Barriers to the Introduction of New Medical Diagnostic Tests

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ABSTRACT

Driven by rapid developments in sequencing technologies, proteomics and other progresses in biological sciences, new diagnostic tests are expected to play a growing role in medicine as well as in tailoring medical treatments to specific patients. The road of a test from bench top to patient is a difficult and incremental process. This report examines the barriers that exist to the introduction of new diagnostic investigations into routine medical practice. These barriers are manifold and include the burden of proof in establishing the scientific validity and clinical usefulness of a new test; regulatory hurdles; issues surrounding costs, coverage, and ensuring appropriate compensation for the work that goes into the development and delivery of a new test; a preference amongst physicians for traditional diagnostic methods that are often less formal and require a higher degree of expert analysis and interpretation; and resistance to more broad-based genetic testing by the general public, including ethical concerns about the possibility of genetics-based discrimination.

Keywords: laboratory diagnostics, regulatory affairs, diagnostic tests, clinical pathology, genetic testing, medical ethics

The relatively low cost of diagnostic testing as a fraction of total health care spending belies the crucial role played by testing in the determination of health outcomes. Cutting-edge diagnostic techniques, such as multivariate index assays based on genomic and proteomic analysis, and new modes of delivery, such as home-based testing kits for sexually transmitted diseases (STDs) and rapid diagnostic tests for other infectious diseases, promise faster, more accurate, more comprehensive diagnoses of diseases. That said, a slow and maladapted regulatory approval process, uncertainties regarding coverage decisions and remuneration, and clinical resistance to new diagnostic methods combine to stifle innovation and to slow the dissemination of advanced diagnostic technologies into mainstream clinical use. Also, ethical concerns regarding the use of genetic information call for a cautious approach to the implementation of public health initiatives that involve widespread genetic screening.

The importance of diagnostic testing in contemporary medical practice cannot be overstated. From routine tests such as pap smears, blood-sugar monitoring, and pregnancy tests, to more advanced techniques involving DNA and protein analysis, diagnostic testing is ubiquitous and performs a necessary and essential function in clinical practice. A study by the Lewin Group estimates that “while diagnostics comprise less than 5% of hospital costs and about 1.6% of all Medicare costs, their findings influence as much as 60%-70% of health care decision-making” (p.1).1 The central role played by testing in determining the overall course of patient treatment highlights the critical importance of the requirement that diagnostic tests be accurate, reliable, and effective.

As medical technology advances and medical practices evolve, the sophistication of the biomarkers, assays, and scientific techniques used to identify pathologies and to diagnose a wide spectrum of diseases continues to evolve. Advanced diagnostic methods involving sequencing and proteomics hold promise in facilitating the diagnosis of rare genetic disorders and hereditary diseases.2 In addition to technological advances, demand for new modes of delivery of diagnostic services is also shaping the development

Abbreviations

STDs, sexually transmitted diseases; PPV, positive predictive value; NPV, negative predictive value; RDTs, rapid diagnostic tests; pLDH, plasmodium lactate dehydrogenase; FDA, United States Food and Drug Administration; UNICEF, United Nations Children’s Fund; CLIA, Clinical Laboratory Improvement Amendments; IVDMIAs, in vitro diagnostic multivariate index assays; CMS, Centers for Medicare & Medicaid Services; CPT, current procedural terminology; AMA, American Medical Association

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of the diagnostics industry. A report by Cambridge Consultants notes that an increased focus on customized and consumer-driven health care has also brought “increased demand for point of care diagnostics and home testing kits which can take the place of traditional laboratory-based testing” (p.4).

Timely delivery of test results is also in demand. Rapid diagnostic testing for infectious diseases, based in rapid microscopy or immunochromatography, might significantly reduce the time lag between the reporting of symptoms and the diagnosis of disease, thus ensuring that patients receive the appropriate medical treatment at the earliest opportunity.

