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Invitae Failure to Detect Rare Mutation Indicative of Intense Lab Pressures in Competitive Market

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NEW YORK (GenomeWeb) – Invitae has identified a quality control issue with certain hereditary cancer tests it provides that has led to two patients receiving a false-negative result when in fact they had a hard-to-detect and rare mutation in the MSH2 gene.

The company realized a few weeks ago that it didn't have the necessary probes in place to detect a rearrangement of exons 1-7 in the MSH2 gene, known as the Boland inversion. MSH2 is one of five key genes associated with Lynch syndrome, a familial cancer syndrome that significantly increases the risk of colorectal cancer and heightens the risk of other cancers.

According to Invitae, approximately one in 14,000 patients undergoing hereditary cancer testing, or around 0.007 percent, has an MSH2 Boland inversion. These mutations show up in approximately one in every 1,250 in patients with Lynch syndrome-spectrum cancers. Based on these numbers, Invitae CEO Sean George said the company estimates between two and 15 patients to have received a false negative result.

In order to identify those affected over several months, the company is retesting 50,000 patients. "That would allow us to be sure that all patients receive the appropriate testing," said Invitae Chief Medical Officer Robert Nussbaum.

Over the last few weeks, since Invitae became aware of the issue, the company has been contacting healthcare providers whose patients may be affected and has already informed the two patients it knows received a false-negative result. Some patients might need to provide another sample for reanalysis.

George said Invitae has added new quality control metrics to make sure this kind of error doesn't happen again, though he emphasized that this was "not a systematic issue that affected the whole production line."

The misstep occurred during the process of moving to a new assay version, when the probes that capture the region where the MSH2 inversion occurs were omitted from the assay. "It's not as if the assay sometimes fails and sometimes is okay, or it's an unstable assay," Nussbaum said. "It's an extremely good assay, if the probes are there."

Invitae's transparency and openness in addressing the issue offers a rare glimpse into how a lab deals with testing errors at a time when the industry is under immense cost pressure and labs are facing unprecedented competition. The incident also raises questions about the general lack of transparency in the lab industry and whether regulations need to be strengthened.

Labs have to meet analytical test validation criteria under the Clinical Laboratory Improvement Amendments and meet accreditation requirements through the College of American Pathologists. But when test systems and lab procedures fail, even if they're reported to accreditors, they're usually not publicized. This makes it challenging to determine how often this type of error occurs in the lab industry.

Under certain circumstances, labs have to report performance issues to CAP, which Invitae has done in this case. CLIA requires the lab to inform affected patients and physicians, which Invitae is also doing.

If a test has US Food and Drug Administration approval, the lab must report instances where a test failure resulted in a patient dying or being seriously injured. But most lab tests don't have FDA approval, and testing errors can result in subtler harms that wouldn't trigger a report.

In the case of Invitae's test, the two patients who received false negative results were from families with a history of Lynch syndrome, and the Boland inversion had been detected in family members. A false negative genetic test result could delay necessary cancer screening, but doctors could also decide to provide more screening based on family history alone.

Invitae became aware of the problem because a genetic counselor suspected that a patient from a Lynch syndrome-like family may have acquired a somatic mutation related to the condition despite having a negative germline result from the company. The genetic counselor asked another lab, Ambry Genetics, to analyze the patient's tumor tissue, to see if there was an acquired (somatic) mutation.

Ambry conducted a test that analyzed both tumor tissue and blood samples in parallel, and detected the germline MSH2 inversion in this patient. "When we saw this mutation and saw that the patient had tested negative elsewhere, we reached out to the ordering clinician," said Brigette Tippin Davis, Ambry's VP of research and development.

"All labs make mistakes sometimes," Tippin Davis acknowledged, but upon follow up with the patient's genetic counselor, she came to understand that this was not a one-off technical oversight where one lab is using a more sensitive assay than another. "It appears that appropriate validation controls and quality control oversight was not happening in this gene region," she said, and other patients might be impacted.

"We don't want to mud-sling, that's not what we want to do. That's not good for the industry," Tippin Davis continued. "This is really about labs having the appropriate quality controls, and if one lab makes a mistake, it can reflect poorly on the whole industry."

Laboratory mistakes certainly occur, though it is somewhat uncommon for one lab to pick up the mistakes of another because second-opinion or follow-up testing is not covered by insurance. Still, occasionally, labs do identify discrepancies with another lab. George said that Invitae has identified issues at other labs three or four times in the last few years.

Tippin Davis acknowledged that Ambry has had discrepant results, which she characterized as one-off errors that other labs have picked up. "We have, all labs have experienced a one-off where a particular rare SNP may be under a primer," and this impacts one patient, Tippin Davis said, but she quickly added that Ambry has not had a quality control issue that was systemic.

"As NGS assays have become cheaper, a lot of startup labs that don't have a lot of clinical experience or oversight [of quality control and validation processes] are popping up everywhere, such that it puts the industry more at risk," Tippin Davis said, adding that there needs to more oversight preventing "risky start-up labs" from causing patients harm. She noted that Ambry provided feedback on FDA's plan to regulate LDTs, and wouldn't be opposed to the agency's oversight, should it occur.

The FDA had sought to regulate LDTs but backed off that plan after the presidential elections last year. But the agency's oversight would have required that labs adhere to a design control process and submit information on significant modifications to assays. Girish Putcha, lab industry professional with expertise in reimbursement and regulatory issues, noted that while it's impossible to know for certain if FDA oversight would have prevented the error in Invitae's case, these two aspects may have helped flag such problems.

