Quality and performance

The promise of personalized medicine is the improvement of patient outcomes. This is achieved by using a patient’s unique molecular or genetic signatures to improve diagnosis, or guide therapeutic or preventive actions. For personalized medicine to be effective, three conditions must be met: technology needs to exist that can accurately and reproducibly read these signatures; adequate knowledge must exist about how varied signatures translate into actual diseases; and, there has to be some ability to take advantage of this knowledge to apply tailored individual treatments. These three concepts are also known as analytical validity, clinical validity, and clinical utility. In other words, it is not enough to be able to technically read a molecular or genetic signature with great accuracy unless the meaning of that signature is well understood and a specific treatment exists that works better for that signature than other available treatments.

To illustrate the application of the concepts mentioned above, consider the simplified analogy whereby a gene can be thought of as a word. Genetic alterations can include deletions of part of the word, addition or replacement of certain letters, or rearrangements. Some of the changes may not have any effect on an individual’s health while other changes may have a profound impact. The word “healthy” could be altered to “heal,” “healthey,” “heklbhy,” “thyheal” and so on. While this example reflects a short word, genes can be hundreds or thousands of “letters” in length, meaning the number of possible changes for one gene can number in the thousands. Different technologies approach this challenge of identifying the signature differently. In one approach, if it is already known that the specific misspelling “thyheal” causes a disease, then a relatively simple test can look only for the presence or absence of that misspelling; however, this would not detect other misspellings that may also be important. On the other hand, full sequencing of a gene could detect the exact letter sequence, and therefore detect any misspelling whatsoever, but simply detecting a misspelling may be insufficient absent adequate knowledge of what the misspellings mean in terms of disease or preferred treatment path.

Drugs that the FDA approves for a subgroup of patients with a specific genetic or molecular signature have what is known as a “companion diagnostic” that is used to read the molecular or genetic signature and determine if a treatment is likely to work. A companion diagnostic is often reviewed by the FDA simultaneously with the drug it is paired with. The FDA reviews not only the ability of these diagnostic tests to accurately read a genetic or molecular signature (analytical validity), but also how this information is used to guide a decision-making process by which the results are applied to diagnose disease and direct treatment (clinical validity and clinical utility). This may include which of the many possible signatures would be an appropriate signal to indicate use of a drug, the strength of a signal needed to trigger use of the drug, etc.

The FDA also considers the benefit-risk balance for the decisions that the diagnostic test enables. When use of a drug involves potentially serious negative side effects, the consequences of an incorrect decision that is facilitated by a companion diagnostic may be different than for a decision between treatments with similar effectiveness and side effects. The FDA takes these very different circumstances into consideration when evaluating the benefit-risk factored into approval of a companion diagnostic. [1].

The diagnostic tests the FDA reviews and approves are known as in-vitro diagnostics (IVD’s). IVDs are sometimes referred to as “kits” since they are often sold and packaged with all the needed materials for the tests to be performed in a local laboratory. As mentioned before, personalized medicine requires accurate testing of genetic or molecular signatures, knowledge of how those signatures translate into disease, and treatments tailored to work for a given signature. While there are technical challenges in assuring accurate tests and testing processes, the most significant

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[1] The FDA only examines clinical utility for companion diagnostics, not for stand-alone molecular or genetic tests.
scientific hurdles that require years of research are typically the processes of linking specific signatures to a disease and developing effective therapies accordingly. Once a new drug and associated companion diagnostic are approved by the FDA, the knowledge linking a specific genetic or molecular signature to a disease and the corresponding FDA-approved therapy become public knowledge. Multiple testing manufacturers will often use readily available technology to quickly create and market competing tests for the same genetic or molecular signatures. Drugs are protected from copying both by patent protection and by FDA exclusivity rules that prohibit other identical drugs from obtaining FDA approval for a number of years. Diagnostic tests, by and large, do not have the same level of protection from market forces. While case law is still being litigated with respect to patenting genes, rulings have largely exempted them from patentability. The underlying testing technologies can be patent protected to the degree that they are unique, but many of the processes are common and not subject to patent protection.

