

Dangerous diagnostics? Regulatory reform in the genomic era

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Kelly Holloway, postdoctoral fellow, *Institute of Health Policy, Management and Evaluation, University of Toronto, Canada*

Fiona A Miller, professor, *Institute of Health Policy, Management and Evaluation, University of Toronto, Canada*

Alberto Gutierrez, partner, *NDA Partners, USA*

Stuart Hogarth, lecturer, *Department of Sociology, University of Cambridge, UK*

Corresponding author: S Hogarth sh339@cam.ac.uk

Introduction

Recent revelations about failings in the regulation of medical devices have focused on implantable devices.¹ But diagnostic devices also have problems, as was made clear in 2016 when the US government took action against Theranos, a high profile diagnostics manufacturer based in Silicon Valley. The pathology laboratory run by Theranos was shut down after government investigations revealed problems with the firm's proprietary diagnostic technologies. Theranos admitted that "tens of thousands" of test results had to be voided or revised for everything from cholesterol levels to pregnancy, with unknown implications for patients. The firm was subsequently charged with defrauding investors, doctors, and patients.²

These revelations provoked a sudden reversal of fortune for Theranos, which was valued at \$9bn (£7bn; €8bn) in 2015 and promoted itself as a poster child for transforming healthcare through diagnostic innovation. Theranos claimed to have developed technology to run multiple clinical tests simultaneously, much more cheaply and quickly than conventional laboratory tests and using only a tiny sample of blood. Theranos's chief executive, Elizabeth Holmes, promoted the idea that this technology would revolutionise pathology and usher in a new era of preventive medicine. Cheap, painless, and convenient testing services would encourage people to monitor their health more often³—a business strategy purpose built to foster overdiagnosis and overtreatment.⁴

Yet the firm's spectacular downfall, the failure of its technology, and the defrauding of its investors was not solely a result of corporate hubris. Theranos should be recognised as a regulatory scandal that shows the potential for harm from unregulated diagnostics ([box 1](#)).

How was this allowed to happen?

Theranos launched in the US market with no review by the US Food and Drug Administration to assess the safety, efficacy, or manufacturing quality of its products. The company profited from a gaping regulatory loophole that creates a bifurcated diagnostics market in the US and elsewhere: test kits sold by manufacturers for use in external laboratories are regulated by the FDA, but tests developed and performed in the developer's clinical laboratories (so called "laboratory developed tests" or LDTs) are rarely subject to FDA authority ([box 2](#)).

Box 1

Harms of poor diagnostics

Patient harms

- False positive results may unnecessarily create psychological anxiety and prompt further diagnostic tests, which may themselves be risky
- Overdiagnosis has some of the same effects but also risks overtreatment, even though the diagnosis and any interventions may be experienced as good care
- False negative results may give patients false reassurance and delay or avert necessary treatment⁷

Problems for doctors

- Poorly evaluated tests hamper doctors' efforts to help patients, waste their time in unnecessary procedures, and open them to the danger of accusations of malpractice and the threat of litigation

Costs to the healthcare system

- Inappropriate tests can waste resources that could have been used to deliver genuine clinical benefits
 - False positive results or overdiagnosis may trigger unnecessary and costly additional tests or treatments⁷
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Box 2

Laboratory developed tests explained

Diagnostic tests can be either *in vivo* (eg, using imaging technology) or *in vitro* (on samples taken from patients). This article focuses on *in vitro* tests. Companies making *in vitro* diagnostics have two routes to market—kits or laboratory developed tests (LDTs).

- *Test kits* are manufactured and sold for use in laboratories, in healthcare facilities (point of care), or at home (over the counter) and are subject to medical device regulations, including premarket review of safety and efficacy of novel tests.
 - *LDTs* are used in the developer's clinical laboratory and marketed as a commercial service. Companies that decide to market their test as an LDT typically send out sample collection kits, analyse the returned samples, and provide customers with an interpretation of the results.
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Theranos is not alone in exploiting this loophole. Many firms in the molecular diagnostics sector choose to commercialise their tests as LDTs rather than as test kits, a cause for concern given that this sector is the fastest growing part of the *in vitro* diagnostics industry.⁸ The sector was worth \$7.3bn in global revenues in 2016.⁹ Calls for stricter oversight of this nascent industry have been made in a succession of high level policy

reports that have exposed multiple failings in the regulatory frameworks for diagnostics in Europe and North America.[101112](#)

Response to these calls for change has been mixed. Canada has made no proposal for regulatory change, and longstanding efforts at comprehensive reform in the US have faltered. In the EU, by contrast, a weak regulatory regime is in the process of major reform. We review policy developments related to two key loopholes in diagnostics regulatory regimes in these three jurisdictions and assess their implications for the protection of public health.

