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Current Trends in Personalized Medicine and Companion Diagnostics: A Summary From the DIA Meeting on Personalized Medicine and Companion Diagnostics

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Abstract

Personalized medicine has reached the mainstream, accounting for more new drug approvals and a promising pipeline of candidate therapeutics. Recent advances in genomics, computational biology, medical imaging, diagnostic technologies, and translational medicine are creating the possibility for scientists to develop diagnostic tools and new treatments for cancer, genetic disorders, and infectious diseases that may be particularly effective in biomarker-defined subpopulations. Drug development under this model creates new challenges that will require the need for increased regulatory flexibility, novel clinical trial designs, and translational science development. In this review, the authors highlight key developmental and regulatory challenges in the advancement of personalized medicines and their associated companion diagnostics with the need for innovative clinical trial designs to support drug/diagnostic development and registration. Further, the clinical complexities of implementing new technologies are considered, such as high-throughput next-generation sequencing in personalized medicine, and offer a glimpse of the regulatory and policy considerations shaping this methodology in multimarker diagnostic development.

Keywords

personalized medicine, companion diagnostics, multimarker diagnostic, next-generation sequencing

Introduction

Definitions Used in the Context of Personalized Medicine

Although the concept of personalized medicine is not new, the scope in which it is defined and described is very broad.[1,2] Many definitions have been proposed to define personalized medicine, but all incorporate the notion of "the right drug for the right patient at the right dose at the right time."[3] Several terms, including *precision medicine*, *stratified medicine*, *targeted medicine*, and *pharmacogenomics*, are often used interchangeably with *personalized medicine*. *Precision medicine*, used more commonly to describe *personalized medicine*, has been defined by the National Academy of Sciences as "the use of genomic, epigenomic, exposure and other data to define individual patterns of disease, potentially leading to better individual treatment."[1] *Stratified medicine*, as defined by the US Food and Drug Administration (FDA), is "the division of patients with a particular disease into subgroups, based on a characteristic of some sort, who respond more frequently to a particular drug or, alternatively, are at decreased risk of side effects in response to a certain treatment."[1] In the European Union (EU), no official definition of personalized medicine exists, but a recent report released by the European Commission described personalized medicine as "a medical model using molecular profiling for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention."[4] The FDA defines targeted therapies[5] as a drug:

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- whose mechanism of action (and presumably benefit) is through modulation of biological processes via interaction with a specific molecular target; or
- that is proposed to have a treatment effect in a subset of patients based on empirical clinical evidence, nonclinical experimental evidence, pharmacological evidence, or biological rationale; or
- for which knowledge of a patient's "status" (eg, through a diagnostic test) can inform any of a number of individualized treatment decisions (eg, dosing, choice of therapy, and monitoring strategy);
- for whom patients are identified for inclusion/exclusion in pivotal trials or for drug use in labeled indication based on a genetic test, biomarker or susceptibility test (eg, bacterial resistance, tumor genetic mutation).

The development of targeted therapies is complicated in part by the fact that significant molecular or genomic heterogeneity exists among diseases and that these differences may be determinants of a clinical response or adverse reaction to treatment with specific agents. In specific cancer types, for example, such heterogeneity can arise from differences in the spectrum of coding sequence mutations, focal gene amplifications, deletions, gene fusions, translocations, or epigenetic changes in the expression profile of a tumor cell.[6] Compared with the "one size fits all" traditional medicine approach, the personalized medicine approach is predicated on the use of genotype-defined therapies in smaller disease subsets. Benefits of this approach usually correlate with drug metabolism, responsiveness or resistance, and the presence of a specific biomarker in patient biological specimens such as the blood or tissue of the patient. The most commonly cited examples of personalized medicine are the development and approval in 1998 of trastuzumab (Herceptin), the first genetically directed therapy for the treatment of HER2-positive metastatic breast cancers.[1] Approximately 30% of patients with breast cancer not responsive to standard therapy overexpress the HER2 oncoprotein. Herceptin was approved in 1998 for patients with HER2-positive tumors, and further research in 2005 showed that it reduced recurrence by 52% in combination with chemotherapy.[7] Further advancements have continued, including the promise of personalized medicine becoming clearer in 2003 following the mapping of the human genome.[8] Deciphering of the human genome sequence significantly helped researchers realize the potential to better understand disease biology at a molecular level as well as identify biomarkers for targeting medicines to specific diseases, improving health, and advancing personalized medicine. The challenges do remain in advancing these successes into routine clinical practice.

