Regulations That Ensure the Quality of Precision Medicine

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Introduction to Personalized Medicine

Personalized medicine is a broad term that encompasses a movement toward use of specific biomarkers and tests to tailor therapy for each patient to optimize outcomes. For health systems, personalized medicine has the potential to improve the efficiency of diagnosis and enable prescribing of the right medications for each patient. In its current form, personalized medicine is largely limited to the use of specific genetic biomarkers to select treatments for subgroups of patients.[1] As the cost of genetic testing decreases exponentially, falling from $40 million per human genome sequenced in October 2003 to $1200 in October 2015, technological costs associated with implementing precision medicine continue to fall (**Figure 1**).[2]

Personalized medicine has many advantages over traditional methods of treatment (**Table 1**[1,3]). Although traditional nontargeted medications may use a one-size-fits-all approach to treatment, personalized medicine allows for the use of targeted treatments for certain patients with specific genetic mutations. It has been estimated that only one-fourth of patients treated with classic cancer treatment regimens respond to therapy, with similarly low rates of treatment success in other domains of medicine (**Figure 2**[4]). Through personalized medicine, it may be possible to improve rates of response in many conditions by treating patients for the specific molecular pathologies underlying their disease.

Examples of Patients Benefitting From Personalized Medicine

Diagnostic tests are a major component of personalized medicine. They are used to predict patient response to therapies, prevent medication-related adverse events, and assist physicians in determining the appropriate medication and treatment dose to match each patient's specific disease features. For instance, in breast cancer, patients with the *HER2* (*ERBB2*) mutation may receive the targeted agent

FIGURE 1. Costs of Sequencing a Single Human Genome: 2003 to 2015[2]