Loophole for laboratory developed tests

There is nothing new about LDTs; historically, much diagnostic innovation has happened within hospital laboratories. What is unprecedented is the burgeoning commercial exploitation of the LDT route to market. Firms that sell LDTs are subject to laboratory regulation in many jurisdictions,[1314](#) but they can bypass statutory medical device regulation and thus premarket review of their products. As a consequence, there may not even be a public record of which LDTs are on the market.

In the EU this loophole is likely to close once new regulations for in vitro diagnostics come into full effect in 2022.[15](#) Under the in vitro diagnostic directive kits were subject to risk based regulation, but many LDTs were exempt because they were manufactured by “health institutions.” This exemption may have been intended to allow hospital labs to bypass statutory review, but it has been interpreted much more generously, creating an easy route to market for LDT firms. A more consistent and comprehensive approach is expected under the new regulation: providing that certain safeguards are in place, health institutions will continue to be exempt, but LDTs that are manufactured on an “industrial scale” will not be. This critical caveat, which has yet to be clearly defined, should ensure that most LDTs produced by commercial companies will be subject to the same requirements as test kits.

By contrast with the EU’s recent and decisive policy reform, the FDA has tried and largely failed to close the LDT loophole for more than 25 years. The agency asserted its legal authority over LDTs in the early 1990s and has taken action against some of the most egregious actions of individual firms, perhaps most famously when it shut down the health related services of leading consumer genetics firm 23andMe for marketing unvalidated tests.[16](#) Like many of its rivals, 23andMe’s core offer to consumers was polygenic risk profiles. Such tests have been widely criticised for providing misleading results based on a premature application of evolving understandings of the genetic basis of disease, and as a gateway to broadening disease categories, overdiagnosis, and the medicalisation of the worried well.

Whatever the success of the FDA’s more piecemeal efforts to tackle aspects of the LDT problem, the agency’s attempts at comprehensive policy reform have been curtailed, battered by shifting political winds and the resistance of clinical laboratories (which, in the US, are typically commercial or are major revenue streams for the health systems with which they are affiliated).[13](#) Draft guidance issued by the FDA in 2014 proposed a significant expansion of oversight,[17](#) which was resisted by much of the laboratory sector. In 2016,

concurrent with the Theranos scandal, the FDA signalled that the guidance would be finalised.¹⁸ However, shortly after President Trump was elected, the agency dropped the plan, issuing instead an LDT discussion paper in 2017.¹⁹

Meanwhile, a coalition of leading US reference laboratories and some large diagnostics manufacturers has proposed a new approach. Their draft legislation would mean that LDTs have some level of premarket scrutiny and could level the playing field for regulation of LDTs and test kits. However, it could reduce the quality of premarket scrutiny overall by undermining the FDA’s authority to collect and review data.²⁰ In response to concerns, the bill was redrafted to clarify the FDA’s premarket review powers, but only for the highest risk diagnostic tests,²¹ and the bill remains a threat to the scope of the FDA’s authority.

Although both the EU and US have made efforts to close the LDT loophole, Canadian regulators remain passive. A 2007 report commissioned by Health Canada identified possible responses to the LDT loophole,²² but thus far Health Canada has done nothing.

The LDT loophole means that many tests are commercialised without undergoing premarket review for safety and efficacy, even when the intended use could have serious effects on patient welfare. The rapidly growing market for “non-invasive prenatal testing” (NIPT) exemplifies the problem. This new approach to prenatal screening can determine the risk of certain fetal conditions using maternal blood samples and is projected to have a market value of \$3.13bn by 2023.²³ There are at least 86 tests on the market globally that were not subject to independent premarket review for safety and efficacy in the US or Canada, though several firms have declared their compliance with EU regulations ([table 1](#)).

Table 1

Regulatory approval of non-invasive prenatal tests and breast cancer prognostics in EU, US, and Canada

		No approved for use		
	Available	EU*	FDA	Health Canada
Non-invasive prenatal tests	86	8	0	0
Breast cancer prognosis	11	8	2	2

* Self certified with CE mark that products are compliant with EU regulations.

