An outdated loophole is letting faulty lab tests hit the market

It is time to close a loophole that allows certain types of diagnostic lab tests to be exempt from regulatory oversight, putting people at risk of making consequential medical decisions on the basis of unreliable results.

Elizabeth Holmes, founder of the medical diagnostics company Theranos, was convicted of defrauding investors in January after a landmark trial in California. Holmes established a multi-billion-dollar company on the basis of false claims that Theranos' diagnostics machines could detect hundreds of diseases from a small sample of blood. But even though Theranos' leaders have been called to account, the loophole exploited to avoid independent review of their devices remains wide open. Regulatory bodies must act to close it.

When the US Congress authorized the US Food and Drug Administration (FDA) to regulate medical devices, including in vitro diagnostic tests (IVDs), in 1976, the agency waived all regulatory requirements for a small number of tests designed, manufactured and analyzed all in the same lab. This made sense then when these tests, referred to as 'laboratory-developed tests' (LDTs), were largely simple screens developed by hospitals, researchers and academic medical centers for their own use. These tests were traditionally used on a small scale, often to diagnose rare diseases and where the lack of demand had created barriers to commercial in vitro diagnostic development. Given the relative simplicity of these screens and the scale at which they were used, regulatory bodies considered LDTs to be of lower risk to patients than commercially available IVDs, which were subject to stringent regulatory oversight. Other countries too, including the European Union, adopted these exemptions, and although the past 45 years have seen substantial technological and commercial changes in the use of these tests, the lack of regularity oversight has remained the same.

The high-profile Theranos case provides a stunning example of how LDTs have moved from small-scale 'in-house' screens to one of the fastest growing and profitable commercial markets in the biotech industry, luring in major companies as well as numerous start-ups. Today's LDTs are increasingly complex, often relying on complicated algorithms and software to generate results and clinical interpretations, and they are marketed nationwide, sometimes by large laboratories or companies. No longer a small segment of the market, these tests now dominate key and growing areas in diagnostics, including noninvasive prenatal testing, direct-to-consumer genetic testing, and tests used to guide the use of therapies in cancer.

For example, LDTs are often used in genetic tests for inherited conditions, including many screening tests administered to all newborns, and represent around one third of prenatal tests used to detect fetal abnormalities. Yet in the United States, none of the more than 40 noninvasive prenatal tests on the market are FDA reviewed. The majority of direct-to-consumer genetic tests, whose use has grown exponentially over the past 5 years, are also LDTs. As these tests become increasingly similar to commercial IVDs that require regulatory oversight, substantial concerns have been raised about the public-health effects of excluding thousands of tests — many of which have considerable implications for patient care — from regulatory review.

The lack of regulatory oversight means that no one knows precisely how many LDTs are in use, let alone how often they fail or how many people have been harmed as a result of their use. Regulators currently do not require makers of LDTs to publicly report adverse events that may stem from the use of their tests, nor is there a system in place to track these events. That is despite reports of cases in which high false-positive results from LDTs used to detect ovarian cancer put patients at risk of undergoing unnecessary, complex and invasive surgeries. Recently, an investigation of prenatal LDTs used to detect chromosomal microdeletions associated with a wide range of devastating disorders revealed alarmingly high frequency of false-positive results (above 80% in most cases). This is a concern, as studies show that many people who test positive for these prenatal screens undergo an abortion without getting a confirmatory test. The lack of oversight to ensure the clinical and analytical validity of these tests poses considerable risks, including the emotional burden of being wrongly diagnosed, detrimental health effects from wrong or delayed treatments, and worsening or prolonged disease.

It is important not to diminish the importance of LDTs in medicine or to imply that they are always less accurate or less reliable than their regulatory board–approved counterparts. In fact, innovations in this area have been fundamental in the move toward precision medicine, particularly in oncology, and have provided accurate and reliable prenatal screening tools, when used appropriately, for certain conditions. Instead, the problem is that the comparatively limited oversight of these tests no longer reflects the risks that these tests can pose, and new regulatory frameworks need to be developed to keep pace with these changes.

The outdated and fragmented regulatory framework that currently covers these diagnostic tests has to be reformed. Tests should be regulated on the basis of risk, not where they are made; the same requirements that already apply to other IVDs should apply to LDTs. Publicly reporting adverse events related to an incorrect test result should be mandatory, and product labels must be reviewed and approved to ensure their accuracy. Applying these regulatory measures to LDTs not only protects patients from harm but also creates a more level playing field for test developers. Patients and providers need to be able to trust their test results for any condition, especially when making critical medical decisions. Regulatory review and oversight would help guarantee that by setting a baseline for the analytical and clinical validity of all tests in the market and by ensuring that the claims made for these tests are truthful, non-misleading and based on sound evidence. ❐

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