Biomarkers as defined by the National Cancer Institute are "biological molecules found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease."[9] A biomarker may be used for diagnosis and early detection (screening), monitoring of disease, prognosis, and prediction of safety and efficacy.[10,11] Biomarkers for a variety of tumor types, such as breast, colorectal, and lung cancer, as well as hematological malignancies have been identified. These predictive biomarkers can identify the patient subpopulations that are most likely to respond to a specific therapy. The use of genomic biomarkers to identify patients who can benefit from treatment with a specific agent has significantly increased the potential to improve drug safety and efficacy as well as improve patient care and accelerate drug development.

As part of the Critical Path Initiative and release of the FDA's landmark report *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*, a national effort was initiated to address the increasing difficulty and unpredictability of medical product development. The white paper diagnosed the reasons for the widening gap between scientific discoveries that may translate into innovative therapeutics to address the nation's largest health problems while concluding that collective action was needed to modernize scientific and technical tools to better evaluate and predict the safety, effectiveness, and manufacturability of medical products.[12] Following the release of this report, the FDA initiated numerous innovative projects and worked to build collaborations with all stakeholders to tackle identified issues.

Evolving Drug/Diagnostic Codevelopment and Regulatory Framework

A considerable number of personalized medicines are approved or are currently in development in disease areas such as oncology, cystic fibrosis, infectious diseases, and genetic diseases, in which patients can be selected for these treatments based on their individual genomic or proteomic characteristics.[13] As cancer is a disease of abnormal genetic function, most of the success in personalized medicine achieved to date is through the application of biomarker-based drug development in cancer and infectious disease research. As our understanding of the intrinsic biology of disease and diagnostic technologies improves, personalized medicines have the potential to transcend clinical research and patient care settings leading to potentially targeted therapies that maximize effectiveness and minimize adverse effects or therapeutic failures. Personalized medicine has typically involved the use of an in vitro companion diagnostic (CDx) device and a targeted therapeutic product, taking advantage of advances in molecular understanding of disease to identify individual risk factors and predict individual therapeutic responsiveness to improve drug efficacy and patient outcomes. A diagnostic device is a type of medical

device that may include in vitro diagnostic (IVD) tests such as assays used in the measurement of genetic factors and/or in vivo tests (eg, electroencephalography, electrocardiography, or diagnostic imaging equipment).[1] In its July 2011 draft guidance, the FDA defined a companion diagnostic devices as "an *in vitro* diagnostic (IVD) device that provides information that is essential for the safe and effective use of a corresponding therapeutic product." Such a IVD companion diagnostic could be used to "1) Identify patients who are most likely to benefit from a particular therapeutic product, 2) Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product, or 3) Monitor response to treatment for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness."[14]

For new molecular entities (NMEs), where it is essential that the safe and effective use of a targeted therapy depends on the use of an IVD CDx device, then the FDA requires the IVD CDx device be cleared or approved in conjunction with the targeted therapy approval.[14] It is also an expectation that the drug sponsor address the need for an approved or cleared IVD to be developed and approved or cleared contemporaneously, when possible, to support the drug's safe and effective use. The use of an FDA-approved IVD CDx device with a targeted therapy is required for inclusion in the instructions for use in the labeling of both the CDx and the corresponding therapeutic product.[14] Only in specific cases will a therapeutic product be approved without approval or clearance of an IVD CDx. The drug must be life saving, support an unmet need, and have a risk-benefit assessment that suggest greater benefit than risk even if the diagnostic is not available.[3,14] However, there is an FDA expectation that the CDx will be subsequently approved or cleared through an appropriate device submission, and the therapeutic product labeling will be revised to reflect the required use of the IVD CDx. In addition, the FDA will consider whether additional measures are necessary to address safety issues presented by the use of the drug in the absence of an approved or cleared CDx.