Nevertheless, despite the potential usefulness of new diagnostic techniques and modes of delivery, many barriers exist to the widespread adoption of innovative diagnostic methods within routine medical practice. These barriers may be divided into the following categories: the scientific burden of proof in establishing the effectiveness of a new test; regulatory hurdles; issues surrounding coverage and obtaining appropriate compensation for the costs associated with the development and delivery of new tests; resistance amongst physicians to new diagnostic methods (ie, a bias toward traditional, gold standard, diagnostic methods that are often less programmatic than new tests and require more expert analysis and interpretation); and social and ethical issues, including resistance to more broad-based genetic testing by the general public. The following sections in this article will examine each of these barriers, drawing on examples of new diagnostic tests with applications within a range of medical practices, including oncology, the treatment of infectious diseases, and the investigation of genetic disorders.

The Burden of Proof in Establishing the Usefulness of a New Test

For a new diagnostic test to be accepted by the medical establishment and widely adopted within routine medical practice, investigators must demonstrate that the technique it uses is substantively superior to already existing methods. The Royal College of Pathologists divides the usefulness of a diagnostic test into 3 distinct components: analytic validity (ie, technical performance), clinical validity (ie, the power of the test to predict the existence of clinical disease), and clinical usefulness (ie, the probability that use of the test will result in improved patient outcome).

More specifically, the analytic validity of a test is measured by its sensitivity (ie, the probability that a sample from an individual with a certain disease will test positive) and specificity (ie, the probability that a sample from healthy individual will test negative), as well as by its converse measures, namely, the positive predictive value (PPV) and negative predictive value (NPV). PPV is the “probability that those testing positive by the test are truly infected,” and NPV is “the probability that those testing negative by the test are truly uninfected.” These 4 measures are typically determined relative to a reference standard test, or gold standard test, that is used to determine which individuals actually harbor a certain disease or diseases and which do not. Another important property, namely, reproducibility, measures the extent to which the same test results are obtained from the same sample by different laboratorians throughout the course of multiple tests.

It is possible that the net usefulness of a new diagnostic test will involve trade-offs between different measures of its performance. A representative example is rapid diagnostic tests (RDTs), which are used to identify infectious diseases. The usefulness of RDTs exists primarily in the timeliness with which test results can be obtained. The value of RDT techniques in public-health settings involving an emergency response to epidemiological outbreaks is clear. However, current RDTs are hampered by the fact that health care professionals have generally believed these tests to be less accurate than the gold-standard reference tests against which they are evaluated. Archibald\textsuperscript{6} writes that “RDTs based on molecular platforms have relatively lower sensitivities or predictive value positive compared with traditional methodologies for investigation or diagnosis of infectious diseases”. Gerst et al\textsuperscript{7} note that malarial-infection RDTs, most of which are based on the detection of histidine-rich protein 2, are of limited use because they persistently give false positive test results after treatment. Hopkins et al\textsuperscript{8} reported that an alternative, plasmodium lactate dehydrogenase (pLDH)–based RDT for malaria had a specificity of 85%, which is far below the recommended standard of 90%. The poorer technical performance of RDTs relative to their gold-standard equivalents slows the pace at which RDTs are being incorporated into clinical practice for the diagnosis of infectious diseases.

Regulatory Hurdles

In the United States, diagnostic tests are regulated by the United States Food and Drug Administration (FDA). The
FDA classifies diagnostic tests as medical devices. Merrill notes that the regulatory framework used for medical devices closely resembles that used to regulate prescription medications. In practice, this means that tests are subject to a lengthy regulatory approval process. A report by Cambridge Consultants states that “FDA regulatory requirements for tests incorporating novel technologies can translate to a three-to-five-year time from submission to approval” (p. 9). This contrasts sharply, for instance, with the regulatory climate in India, in which a framework for regulating medical devices does not exist.

An example of how the onerous FDA approval process can impede the dissemination of new diagnostic tests is the iDiagnostics human immunodeficiency virus (HIV) home testing kit Rapid HIV Test–Blood and Rapid HIV Test–Urine (Sugar Land, TX). The company, which has also developed test kits for syphilis, gonorrhea, chlamydia, hepatitis B, and hepatitis C, claims that its HIV test is accurate and reliable and is capable of detecting the presence of HIV infection within human blood in as little as 3 minutes. The company’s diagnostic tests are approved by the World Health Organization and the United Nations Children’s Fund (UNICEF), its factories are certified by the International Standards Organization (ISO), and its tests are widely used within the developing world. However, despite the effectiveness of these tests and the obvious usefulness and convenience of home-based testing for STDs, iDiagnostics has failed to receive FDA approval to sell any of its home-based testing kits in the United States.

