FDA Issues Safety Communication About Genetic Non-Invasive Prenatal Screening Tests

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Key Takeaways:

- The safety communication acknowledges that FDA has historically exercised enforcement discretion over laboratory developed tests yet expresses concern that most LDTs have not been reviewed by FDA.
- The timing of the safety communication coincides with discussions FDA is having with Congress regarding its regulation of *in vitro* diagnostic tests and may signal that the agency intends to increase its oversight of certain types of LDTs.

Last week, the Food and Drug Administration (FDA) issued a safety communication warning the public about the potential risks of false results with genetic non-invasive prenatal screening tests (referred to as "NIPS" or "NIPT"). These *screening* tests are intended to provide an assessment of the patient's *risk* of carrying a fetus with a chromosomal disorder. Prenatal *diagnostic* tests, in contrast, are intended to more definitively confirm or rule out whether a specific genetic disorder or condition is present in the fetus. Prenatal screening and diagnostic tests are widely offered to pregnant patients. Current guidelines from the American College of Obstetricians and Gynecologists recommend that prenatal genetic screening and diagnostic testing options "should be discussed and offered to all pregnant patients regardless of maternal age or risk of chromosomal abnormality."

NIPS have been in use and available to patients for years. FDA's main concern with NIPS appears to be that FDA has not reviewed the performance of most of these tests because of their regulatory status. Perhaps most tellingly, the safety communication was released just as Congress is considering the Verifying Accurate Leading-Edge IVCT Development (VALID) Act and other legislative initiatives addressing FDA's regulatory authority over laboratory developed tests (LDTs).

According to the safety communication:

> *All NIPS tests on the market today are offered as laboratory developed tests (LDTs). Most LDTs, including NIPS tests, are offered without review by FDA. While LDTs are medical devices under the Federal Food, Drug, and Cosmetic Act, FDA has had a general policy of enforcement discretion for most LDTs since the Medical Device Amendments were enacted in 1976. That means that FDA does not generally enforce applicable regulatory requirements for most LDTs. FDA is continuing to work with Congress on legislation to establish a modern regulatory framework for all tests, including LDTs.*

The VALID Act would create a new framework that would authorize FDA to regulate all diagnostic tests (i.e. commercial *in vitro* diagnostic (IVD) test kits as well as LDTs) as In Vitro Clinical Tests (IVCTs) under a risk-based framework that would be separate and distinct from the medical device framework. NIPS tests would be regulated by FDA under the VALID Act, if it is passed. The VALID Act broadly defines an "IVCT" as a test that is "intended to be used in the collection, preparation, analysis, or *in vitro* clinical examination of specimens for the purpose of identifying, diagnosing, screening, measuring, detecting, predicting, prognosing, analyzing, or monitoring a disease or condition, or selecting, monitoring or informing therapy or treatment for a disease or condition."

The safety communication recommends that patients discuss the benefits and risks of NIPS tests with a genetic counselor or other health care provider before deciding to get these tests in the first place and before making any decisions about their pregnancy as a result of such testing. In some cases, confirmatory diagnostic testing may be warranted which may require invasive procedures that carry a small risk of

miscarriage and may involve the use of laboratory developed tests that also have not been reviewed by FDA.

FDA's safety communication also encourages NIPS test developers to work with FDA toward authorization, clearance, or approval of their tests. Even in the absence of legislation specifically providing FDA with authority over LDTs, it is possible that FDA will take enforcement action against NIPS developers that do not work towards obtaining FDA clearance or approval and continue to make claims regarding the accuracy of their tests. For example, after issuing a safety communication with respect to pharmacogenetic tests in November 2018, FDA contacted several firms marketing LDTs with claims to "predict how a person will respond to specific medications in cases where the relationship between genetic (DNA) variations and the medication's effects has not been established." Many laboratories responded by removing specific medication names from their labeling, including promotional material and patient test reports. One company received a warning letter in April 2019 for continuing to market a pharmacogenetic test without obtaining marketing clearance or approval from FDA.

FDA's regulatory authority over LDTs has been in flux for decades. Although FDA acknowledges that it does not generally enforce applicable regulatory requirements for most LDTs, this latest safety communication could be a signal that the agency's oversight of certain LDTs may increase.

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