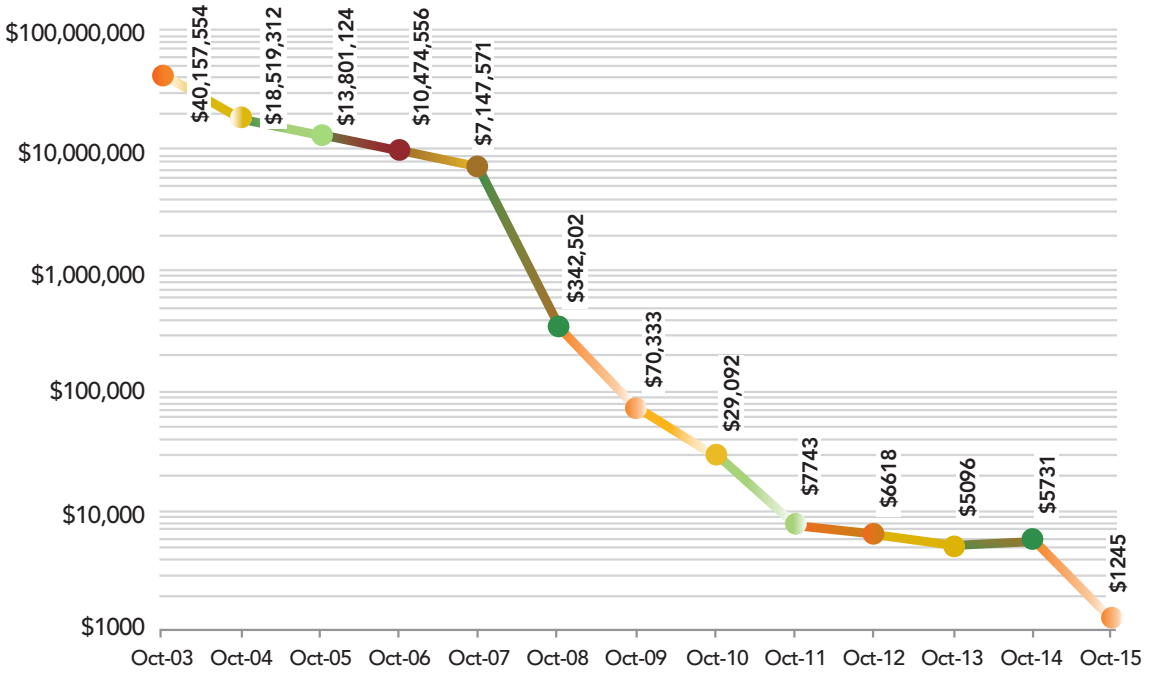
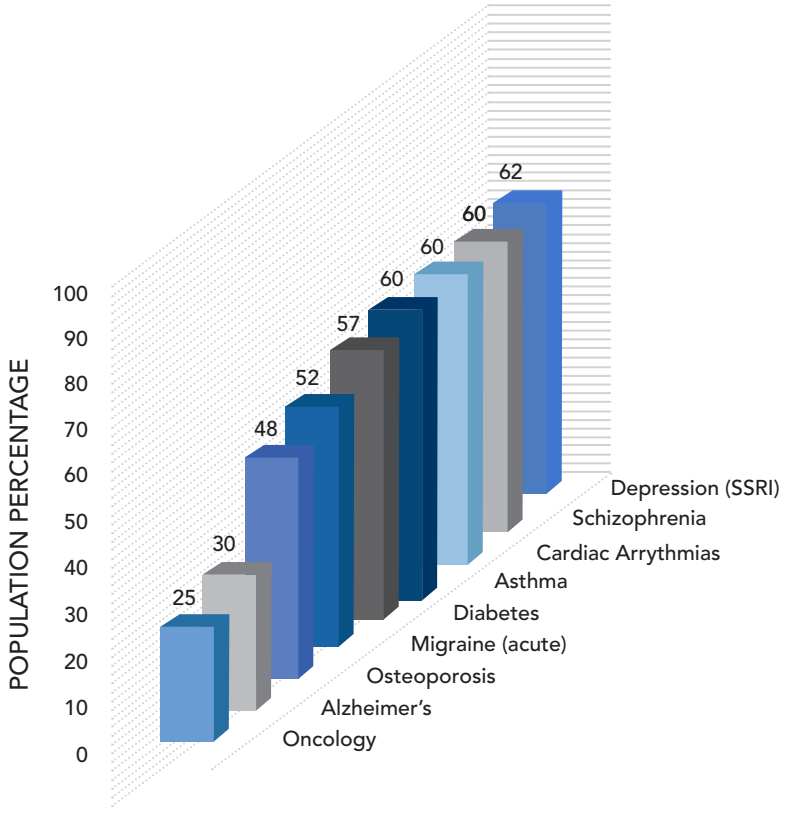


TABLE 1. Personalized Medicine Versus Traditional Medicine[1,3]

PERSONALIZED MEDICINE	TRADITIONAL MEDICINE
• Liquid biopsy: noninvasive and captures more characteristics of cancer that are not limited to a single area of the body	• Prevents adverse effects, predicts dosing, and improves compliance Tumor biopsy: ◦ invasive and does not capture the heterogenicity of cancer ◦ limited to 1 area of the body to which cancer metastasizes
• Individualized and genetically targeted medicine	• Trial and error to find the right medication
• Recruit patients most likely to respond in clinical trials	• One-size-fits-all approach in clinical trials
• Prevents adverse effects, predicts dosing, and improves compliance	• Large percentage of patients do not benefit

FIGURE 2. Medication Response Rates in Selected Conditions[4]



SSRI indicates selective serotonin reuptake inhibitor.

trastuzumab.[5] Similarly, in patients with lung cancer, testing for levels of PD-L1 helps determine if the patient is a candidate for treatment with immunotherapies.[6,7]

Targeted therapy is not limited to treatment of patients with cancer. A genetic screening tool has been developed to help prevent a life-threatening hypersensitivity reaction in patients with HIV receiving treatment with abacavir.[8,9] Also, patients receiving abacavir are tested for the HLA-B*5701 allele, which is associated with abacavir-related hypersensitivity reactions.[9]