In the United States, unless already approved or cleared for an intended use, diagnostic devices, including the CDx test, investigated in a clinical trial of a therapeutic product to inform clinical decisions are considered investigational devices. If the CDx is used to guide critical treatment decisions, such as patient selection, assigning patients to trial arms, or selecting therapeutic doses, it may be considered a significant risk device under 21 CFR 812.3(m)(3) because it presents a potential for serious risk to the health, safety, or welfare of the subject.[3,14] The development of targeted therapies and their accompanying biomarker is a critically important area of personalized medicine. If a diagnostic device and a therapeutic product are to be studied together in the same investigational study to support co-registration of both the drug and device, both products must comply with investigational new drug (IND) regulations (21 CFR part 312) and the investigational device exemption (IDE) regulations.[14] In order to conduct a study in which the diagnostic device is viewed as significant risk, a sponsor will be required to submit for approval of an IDE application and conduct the trial under full provisions of the IDE regulations.[2,3] In determining the applicability and need for an IDE, key questions to consider when assessing the risk to subjects and whether an IDE filing will be required for a CDx in support of the investigational therapy are as follows[3]:

- Will use of the investigational test results lead to some trial subjects forgoing or delaying a treatment that is known to be effective?
- Will use of the investigational test results expose trial subjects to safety risks (eg, adverse events from the experimental therapy) that (in some "net" sense) exceed the risks encountered with control therapies or nontrial standard of care?
- Is it likely, based on a priori information about the investigational therapy, that incorrect test results would degrade the safety or efficacy of subjects' treatment?
- Does specimen acquisition, done for investigational testing and outside the standard of care, require an invasive sampling procedure that presents significant risk?
- What would the risk of the trial be if the test did not exist?

In the EU, the regulation of CDx devices differs from that of the US. In contrast to the US, where personalized medicines and their approval are closely linked with their corresponding CDx, the current EU regulatory framework for the marketing of medicinal products and the corresponding CDx does not currently have a mechanism for premarket review. Medicinal products fall under the regulatory framework for medicinal products, while CDx devices are covered by the In Vitro Device Directive (IVDD).[4,15,16] Sponsors registering CDx devices in the EU are required to comply with the essential requirements set out in the IVDD in order to "CE Mark" their tests and allow for commercialization within the EU. In many cases, the dossiers to support the CE Marking of IVD tests, including CDx, do not get formally reviewed by third-party–notified bodies or by health authorities.[15] Regulatory oversight on IVDs including CDx is anticipated to change in the near term, with the recasting of the IVD Regulation, which was first published by the European Commission on September 26, 2012. While the regulation is currently undergoing review, it will establish a premarket review process for most IVDs. Most notable is the fact that there is a carve out in the IVD

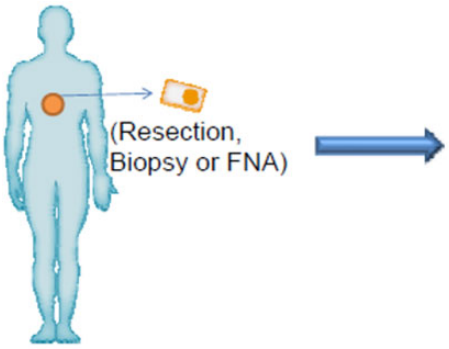
Regulation defining the CDx test and the fact that, much like the US, approval of the drug will be linked to approval of the CDx test.