Although diagnostic kits that are developed by independent medical device manufacturers and sold to medical laboratories (and directly to consumers) are subject to strict regulatory guidelines and a lengthy FDA approval process, the FDA has tended not to regulate new assays developed in house by medical laboratories. Instead, the FDA has mostly left these home-brew tests to be governed by much less stringent, non-FDA regulations, such as those contained in the Clinical Laboratory Improvement Amendments (CLIA). This regulatory loophole for lab-based test development has allowed clinical laboratories to develop innovative tests and to bring new and improved diagnostic methods into clinical practice in a timely and cost-effective manner.

Recently, however, new lab-developed diagnostic methods have been more closely scrutinized by the FDA; an example is in vitro diagnostic multivariate index assays (IVDMIAs). These tests screen patient samples for many different biomarkers that indicate relative levels of gene expression and then apply a weighted algorithm to predict the presence or absence of a particular disease. An example of an IVDMA is the Oncotype Dx test for breast cancer (Genomic Health, Inc, Redwood City, CA). The test measures the expression level of 21 different genes and then uses an algorithm to predict the probability of the recurrence of cancer. In 2006, the FDA issued a communication to CLIA-certified laboratories stating that the use of a weighted algorithm means that IVDMIAs constitute a new and distinct class of diagnostic test and that tests that use weighted algorithms are therefore to be subject to FDA regulations that govern IVDs. This tightening of the regulatory grip of the FDA on certain home-brew diagnostic tests threatens to put a stranglehold on the development and implementation of innovative diagnostics by clinical laboratories throughout the country.

### Issues Surrounding Costs, Coverage, and Compensation for Diagnostic Research and Development

Beyond the need to establish the scientific validity and clinical usefulness of certain tests and to obtain FDA approval for their use, the high costs associated with many new diagnostic technologies also create significant barriers to their widespread adoption. In the United States, large payers such as private health insurers and the Centers for Medicare & Medicaid Services (CMS) make the final decision about the conditions (if any) for which a new test will be covered. The Lewen Group notes that “there is no uniformly applied method for making coverage decisions for diagnostics, and decisions often seem to be ambiguous, arbitrary or redundant” (p.5). Moreover, payers “increasingly require evidence linking diagnostic test use to health and economic outcomes” (p.5). Providing such evidence, however, can be challenging because it is difficult to separate the various causal factors that determine health outcomes of specific patients to precisely quantify the relative contribution made by a diagnostic test.

Coverage for a new diagnostic procedure is sometimes extended in principle. However, in practice, diagnostic-test providers often still face challenges in obtaining sufficient compensation for the costs associated with the development and delivery of the test. The level of remuneration for a specific test is determined by the current procedural terminology (CPT) code, which is assigned to it by the American...
Medical Association (AMA). Billings cites the example of a complex DNA-sequencing diagnostic developed by a small, United States−based clinical laboratory. The test costs nearly $3000 to administer and is associated with a CPT code that would allow it to command more than $4000 in remuneration. Nevertheless, Billings reports that “extensive payment experience data indicated that laboratory providers of this test who sought payment from CMS or major private insurers might expect to recoup, on average, $1,500 or less”. Clearly, a dysfunctional payment system that fails to adequately compensate diagnostics providers serves the interests of neither service providers nor patients.

**Resistance from Health Care Professionals Who Prefer a Traditional Approach**

An additional barrier to the introduction of novel diagnostics comes not from payers but from physicians, many of whom exhibit a preference for traditional, gold-standard tests and diagnostic methods that require professional expertise for analyzing and interpreting test results. It is colloquially known, for example, that there exists a fair degree of variability in the reproducibility of diagnostic determinations based on clinical imaging. Nevertheless, many physicians seem reluctant to replace established, expert-driven methods with new diagnostic techniques that offer higher levels of objectivity and reproducibility. As Billings remarks, “even when laboratory tests appear to have superior utility, experts often are reticent to change traditional approaches” (p.917). This reticence on the part of physicians to embrace improved diagnostic methods often undercuts the research and development efforts of clinical laboratories and other health-services companies within the diagnostics industry.

