FDA Stepping Up Actions Against PGx Testing, Forcing Some Labs to Stop Reporting Drug Information

Aug 16, 2019 | Turna Ray

NEW YORK – The US Food and Drug Administration last month intensified regulatory actions against labs offering pharmacogenetics services without premarket clearance or approval in an apparent attempt to prod more firms to submit their tests for regulatory review.

At least one lab engaged in discussions with the agency before the latest regulatory sweep, while others interviewed for this story indicated they are seriously considering taking their tests through FDA review. However, most industry players revealed that the agency's communications have been vague, lacking specific guidance as to what companies should do to come under compliance.

As a result, most labs are scrambling to decipher regulatory expectations, and in the interim, companies are reporting only PGx variants detected in patients and removing any mention of drugs or drug classes from their online marketing materials or lab reports. Labs that employ medical liaisons or have reports that can interface with clinical decision support are relying on those resources to ensure that healthcare providers can still understand the potential clinical significance of detected PGx variants on their patients.

In addition to reining in commercial labs doing PGx, GenomeWeb has learned that the agency has asked at least one population health study — the NIH's All of Us Research Program — to only return to participants information on genetic markers that are in FDA-approved drug labeling. The All of Us program plans to report certain clinically actionable genetic markers, including PGx variants, to participants.

In an email, an NIH spokesperson confirmed that the program is collaborating with the FDA on an investigational device exemption (IDE) submission. The FDA requires sponsors to file for an exemption before an investigational device that poses significant risk to human subjects can be used in a clinical study, and previously it has even asked researchers to file IDEs before they can use genomic sequencing to inform patient care within federally funded studies.

The FDA had indicated in recent months that it plans to regulate PGx testing. In a safety alert last November, the agency cautioned patients and healthcare providers against changing treatments based on PGx tests without its approval. The FDA also said at the time that it was looking into companies selling PGx testing for unapproved uses.

In April, the agency sent a warning letter to Inova Health System's genomics lab in Virginia for marketing its MediMap test without approval. Subsequently, the health system decided to stop providing PGx testing entirely.

Industry insiders fear the agency's recent persistence in regulating PGx testing will have a chilling effect on the space, forcing labs to either stop offering such services like Inova or restricting labs from reporting PGx

variants alongside any drug information and making it difficult for physicians to use them in clinical decision-making.

In a statement, an FDA spokesperson acknowledged regulators are continuing to monitor this issue and that the agency has communicated with other sponsors about their marketing claims without naming specific sponsors. "We maintain our commitment to look into the marketing of pharmacogenetic tests with claims to predict how a person will respond to specific medications in cases where the relationship between genetic variations and the medication's effects has not been established and is not described in the drug labeling," the spokesperson said.

However, industry insiders have been critical of the FDA's tactics and feel the agency is trying to regulate the practice of medicine and control the dissemination of scientific knowledge. "A lot of people in the field are of the opinion that the FDA may have reached too far in terms of trying to regulate the knowledge around PGx," said one PGx expert at an academic institution, who asked for anonymity to avoid the FDA's attention.

"Everyone recognizes the FDA has an important role in regulating the claims of a commercial product if they're not supported scientifically," he said. "But, the notion that they are the only ones with the ability to say whether something is scientifically supported or not, that's not even consistent with most of medical knowledge."

Vague communication, aggressive tactics

Two companies, Myriad Genetics and Genomind, announced recently that they have had interactions with the FDA about their PGx offerings.

Myriad Genetics announced this week during a call to discuss its fiscal year 2019 financials that it had shared evidence on its GeneSight psychotropic PGx test with the FDA earlier this year, but more recently, the agency had reached out asking the company to make certain changes to the test. The company said it disagrees with the changes the FDA has requested, but it is in discussions with the agency and has submitted a proposal about how it plans to report GeneSight results to doctors.

The GeneSight report has historically presented the impact of pharmacogenes on drugs in color-coded groups: green representing drugs that should be "used as directed," yellow indicating a "moderate gene-drug interaction," and red for a "significant gene-drug interaction." At the time this article was published, the website still featured a sample report that displayed results in this way. Industry analysts believe that Myriad will likely push to keep its color-coded system, but if the FDA gets its way and Myriad has to stop mentioning drugs in its report the way other labs have, then it may negatively impact physician uptake of the test.

According to Genomind CEO Shawn Patrick O'Brien, the company voluntarily reached out to the FDA last year to discuss how to achieve regulatory clearance for its PGx test. More recently, the agency informed Genomind that it intended to regulate the entire PGx space. It became clear that the FDA wanted companies to stop mentioning drugs or drug classes associated with genetic variants in reports, said O'Brien, and the company complied.

Last week, Genomind announced a new, more focused PGx report that relays information on 24 genes implicated in mental health. The company is also increasing its pharmacogenomic expert counseling resources and will add real-time chat capabilities to its clinician portal.