Personalized medicines comprise 12% to 50% of company pipelines.[17] An increasing percentage of new approvals are for targeted therapies, particularly with orphan molecular subsets. Between 2010 and 2013 (as of December 6, 2013), 55% of rare disease approvals were for targeted therapies.[18-20] The FDA defined an "orphan subset" of a nonrare disease or condition in the Orphan Final Rule on June 12, 2013, as "the use of the drug in a subset of persons with a non-rare disease or condition may be appropriate but use of the drug outside of that subset (in the remaining persons with the non-rare disease or condition) would be inappropriate owing to some property(ies) of the drug, for example, drug toxicity, mechanism of action, or previous clinical experience with the drug."[21] Many rare biomarker-defined diseases are serious, life threatening, and poorly understood with limited available treatment options. Similar to most rare disease programs, drugs developed for these smaller subsets of populations involve smaller, compressed clinical development programs with limited opportunity for study replication. Many of the FDA's "Breakthrough Designations" are for targeted therapies and require the use of a biomarker or a drug product codeveloped with a CDx, according to a recent review of publicly announced designations.[22] For many promising investigational treatments for serious or life-threatening diseases, a timely standard regulatory approval may be unlikely or impossible because of practical, scientific, or ethical reasons. These challenges, compounded with the urgent medical need of many of these therapies, create a need for regulatory flexibility and novel paths for expedited regulatory review. To address the difficult regulatory challenges of transforming scientific discoveries into important treatments for patients with serious or life-threatening disorders, the FDA, the US Congress, and the public have all endorsed the need for regulatory flexibility to speed access to new treatments while preserving standards for safety and efficacy. The FDA has created a number of regulatory paths for expediting the review process for important therapies through several programs including Priority Review, Fast Track, Breakthrough Designation (BTD), and Accelerated Approval (AA).[23,24] The AA pathway was promulgated by the FDA in 1992 in response to the AIDS crisis and was codified into law by Congress with the passage of the FDA Modernization Act of 1997.[25] The 2012 passage of the Food and Drug Administration Safety and Innovation Act (FDASIA) amended the AA provisions to reflect recent advances in science and create a significant and valuable opportunity to advance the translation of promising scientific discoveries into new treatments for rare disorders.[26] The AA program provides that when evaluating therapies for serious and life-threatening diseases with substantial unmet medical need, the FDA may approve a treatment based on an efficacy evaluation using a surrogate endpoint that is "reasonably likely to predict clinical benefit."[24] Thirteen of the 14 AAs in 2013 were approved for rare diseases.[19] The BTD, the newest program, established by the 2012 passage of FDASIA, is applicable for drugs that are "intended, alone or in combination with 1 or more other drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may provide substantial improvement over existing therapies on 1 or more clinically significant endpoints."[24] The Agency and pharmaceutical industry have responded enthusiastically to the new program. As of April 7, 2014, a total of 40 drugs have been granted BTD, and of the 6 that have already been approved, 5 were for rare diseases.[19,27] To address some of the complexities raised by CDxs associated with therapies achieving BTD, in September 2013, a report was released by a working group, spearheaded by Friends of Cancer Research (FOCR), highlighting optimal processes and novel risk-based approaches that would allow CDx development to remain on pace with the expedited development of the companion Breakthrough Therapy.[28]

Despite the remarkable advances in the personalized medicine field, the development of biomarker-guided therapies and their corresponding diagnostics continues to raise a number of scientific, regulatory, policy, sponsor coordination, and review management challenges. This review will explore some of the key challenges facing innovators and potential options for addressing these challenges to facilitate growth in the rapidly evolving field of personalized medicine.

Scientific and Clinical Trial Issues

Comprehensive views from large-scale sequencing of cancer genomes including large-scale collaborative sequencing projects such as The Cancer Genome Atlas and the International Cancer Genome Consortium have shown that cancers are heterogeneous diseases with tumor genotype variations occurring between patients or in evolving subpopulations of cancer cells across different regions of a patient's tumor.[29-31] This interpatient and intratumor genomic heterogeneity, shown to correlate with clinical features of disease, drug response, and patient outcomes, suggests that there is a high likelihood that effective personalized medicines will need to address patient-specific molecular abnormalities and changes in the tumor microenvironment. Oncologists are increasingly using molecular profiling of a sample of primary or metastatic tumor to guide therapy selection for individual patients. The process of identifying relevant markers and therapy selection is further complicated by the increases in the number of actionable mutations in cancers and tissue requirements for diagnostic testing (Figure 1).[32] The