Other treatments may promote better use of existing treatments, including warfarin, which is known for its highly individualized dosing and narrow therapeutic index. Many factors play a role in determining the right dose of warfarin. In addition to patient's weight, age, gender, race, height, lifestyles and current medications, several genes also influence the concentration of warfarin in the body and thereby dosing. The CYP2C9 gene encodes for an enzyme that is important in the metabolism of warfarin.[10] Analyzing expression of CYP2C9 and other genetic variants may be helpful in determining the appropriate dose and optimizing therapy.[11,12]

Liquid Biopsy

Liquid biopsy involves noninvasive testing of body fluids to detect tumor DNA and analyze tumor genetic material to optimize patient treatment and management. Samples may be obtained from saliva, cerebrospinal fluid, blood, urine, and seminal fluids.[3] As part of personalized medicine, liquid biopsy is less invasive than traditional biopsy methods and may reveal more of the genetic heterogeneity of the genetic features of cancer.[3] Examples of liquid biopsy technologies include Progensa, CellSearch, and AlloMap.

Although liquid biopsy cannot yet replace tissue biopsy, its results can provide information to supplement tumor biopsy. One example is the Progensa prostate cancer antigen 3 (PCA3) urine test, which is FDA-approved for use in men 50 years and older with 1 or more previously negative prostate biopsies. Both PCA3 and prostate-specific antigen (PSA) concentrations are measured from the urine and the ratio of PCA3 to PSA is calculated. The ratio can help physicians determine the chance of a positive prostate biopsy.[13] »

TABLE 2. FDA's Proposal for Classifying LDTs Subject to, and Exempt From, Premarket Review[19]

LDTS SUBJECT TO PREMARKET REVIEW	LDTS EXEMPT FROM PREMARKET REVIEW
• LDTs with analytically and clinically invalid data	• Low risk LDTs • LDTs for rare diseases
• False advertisement by the manufacturer of LDT	• Traditional LDTs[a] • LDTs for public health surveillance only[b]
• High-risk LDT that can cause death and serious health consequences	• LDTs used for transplant cross-matching, allele type, and antibody monitoring • LDTs for forensic use only

LDT indicates laboratory-developed test.
[a]Traditional LDTs are based on parts that are legally marketed for use in a clinical setting. The test results are interpreted by qualified laboratory personnel without reliance on technological automation.
[b]LDTs related to the assessments of public health practice for disease prevention by public health officials.

TABLE 3. FDA's Proposal for Classifying LDTs Subject to, and Exempt From, Premarket Review[19]

LDTS SUBJECT TO PREMARKET REVIEW	LDTS EXEMPT FROM PREMARKET REVIEW
First year	Identify serious adverse events for all LDTs (excluding LDTs exempted from premarket reviews)
Second year	Premarket review of high-risk LDTs that are used in the same way as a preapproved IVD
Third year	Premarket review of moderate-risk LDTs that are used in the same way as a preapproved Class II device
Fourth year	Premarket review of LDTs not addressed or reviewed in the previous 3 years

IVD indicates in vitro diagnostic; LDT, laboratory-developed test.

The CellSearch circulating tumor cell (CTC) test is a blood test, approved by FDA in 2007, that monitors disease progression in patients with metastatic prostate cancer. A high level of CTCs in the blood indicates a worsened prognosis and poor treatment response. At baseline, patients with low CTC counts have higher survival rates than patients with high CTC counts.[14] Physicians can order non-invasive CTC counts anytime during treatment to monitor cancer progression and tailor therapies accordingly.[3]

AlloMap is an FDA-approved blood test widely used to predict the risk of rejection in heart transplant patients 15 years and older while saving them from invasive tissue biopsies.[15] International Society for Heart & Lung Transplantation guidelines recommend the use of AlloMap as a noninvasive means of monitoring patients for potential heart transplant rejection.[16]