Genomind has always employed "medical liaisons" with expertise in clinical pharmacology, who walk physicians and nurse practitioners through test results and their implications on patients. "We anticipate

that physicians and care providers looking at doing PGx will need more consultation to understand the knowledge they need to make an informed decision on a patient," O'Brien said.

Multiple sources said OneOme has also been contacted by the FDA and has stopped reporting drug information, but the company declined to comment for this article. A number of firms, including Color, no longer mention any drugs on their websites and only list the pharmacogenes and variants they report on. Admera Health's website currently lists neither any drugs nor the genes and directs physicians to the FDA's webpage on PGx markers in drug labeling and the PharmGKB database. The company didn't respond to a request for comment.

Executives at other labs contacted by the FDA, and industry insiders knowledgeable of these interactions, declined to comment on the record for this article, but several agreed to being quoted anonymously or to talk on background to avoid further attention from the agency.

Consistently, these sources recounted how the FDA appears to be going down a list of PGx labs, sending them letters that reference the warning to Inova and asking labs to interpret what that means for them from a regulatory standpoint. The letter labs are receiving contains no guidance as to what specific actions they must take to make PGx testing compliant under FDA regulations, sources said.

"The FDA basically says,'Read this letter and see how it applies to you,'" one executive at a PGx testing firm said, describing the vague interactions it has had with the agency regarding its offering. The source asked to remain anonymous, not wanting to "pick a fight" with the FDA, but said the agency was employing aggressive tactics against small labs.

"Nobody can survive the full weight of the FDA. If they wanted to make your life miserable or shut you down, they would," the executive said. Hoping to avoid further difficulties, this lab replied to the FDA's letter and provided information about its test, and is even considering filing for 510(k) clearance.

"This is kind of a conundrum for me," the executive said. "Why would I want to [seek FDA clearance] when our testing service is not a device and my lab is running an LDT under CLIA."

The FDA's push to regulate PGx testing brings into question the agency's authority to regulate LDTs, which the lab industry has long contested. Former FDA Commissioner Scott Gottlieb managed to strike a conciliatory tone with industry by promising to advance a new regulatory framework for all diagnostics, including lab tests, through Congress.

But, last December, members of the House of Representatives released a new draft bill that was almost entirely influenced by the FDA and largely supplanted the framework industry stakeholders had been working on with legislators. The FDA's version would give the agency explicit authority to regulate all diagnostics, whether developed as a test kit or as a lab service, and remove problematic tests from the market.

This didn't sit well with members of the lab industry and pathologists who fundamentally disagree that lab services are akin to the medical devices that the FDA regulates. This historical tension is stirred up every time the agency seeks to regulate a portion of the lab testing market.

And, if the FDA has been vague in its latest interactions with labs performing PGx tests, as sources have claimed, then this background may be why. "FDA is going to each company individually ... and asking them to take actions when they don't really have a policy on how to take actions," O'Brien said. "They don't have an agreed-on policy on how to regulate this industry yet."

The FDA, of course, has always insisted that the existing laws are sufficient to regulate LDTs. While it has chosen not to regulate LDTs, and left oversight largely to CMS under CLIA, it does have the authority to lift

enforcement discretion when it sees fit.

"The FDA remains committed to pursuing legislation relating to *in vitro* clinical tests," the agency spokesperson said. "*In vitro* diagnostics, whether they are LDTs or not, are devices within the meaning of the Federal Food, Drug, and Cosmetic Act, and therefore, they are subject to applicable device requirements under the statute and regulations … Although the FDA has generally exercised enforcement discretion for LDTs, the agency retains authority to take action when appropriate, such as to address significant public health concerns."

When asked to cite the public health issues that spurred the agency to take action, the spokesperson said the FDA is aware that healthcare providers may have inappropriately changed patients' medications based on PGx tests that claim to inform dosing or regimens of some antidepressants. The FDA did not provide any specifics beyond that.

The agency has also previously expressed concern that consumers with easy access to tests online may change drug regimens or dosing on their own, without consulting a doctor, based on unproven claims. Industry players also bristled at that suggestion, asserting that the agency has never produced evidence that this is occuring.

Researchers led by Robert Green at Brigham and Women's Hospital looked at whether consumers getting direct-to-consumer genetic testing were using PGx tests to change treatment decisions. They found that out of nearly 1,000 individuals more than 90 percent had an atypical PGx result, but only 54 said they altered a drug or started a new therapy based on the results, and 45 of those individuals said they consulted a doctor before making those changes. Although this study relied on self-reported data from participants, it suggests that less than 1 percent could have made unsupervised medication changes based on their genetic test results.

However, within the NIH's All of Us Research Program, the aim is to eventually genomically test 1 million study participants. In the *New England Journal of Medicine* this week, the study investigators said they expect that 90 percent will have actionable PGx findings. Although far fewer may actually be on the medications that are flagged in reports and require changes, even a 1 percent rate of unsupervised changes could mean an effect on thousands of patients, and that is likely to heighten the FDA's public health concerns.