Testing Panel for Lung Cancer Treatment	
EGFR mutation	Sequencing/PCR
EGFR amplification	FISH
ALK	FISH
KRAS mutation(s)	Sequencing/PCR
ERCC1	IHC/RNA
BRAF	PCR/sequencing
ROS1	FISH
MET	FISH/IHC
FGFR1	FISH

Figure 1. Sample testing algorithm in non–small-cell lung cancer.

limited availability of tumor tissue samples also does not adequately represent molecular heterogeneity between and within patients, requiring multiple tests that can become costly for the patient.[31,32] The failure to recognize heterogeneity and not identifying responsive subgroups in developing targeted therapies can have negative or suboptimal consequences, particularly for drugs that have efficacy only in subgroups of patients with specific molecular phenotypes. The paradigms for development, evaluation, and administration of personalized cancer treatments have historically been developed around the primary site of the disease. The standard approaches for developing most cancer therapies have been built on a rigid sequence of clinical trials. This approach was developed as standard chemotherapy agents with broad applicability across many patients and diseases were being investigated. In the era of personalized medicine, the idea of aligning patients who carry a specific molecular signature with a specific targeted therapy has resulted in higher response rates than have been previously seen.[33] Pharmacogenetic-based approaches linking strong genetic associations to adverse drug reactions (ADRs) can also lead to identification of individuals at risk of and provide insight into the mechanisms underlying the ADRs for individual patients.[34] As a greater magnitude of clinical effects are expected and seen earlier in the drug development process, early phase trials are beginning to support approval, and the time period between "early development" and "registration" is shorter.[35] According to the FDA, most of the industry-sponsored cancer clinical trials in the US are uncontrolled, open-label studies[35] (Figure 2). The majority of BTDs are granted based on uncontrolled, open-label phase 1/2 trials, and most NME approvals under Subpart H (Accelerated Approval) are based on phase 2 trials.[36] Randomized controlled trials (RCTs), which typically focus on incremental treatment effects in the overall population, are suboptimal for the evaluation of molecularly targeted therapies. For example, in clinical trials that are not restricted to patients expressing molecular subtypes of a disease, drugs that would have had clinical utility in molecular subgroups of patients would not have shown efficacy in larger groups of patients with different molecular phenotypes. This misinterpretation of the clinical trial results and generalizability of those findings to overall patient populations would result in these drug candidates being "lost in the mix."

Multimarker Diagnostics and Development Complexities

As the numbers of clinically significant genetic variants have increased, genomic testing technologies have become increasingly feasible in clinical practice, moving from single mutations to multiplex evaluations in multiple cancer genes.[37-39] Given our current understanding of intrapatient heterogeneity and clonal evolution, testing one molecular abnormality at a time in serial trials using the traditional clinical research framework is neither practical nor sustainable.[30,31] Novel technologies, including next-generation sequencing (NGS), can yield further insight into the mechanistic understanding of oncogenic drivers and sensitivity/resistance mechanisms to identify corresponding druggable targets. NGS will also enable both multiple and parallel analyses for mutations and help address the problem of limited patient samples.[40] The FDA describes NGS as "a technology parallelizing the genetic sequencing process, allowing for the production of thousands or millions of sequences concurrently (also referred to as "high-throughput sequencing")."[1] Improvements in genomic technology and the adoption of NGS in clinical practice provide a unique opportunity to modernize clinical trials and better utilize such genomic information by identifying patient molecular abnormalities and matching them with the appropriately selected targeted therapies. These recent advances in NGS technologies demand rational and flexible approaches to CDx development to reflect

Phase	1	1/2	2	2/3	3
Randomized	12%	38%	57%	89%	98%
Safety/Efficacy	38%	86%	68%	89%	66%
Open-Label	98%	95%	87%	60%	56%
Parallel	17%	21%	35%	80%	88%

Figure 2. Scope and design of active, industry-sponsored cancer trials in the US as obtained from clinicaltrials.gov (as of September 2013).

the times and rapidly deliver critical precision medicines to patients.

There are several regulatory and development strategic considerations when employing a multiple marker diagnostic approach, such as NGS, in a targeted therapy development program. The following section will explore challenges and opportunities in implementing a multiple marker approach in clinical trials and clarifying the regulatory framework integrating NGS into the drug/CDx codevelopment model.