Regulatory pathways

Importantly, diagnostic tests can take one of two paths to market. Each path involves a different oversight system managed by different federal agencies. The FDA oversees companion diagnostics and stand-alone IVDs. The Centers for Medicare and Medicaid Services (CMS), in cooperation with the Centers for Disease Control and Prevention (CDC) and the FDA, oversees another category of tests known as laboratory-developed tests (LDTs). LDTs are also sometimes called “homebrew” tests.

While medical tests are generally subject to FDA oversight and approval, LDTs historically represented tests conducted by colleagues within the same institution for unique circumstances or were tests generally not commercially available as IVD kits. After a series of high-profile deaths due to poor quality Pap smears, Congress passed the Clinical Laboratory Improvement Amendments of 1988 (CLIA) which created a certification program aimed at ensuring high quality testing performance of laboratories conducting tests on human samples. CLIA certification involves process- and standards-based quality assurance mechanisms be in place and allows laboratories to not only perform FDA-approved tests, but also to modify FDA-approved tests or even create new testing processes from scratch. Using this flexibility, CLIA labs can use the knowledge revealed about a newly FDA approved drug and companion diagnostic to recreate and market an LDT version of a companion diagnostic test without having to seek FDA approval or perform equivalent clinical validation.

FDA maintains they have the ability to formally regulate LDTs and the current absence of active oversight of LDTs is a function of regulatory discretion by the FDA and not because the FDA lacks the statutory authority to do so. In fact, the FDA has signaled its intention to begin oversight of high-risk LDTs, although the agency has not yet issued a formal framework for this oversight [1].

The creation and use of LDT copycat versions of IVD companion diagnostic tests may have the effect of lowering the price of such tests through market competition. However, the lack of market protection for IVDs also has the effect of reducing the willingness of device manufacturers to invest the time and money needed to generate the knowledge necessary to translate genetic and molecular signatures into utilizable knowledge of disease and treatment. Further, given the close connection between the performance of a companion diagnostic and the effectiveness of the associated treatment, some have expressed concern that lack of equivalent validation requirements for LDTs may lead to poorer, or at least less predictable, patient outcomes when LDTs are used as companion diagnostics.

Real-world challenges

Another important consideration with diagnostics is the growing problem of needing to use multiple individual tests to determine which of several personalized medicines are most appropriate for a patient. In the case of lung cancer, there have been more than a dozen different genetic signatures identified as important subsets of this type of cancer. To date, however, targeted therapies have been developed for only a few of these signatures, and each has an associated FDA-approved companion diagnostic test. If a dozen different therapies are ultimately developed, there could be 12 different tests that must be performed on a patient’s tumor to determine optimal treatment, which could
be difficult given a limited biopsy size. In the future it will be desirable from a logistical and cost standpoint to analyze signatures in a more comprehensive way, either by testing a broad panel of genetic signatures at once, or by fully sequencing the tumor’s genome. Either approach will require modifications to the current paradigm of pairing individual drugs with single gene tests. The recently announced LungMAP trial is one of several clinical trials that will use a broad-based approach by testing simultaneously for multiple lung cancer genetic signatures with the intent of facilitating directed treatment by any of a number of targeted therapies [2]. A further example of the evolution of testing approaches is the 2013 approval by the FDA of the Illumina MiSeqDx gene sequencer. This testing platform provides the capability of fully sequencing genetic areas of interest.

Lastly, while the FDA has responsibility for safety and efficacy, they are only the initial gatekeepers of performance of personalized medicine tests and therapies. Real-world effectiveness may be different than the effectiveness seen in clinical trials for a number of reasons. Different patient populations, additional changes in technology, use of tests and drugs in ways that are different than those approved by the FDA, and advances in scientific understanding can all alter the real-world outcomes. As an example, clinical trials designed for the approval of a targeted therapy may only test the therapy in patients with a specific genetic or molecular marker. In such a case, if a drug were to be approved then there would be an absence of information on the effectiveness of such a therapy on patients who do not carry the marker. The FDA has provided guidance on research designs in personalized medicine that outlines important research design considerations [3]. Monitoring and learning from real-world experiences remains an important challenge to ensure optimal outcomes for patients, and the FDA, healthcare providers, researchers, and payers will all have important roles in ongoing monitoring of tests and targeted therapies.

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