Green, who directs a translational research program at Brigham and Women's Hospital called Genomes2People, believes the FDA is doing what it feels is right for public health but is also placing an unfair burden on researchers by requiring they submit an IDE. "Research studies don't have budgets for that, and they don't have time for that," said Green, who has had his share of interactions with the FDA in this regard when he was trying to launch a newborn sequencing study, called BabySeq, a few years ago. "It's a tremendous slowdown that burns up your budget."

Still, according to sources, the agency is at least allowing All of Us to report back PGx results that can be supported by drug labeling. In the commercial setting, if labs are deciding as a result of FDA oversight to only report the genetic variants, but isn't interpreting that data in the context of drugs, this may be more problematic from a public health standpoint.

While the FDA hasn't gotten in the way of people accessing their raw genetic data, Green believes the agency may have painted itself into a corner where it's okay to give people the raw data but it's not okay to give them interpret genetic data. The result is that people can still get their genetic data, he observed, "but it's a completely unregulated Wild West as to how they use that."

PGx expert Mary Relling, chair of the Pharmaceutical Sciences Department at St. Jude Children's Research Hospital, expressed concern about the scrubbing of drug information from test reports. "We think that

would make the test results impossible to use by clinicians," said Relling, who also co-chairs the Clinical Pharmacogenetics Implementation Consortium (CPIC), a well-recognized expert body in the field, which develops guidelines on PGx variants that healthcare providers can use to guide treatment and dosing decisions.

"Not providing genetic variants is completely unacceptable," she said. "Not providing some kind of functional interpretation of the phenotype based on those genotypes is completely unacceptable. Not being able to provide what drug may be impacted is also unacceptable."

However, Relling has been vocal about the fact that some companies have been marketing PGx tests touting drug-gene relationships that lack evidence, giving FDA cause for concern. Recognizing that this is problematic for clinicians using PGx tests, CPIC recently indicated that it may start issuing guidelines for non-actionable pharmacogenes that lack evidence and shouldn't be used in clinical decision-making.

"There are some companies that are linking genetic test results to drugs that they shouldn't be doing," she said. "That's wrong, and it would be better to not provide a drug name than to provide the wrong drug name."

Controlling knowledge?

Relling said that CPIC and the FDA have always had regular interactions, and in recent calls, CPIC leaders have floated the idea of hosting a stakeholder meeting to discuss FDA positions on PGx testing. Such a meeting would allow industry players to garner more clarity around FDA's thinking. For example, the FDA has suggested in its safety alert and warning letter to Inova that clinically valid PGx claims are only those that can be supported in FDA-approved drug labeling.

However, there are many drug-gene indications that expert bodies like CPIC have determined to be clinically actionable, but there aren't FDA-approved drug labels with this information. Recently, Relling and Teri Klein of Stanford University, who is CPIC co-principal investigator, took issue with the FDA's assertion in the warning letter to Inova that "the relationship between CYP2C19 genotype and drug response to escitalopram and sertraline is not established." They pointed out that CPIC experts have concluded after a review of the literature that CYP2C19 phenotypes are actionable for these two antidepressants.

The fact that the FDA seems to be suggesting that only it can determine what is scientifically valid genetic information, is a major point of contention with industry insiders and PGx experts.

CPIC guidelines are widely accepted as a source of scientifically valid information on actionable pharmacogenes. The investigators in the All of Us program, for example, were certainly expecting to report on PGx variants in CPIC guidelines, and wrote as much in their latest *NEJM* paper. The NIH was unwilling to discuss its ongoing interactions with the FDA about PGx testing within the research program, but at least according to sources, the agency would like All of Us to report only variants in drug labeling.

"FDA is trying to act like they are the be-all source of PGx information," said the executive of the PGx testing firm that had recently heard from the FDA. "CPIC is more advanced than the FDA is on any of this stuff, but [FDA appears] to not be recognizing any other sources of information."

Meanwhile, UnitedHealthcare recently extended coverage to multi-gene panels for guiding the use of antidepressants and antipsychotic drugs for patients with major depressive disorder — a decision that both Myriad and Genomind hailed in press releases as a positive milestone. The policy includes a table of specific genes and drugs that have sufficient evidence according to CPIC to be actionable. This list, counter to the FDA's position, cites CPIC guidelines on the impact of CYP2C19 on escitalopram and sertraline.

To Genomind's O'Brien, the FDA's attention and the UHC coverage suggests that PGx testing is slowly becoming mainstream. "This is a tipping point for our industry," he said, acknowledging that it will be a challenge for the FDA to figure out how to regulate this field and what sources of evidence beyond what's in drug labeling it will accept. "It's going to take everybody involved in the industry to work together to ensure that we get an outcome that's good for our patients."

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