Developing NGS technologies into analytically validated companion diagnostics that can be used for patient care presents many of the same developmental and regulatory challenges inherent to the codevelopment of single-marker CDx tests. These challenges include determining the need for the CDx, timing and alignment of the development strategies of the two products, and having a sufficient analytically validated test(s) at the time of initiation of the pivotal trial.[41,42] To implement NGS for clinical trials, several challenges such as assay design, costs, tissue samples, analytical test and clinical validity, clinical laboratory implementation, the availability of results, trial design and endpoints, and data analysis need to be considered.[43] Most NGS applications are in clinical research or for investigational purposes only.[43] Many clinical research centers and biotechnology companies are running CLIA-certified laboratories for their NGS-based cancer diagnostic tests.[44] Whole-genome sequencing (WGS), in which the entire human genome (includes both gene-coding and noncoding regions) can be evaluated, is a still rapidly evolving technique, with currently no consensus on how to adequately analytically validate performance.[43]

Establishment of the analytical and clinical validity of each variant is not practical or even feasible, since the clinical relevance of most of these markers is currently unknown.[43] Some of the most frequent challenges seen by the FDA related to review of accuracy and performance of multimarker tests include preanalytical issues, lack of clinical samples covering all genotypes, lack of reference method with an appropriate comparator, lack of literature to support clinical validity, and complex clinical validation with tests evaluating a panel of alleles or complex algorithms.[41] Other regulatory issues that need to be considered for multimarker test development include the development of relevant standards and proficiency panels and, when possible, acceptance of the use of literature bridging to support clinical validity and utility.

Many recurrent genetic abnormalities implicated in non–small-cell lung cancer have been identified using NGS technologies using multiplex genotyping and high-throughput genomic profiling.[45] For meaningful progress to occur to improve clinical responses, future clinical trials with personalized medicines will require dedicated screening of multiple gene variants to define the appropriate molecular patient populations to match with targeted therapies. The scarce amount of tissue material that may be feasible to be obtained for diagnostic workup of a suspicious lung nodule, for example, may be insufficient to optimally perform serial diagnostic testing for all of the clinically relevant gene variants. NGS technology could allow multiple and parallel analyses for mutations with one sample, making it an ideal technology for such settings. Figure 3 describes a proposal for a global lung cancer patient screening network strategy in which a multimarker test such as NGS may be used to support patient screening in clinical trials and CDx development.[32] This model encompasses a network of designated local and regionally located screening laboratories that can serve as a central reference lab for patient samples. These laboratories would be selected based on their ability to generate high-quality data that meet the applicable regulatory requirements. Prior to implementation, preanalytical steps and standard operating procedures for sample preparation will be developed to ensure that the operational aspects are standardized throughout the network.[32] This type of network may be applied for various clinical trial designs, including NGS-driven screening protocols.

To address some of the multimarker test complexities, since only a restricted amount of actionable genes and mutations may serve as biomarkers for clinical trials, analytical validation can potentially focus on adequate subsets of genetic markers, as determined by an institution's complement of clinical trials.[41] In terms of accuracy of NGS-based testing, other potential strategies recommended by the Agency for analytical evaluation for specific assays, genes, and panels include the following[41]:

- Sequencing clinical samples from the intended use population and comparing to reference method results
- Sequencing procured samples that span the relevant classes of variants and comparing to reference method results