FDA's Regulation of In Vitro Diagnostics, Laboratory Developed Tests, and Companion Diagnostics in Relationship to Personalized Medicine

A companion diagnostic medical device is defined as an in vitro diagnostic (IVD) used to determine the safety and effective use of a therapeutic product. Companion diagnostics can identify the groups of patients highly likely to respond to a medication, predict side effects, and monitor response to a medication.[17,18] The FDA also categorizes laboratory-developed tests (LDTs) as a type of IVD that detect analytes such as DNA.[19]

Traditionally, the Centers for Medicare & Medicaid Services (CMS) has had jurisdiction over LDTs through the Clinical Laboratory Improvement Amendments (CLIA) Act, while the FDA regulates IVDs as medical devices. Although LDTs are considered IVDs and supposedly regulated by the FDA, the agency has exercised enforcement discretion in the past and exempted some LDTs from the extensive processes needed to attain premarket approval.[19,20] For instance, the Trofile co-receptor tropism assay by Monogram Biosciences was used in the clinical trials program for maraviroc before the drug's approval in 2007. Because this assay was important in selecting patients for treatment with maraviroc, as the antiretroviral drug is only indicated for patients with CCR5-tropic HIV-1, the FDA decided to forgo premarket review of the assay prior to sale.[20,21]

An example of the FDA subjecting an LDT to premarket approval occurred in 2005 when a warning letter was issued to Agendia BV for its MammaPrint breast cancer recurrence assay. FDA officials were concerned about a lack of data showing clinical benefits to the patients. The FDA only gave its approval in 2008 for marketing of MammaPrint after the makers proved the test clinically beneficial to patients with breast cancer.[22] As part of the process, the FDA also reclassified MammaPrint as an IVDMIA (in vitro diagnostic multivariate index assay), a type of LDT.[20]

A lack of consistency in the regulation of LDTs, however, may hinder manufacturers from producing high-quality screening tests that meet the standard of care for safe and effective medication use in patients. For example, the FDA issued a safety alert in September 2016 regarding ovar-

ian cancer screening tests. In the alert, officials stated that there are no screening tests currently accurate enough to detect ovarian cancer, contrary to many companies' advertisements. They warned that unreliable tests may lead to false-positive or false-negative results. A false-positive result may lead women to use other medical tests and undergo needless surgeries, increasing healthcare costs, whereas a false-negative result may delay necessary treatment in asymptomatic women at higher risk of developing ovarian cancer.[23]

After posting a draft on the LDT regulations in 2014, the FDA organized the comments received and posted a revised discussion paper on LDT regulations in 2017. The revised document is a working guidance, as the FDA invites further comments and suggestions.[19] However, considerable feedback has already been incorporated. In development of the current draft, the FDA interpreted over 300 sets of comments, summarizing them into several common themes regarding adoption of LDT guidelines, including[19]:

- Risk-based classification, oversight, and review of LDTs
- Premarket review for selected LDTs
- Analytically driven and clinical validity-driven assessment of LDTs for approval
- Grandfathering of LDTs already on the market
- LDT performance and validity of the test for approval

In the paper, the FDA proposed exempting certain LDTs from premarket reviews while subjecting other LDTs to premarket reviews (**Table 2**[19]). According to the agency, the current risk-based protocols for the premarket reviews of LDTs may not be adopted into common practice for at least 4 years (**Table 3**[19]).[19] Through this process, the FDA and CMS will divide responsibilities to ensure that quality standards are followed for all new and existing personalized medicine diagnostic assays.[19]

Conclusion

As the potential and value of personalized medicine continues to be realized, regulation of this expanding field continues to be a challenge. However, these challenges are positive in that they are a sign of a burgeoning field with great potential for growth and advancement. As the scope of personalized medicine widens, regulations for diagnostic tests will continue to be important. Ensuring the tests' quality and appropriate is a critical area for FDA oversight. ■

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