"Elements of design control, including, for example, risk analysis, should have identified any unintended consequences or problems resulting from modification of the assay," he said. "Similarly, the FDA's requirements for assay modifications presumably would have shone a brighter light within the lab itself on the implications of any change, even before any actual agency review."

Heidi Rehm, director of the Laboratory for Molecular Medicine at Partners Healthcare Personalized Medicine, also acknowledged that her lab has found very straightforward sequence variants other labs have missed a few times. She said the industry doesn't have a good sense of how widespread errors like this are, precisely because labs don't commonly reanalyze patients tested by other labs.

"My guess is that it's much more widespread than any of us would like," said Rehm. "I don't think any lab is immune to it."

"Given the lack of transparency in the current regulatory paradigm, it's impossible to know how frequently this happens," said Putcha, who has previously directed clinical labs such as Ariosa and Crescendo. "But it certainly does happen."

Invitae's error comes during a period of rapid change for the genetic testing industry. While testing of specific genes was historically conducted by one or two labs with deep clinical and lab expertise in those genes or a disease area, Rehm reflected that labs are now employing high-throughput genomic testing operations to scale testing to all disease areas and bringing prices down for their customers. "However, this move, and the extreme cost pressures to keep test prices low, has made it impossible to maintain the deep clinical and laboratory expertise needed to manage the nuances of every disease gene," she said, estimating that most labs are losing money right now.

Rehm is leading efforts to encourage labs to be more transparent when it comes to classifying genetic variants by submitting them to the public database ClinVar. Invitae is among the top submitters, and Nussbaum said that the company has a formal process for reaching out to other labs to discuss variant classification discordances, so entries into ClinVar can be updated.

However, Invitae's overall business strategy has been to aggressively increase the number of genes it tests for across a variety of indications, while lowering its cost of goods sold, in an effort to make genetic testing more accessible and affordable. In the second quarter, Invitae posted $14.3 million in revenues but a net loss of $28.6 million.

The firm recently announced it was acquiring Good Start Genetics and CombiMatrix to expand into reproductive health testing, and simultaneously said it had entered into an agreement to sell $73.5 million of its stock in a private placement. According to George, to date, the company has invested more than $400 million to run its tests at scale, in a high-throughput, high-quality manner.

"Some laboratories have invested more effort in ensuring their technology and individual tests are adequately poised to detect all variation but others have not invested as deeply, as they compete in the highly competitive genomic testing market," Rehm said. "Sometimes labs have the best intent for all their tests but simply don't have staff that have deep experience in all disease areas, making it haphazard whether they are adequately prepared to support the special testing and interpretation aspects of each disease area."

Some genes, as in the case of the MSH2 Boland inversion, require special approaches to detect all mutations, but researching and validating all types of variations in every gene implicated in ever disease "is nearly impossible," Rehm added.

However, Invitae did specifically advertise its ability to detect this particular mutation, and other test providers have not remained quiet about a competitor's shortcomings. The error came to light during a period of unprecedented competition in the industry. There are eight to 10 new genetic testing products entering a market daily containing 70,000 tests. Hereditary cancer testing is a particularly cutthroat space, where labs are launching next-generation sequencing panels that gauge multiple genes cutting across different cancers.

GenomeWeb was tipped off to the issue earlier this week by an individual who vaguely identified himself as being in the lab industry. Once the incident became public on a lab industry website, a representative from Myriad Genetics contacted GenomeWeb to highlight it as a real-world example of the problems with low-cost, low-quality labs.

Andrea Forman, senior genetic counselor at Fox Chase Cancer Center, said she first learned about the issue with Invitae's assay in late July through an Ambry employee whom she declined to name. "I find that interesting that they wouldn't reach out to the lab but to a genetic counselor who was not involved with the case," Forman said. The official did not name Invitae but noted that the error happened with a "42-gene panel" for hereditary cancer testing, which pointed Forman to Invitae as the lab that conducted the testing.

A few days later, an Invitae employee contacted her to discuss the lab error and the possibility that a limited number of patients may have had a false negative result. The call came despite the fact that Fox Chase has never had a patient with an MSH2 Boland inversion and it orders testing through several different laboratories.

"I appreciate that Invitae is being outspoken about it," Forman said. She is reassured that Invitae is clearly trying to make right its mistake, but incidents like this make her even more cautious about evaluating a patient's results.

All labs and tests have limitations, she cautioned, and ultimately it falls on the genetics expert to understand them. Forman pointed out, for example, that some labs offering hereditary cancer or Lynch syndrome testing don't even assay for the MSH2 Boland inversion.

"If anything, this case highlights the importance of providers understanding these limitations, so when you do get a report back, you look at the family history, and the negative result, and you think, 'I really expected something to come back positive. I wonder if there was a mistake here,' [and then] they can recognize that and follow up."

Meanwhile, Invitae has set up a high-throughput reanalysis assay in its lab to quickly retest samples from patients with faulty tests to identify those impacted by false negative results. The company declined to quantify how much it will cost to retest those patients, but because the retesting assay will be focused on detecting a very specific mutation, lab industry insiders estimated it is possible to do the analysis for under $10 per sample.

Invitae has maintained that this error is not reflective of a systemic problem with its lab processes, and that they've put the proper measures in place to ensure this doesn't happen again. George pushed back against competitors who would characterize the company as a low-cost provider taking shortcuts in the testing process. "There is nothing cheap about what Invitae has been doing for the last seven years," George said. "We've invested more than $400 million in the ability to run these tests at scale."

Still, retesting 50,000 samples will surely have an impact on a company that accessioned around 30,500 samples for testing during the second quarter and is projecting accessioning 110,000 to 120,000 samples this year.

In Friday trade on the New York Stock Exchange, Invitae's stock declined around 5 percent to close at $9.84.

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