Such discretionary use of regulatory review is even more apparent in breast cancer prognostics, which guide postadjuvant treatment decisions. Several proprietary tests have been developed, but although they are broadly similar, the regulatory approach differs. Some tests are sold as regulated kits whereas others are sold as unregulated LDTs, including the market leader, Oncotype DX, which has a list price of \$4620 and generated \$340.8m in revenue for Genomic Health in 2017.[24](#)

Yet as the draft US legislation on LDTs indicates, levelling the playing field between kits and LDTs may do more harm than good if it means that all tests are subject to a lower regulatory bar for safety and efficacy. The danger of such an approach is shown by a second loophole—risk classification—which new EU regulation will shrink, even as draft US legislation threatens its expansion.

Risk classification loophole

Diagnostic device regulations are risk based; tests classed as higher risk are subject to greater regulatory scrutiny and stricter evidentiary standards. Higher risk devices are typically subject to premarket review, but classification schemes vary across jurisdictions, and this creates a second regulatory loophole for molecular diagnostics, particularly in Europe.

The EU's current risk classification system is uniquely inadequate. Under this system nearly all tests are classed as low risk, allowing manufacturers to self declare regulatory compliance and give the product a CE mark, which indicates conformity with EU regulations. The OvaCheck test for ovarian cancer shows the problem. Even though the FDA issued a warning letter about this test in 2004, and then determined that the test did not accurately predict or detect ovarian cancer,[25](#) OvaCheck was CE marked for sale in Europe by the manufacturer in 2010.[2627](#)

Once fully implemented, the EU's new regulation will close this regulatory loophole.[15](#) The new regulation places most molecular diagnostics in a higher risk category, meaning they have to go through premarket review by a notified body (the regulatory authority that assesses compliance with regulations). As a result, a far broader range of diagnostic tests will be subject to independent scrutiny before they can enter the EU market.

The US, however, is moving in the opposite direction, proposing to downgrade diagnostics that were once deemed high risk and draft legislation threatening to excuse lower risk tests from any premarket review. Thus tests for conditions such as HIV and hepatitis C virus would be deemed lower risk and require less rigorous scrutiny before marketing.

What has been the effect of the EU's regulatory loophole? A clear example of the public health implications is provided by cervical cancer screening. Molecular tests for human papillomavirus (HPV) emerged in the 1990s as a new approach to cervical cancer screening, aiming to supplement or replace the traditional smear test, which has repeatedly been mired in scandals of both over detection and under detection. HPV tests are rated as higher risk tests in the US and Canada and must have premarket review, but in the EU the tests are classified as low risk and manufacturers self certify regulatory compliance. Only seven HPV

tests have been approved by the FDA and five by Health Canada, but 87 tests are authorised for sale in the EU. The high number of HPV tests in the EU is concerning given that in 2012 most of the 125 HPV tests available worldwide did not have validation studies published in peer reviewed journals.²⁸ Given that HPV is far more prevalent than cervical cancer, poorly validated tests risk substantial overdiagnosis. The new EU regulation should allow greater assurance that the CE mark can be trusted as a credential of safety and efficacy.

Conclusion

It remains to be seen whether genomics will transform medical practice, but the molecular diagnostics sector continues to grow rapidly. The EU's strengthened regulation for in vitro diagnostics shows that policy makers can respond to these new challenges, although vigilance will be needed to ensure that the new system achieves its public health potential. By contrast, Canada's inaction is notable. Meanwhile, the FDA's failure to progress its proposals for enhanced oversight of LDTs means that the world's largest diagnostics market remains dangerously bifurcated—a medical device industry that can choose whether its products are FDA regulated is bad for patients, clinicians, and healthcare systems. Stakeholders should also be concerned about the current industry sponsored draft legislation circulating in the US Congress.

As the example of Theranos indicates, we must be sceptical of bold claims for the transformative potential of new diagnostic technologies. Regulatory agencies have a critical role in scrutinising the scientific data behind the corporate hype. Stakeholders must continue to press for robust evidence and rigorous evaluation as safeguards against premature commercialisation.

Footnotes

- Contributors and sources: AG was head of diagnostics at the FDA. All other authors carry out research on diagnostic device regulation. KH led the drafting of the paper, with substantial contributions from SH, FM, and AG. All authors contributed to the conceptualisation and contributed to the revision of the final submitted version. SH is the guarantor.
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