, the FDA notified the US Congress on 31 July that it plans to issue guidance on the regulation of such tests. At the same time, the agency published a Draft Framework Guidance outlining how the regulation would be carried out. The official proposal won't be open for public comment until the end of September, and it will likely be years before the regulation is finalized and then fully implemented. But laboratories like ARUP are already worried about how it will affect business—and patient care.

"The concern is that if we have hundreds of tests falling into this new framework, we have to start making decisions on which we do the work for first, and which we put off," says Mark Astill, vice president of research and development at ARUP. "We'll spend a lot more time revisiting the medicine we've already been practicing rather than addressing new technologies." Even if there is a five-year window to complete the trials and paperwork necessary for the new approval, Astill says it will take time and money away from normal operations. And this could be reflected in the cost of the tests.

Casting a wide net

Lab-developed tests aren't just made for rare diseases such as those that ARUP specializes in. The vast majority of genetic tests fall into the new regulation, as do certain tests for the presence of antibodies and for vitamin

levels, microbiology cultures, microscope analyses—including Pap smears—and some particularly tricky tests required to match transplant donors to recipients, just to name a few.

At some academic laboratories where clinical tools are tailored to the research needs of scientists at the institution, nearly every test offered is considered a lab-developed test. "We do all kinds of genomic testing for the entire human lifespan, ranging from eight-week fetal cells to cancers," says Shashi Kulkarni, director of the clinical genomics lab at Washington University School of Medicine in St. Louis. "And 99.9% of our tests are lab-developed tests."

Kulkarni says he already collaborates with government agencies—including the CDC, the National Institute for Standards and Technology and the National Center for Biotechnology Information—to ensure that his lab is using the most up-to-date techniques. And he receives oversight—ranging from lab visits to blinded specimens he must test—through three existing frameworks, administered by the Centers for Medicare & Medicaid Services, the College of American Pathologists and the FDA's Clinical Laboratory Improvement Amendments regulations.

"If this change in FDA regulations goes into effect, it's going to significantly increase the cost of our clinical tests, and it might actually lead to the closure of many clinical labs," Kulkarni says. Establishing the clinical relevance of every genetic test, he says, will be too time-consuming for small labs to take on. "We might not be able to have all these tools in our repertoire to help patients anymore." Samples could instead be sent to larger, off-site laboratories that have the resources to push their lab-developed tests through the approval process—but that often means extra time waiting for results and higher costs.

Risk stratification

The FDA notes that not all lab-developed tests carry the same risk profile, and the framework they're proposing reflects that. Advisory committees would be created to help stratify these tests into low-, medium- or high-risk categories. Tests that fall into the high-risk group will require the most information—clinical trials and evidence of clinical relevance—for approval.

"Globally, things that tend to be riskier include diagnosing someone with a serious

Put to the test: ARUP Laboratories.

disease when they've been asymptomatic," says Katie Serrano, deputy director of the FDA's Division of Chemistry and Toxicology Devices. "Screening tests, just because of the broad nature of them, also fall into this same thought, and then any kind of diagnosis of the severity of a disease." Already, the agency has lumped a number of lab-developed tests into an exempt category—those that are only used for forensic or law-enforcement purposes as well as those tests that have existed since 1976 (when the current framework was established). Tests for rare diseases or tests for which no FDA-approved alternative exists—if deemed low-risk enough—could also be exempted after they go through an initial analysis.

"Part of the concern four years ago, when this first started being discussed, was that it wasn't clear they were differentiating between tests," says William Clarke, director of clinical toxicology at Johns Hopkins Hospital in Baltimore. "I think the framework proposed is actually pretty reasonable, and they took a quite measured approach."

Within two years of issuing final guidance, the FDA hopes to be able to release further details on what criteria will be used to assign risk categories to lab-developed tests—in the meantime, they plan to establish advisory committees consisting of experts from the field to help them determine how this risk assessment should work. Until then, many labs—including commercial, for-profit ventures that have largely declined to make statements on the proposed regulations—are holding out on an opinion. "It's so new that it's really not clear how it will impact everyone," Clarke says.

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