A bias towards traditional methods and current practices exists not just amongst physicians from the developed world but also among those in the developing world. Nightingale discusses the efforts of Chris Drakely, PhD, from the London School of Hygiene and Tropical Medicine, to introduce an RDT for malaria in sub-Saharan Africa. The standard diagnostic test for malaria is microscopic examination of a blood sample to detect blood-borne parasites. However, because of the prevalence of inadequately equipped or nonexistent laboratories and an underdeveloped medical infrastructure in third-world countries, doctors often forgo explicit testing for malaria in favor of prescribing antimalarial drugs to patients solely based on their symptoms. The result is wide-scale over prescription of antimalarial drugs to patients not infected with malaria. This constitutes a huge expense to underfunded, developing-world medical systems and a danger to these patients, who are not being properly treated for the causes of their symptoms. Given such circumstances, the use of RDTs that require no microscopic examination and can quickly detect parasitic antigens within blood samples would seem to be an ideal solution. Nevertheless, based on his development work in Tanzania, Drakely reports a general resistance among health care professionals to embrace “unproven” diagnostic methods such as RDTs and stated that patients who tested negative were nevertheless commonly prescribed antimalarial drugs as a precaution.

**Ethical Concerns Regarding Genetic Testing and the Possibility of Genetic Discrimination**

Mapping of the human genome and advances in genomic analysis have given health care professionals powerful new tools with which to predict, diagnose, and monitor disease. The Royal College of Pathologists notes “the potential for the analysis of inherited genetic variations to provide detailed information on a person’s susceptibility to many common illnesses, as varied as diabetes, vascular disease and cancer” (p.1). Techniques that analyze DNA and protein expression in tissue will facilitate more accurate biological classification of disease, enable the prediction of severe adverse reactions to certain drugs, and allow for the widespread screening of populations for the early detection of disease.

However, ethical concerns regarding the potential for the misuse of genetic information complicate the issue of genetic testing. Apprehensions about the possibility of genetic discrimination are legitimate. The case of a dispute between Arizona State University and the Havasupai Indians over improper use of DNA from members of the tribe highlights the need for proper design of informed consent in genetic testing. Initially Arizona State University began studies related to the tribe’s high incidence of diabetes and later used their DNA to study other things, including schizophrenia, inbreeding and theories of the tribe’s Asian origins that contradict their traditional stories. The potential for genetic discrimination in employment settings was
highlighted in 2002, when Burlington Northern Railroad agreed to pay $2.2 million in damages to employees who were unknowingly tested by the company to determine whether they were genetically predisposed to carpal tunnel syndrome.15 In response to such high-profile cases and mounting public concern, the federal Genetic Information Nondiscrimination Act of 2008 was introduced to expressly prohibit the use of genetic information in health-insurance and employment decisions. For the benefits of genetic testing to be fully realized, it will be necessary to ensure that the legal safeguards currently in place are sufficient to protect the rights of individuals to privacy and nondiscrimination regarding their genetic information.

Conclusion

Recent advances in medical technology have led to the development of new and innovative diagnostic tests with the potential to supplant existing methods and to improve the accuracy and timeliness of diagnoses for a wide variety of diseases. However, as my report highlights, substantial barriers exist to the ready dissemination of cutting-edge diagnostic methods into routine medical practice. Overall, there is a need to develop a smarter, less burdensome regulatory mechanism for diagnostics and a more receptive clinical approach, to facilitate diagnostic innovation and the timely adoption of improved diagnostic methods. At the same time, health care professionals must be extremely careful to ensure that any sensitive information gathered about patients through genetic testing is kept confidential and not used as a basis for discrimination. Embracing the power of advanced diagnostic technologies while simultaneously ensuring the privacy rights of patients should allow health care professionals to use the next generation of medical diagnostics to maximize the potential of those tools to improve human health. LM

Conflicts of Interest: none reported

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