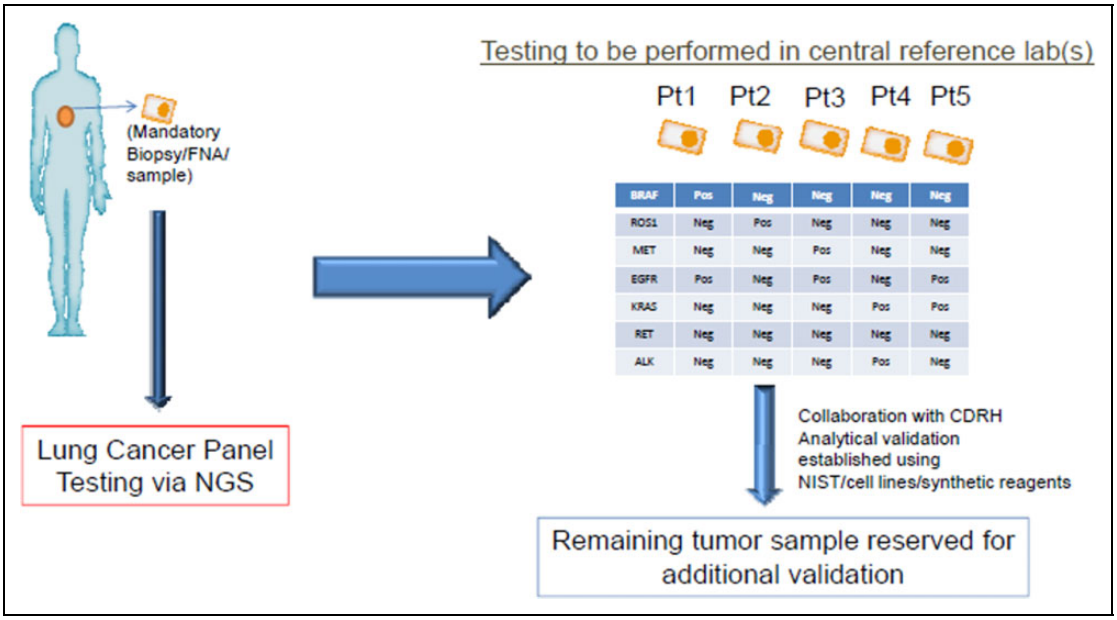


Figure 3. Proposed testing paradigm to support patient screening and companion diagnostic development.

- Sequencing well-characterized reference sample(s) and comparing to reference sequence

Since it will be impossible for the Agency to assess the NGS platform's performance for every single variant, the Agency is currently exploring the possibilities for identifying a representative set of markers that could be assessed to gain an understanding of the performance of the entire sequencing-based platform.[1] In the absence of clinical studies to support the establishment of clinical validity for NGS-based tests, sufficient supporting literature and professional society recommendations may be accepted. However, if the above-mentioned supporting information is not available, clinical studies will be required to support the validation of clinical performance.[41]

The FDA has made good progress toward establishing the assessment framework of FDA-regulated multimarker systems and is continuing to work in collaboration with stakeholders on best practices and standardization initiatives.[41] As the FDA is facing rapidly evolving NGS technology and increased sponsor interest in providing genomic data to support regulatory submissions, it is highly encouraged that sponsors meet with the Agency early and often to gain clarification on the appropriate regulatory approval path forward and to advance the applications for NGS development and use.

The complexities of many variations in genes present a major challenge both in clinical study design and regulatory strategies. In order to meet the challenges of the evolving science, a shift in the current clinical research paradigm is needed to understand the clinical impact of heterogeneity on therapeutic effectiveness and to rapidly translate scientific innovations into the clinic. With this perspective, we will review innovative clinical trial designs that help to address the challenges of time, cost, and failure rate of current clinical trials while supporting drug/CDx codevelopment. These designs may use NGS to characterize the molecular signature to appropriately match patients with molecularly targeted therapies.

Innovative Biomarker Integrated Clinical Trial Designs

To help address the problem of disease heterogeneity, clinical trial designs that are driven by predictive biomarkers can be employed, enabling both evaluation of new treatments and identification of the patient subgroups that will have the most benefit. In the context of an RCT, the selection of a subpopulation of patients within a broader population in which the efficacy of a treatment is most likely to be demonstrated is referred to as enrichment.[46,47] Enrichment for the purposes of detecting a drug's effectiveness is defined by the FDA as "the prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population."[47] Enrichment designs can improve the efficiency of a trial by increasing the power of the study and minimizing the required sample size or duration. However, if the effect of a treatment is heterogeneous across a population, the potential increase in efficiency associated with an enrichment approach will be compromised, as these results cannot provide any positive risk-to-benefit ratio of using the treatment in any specific subgroup.

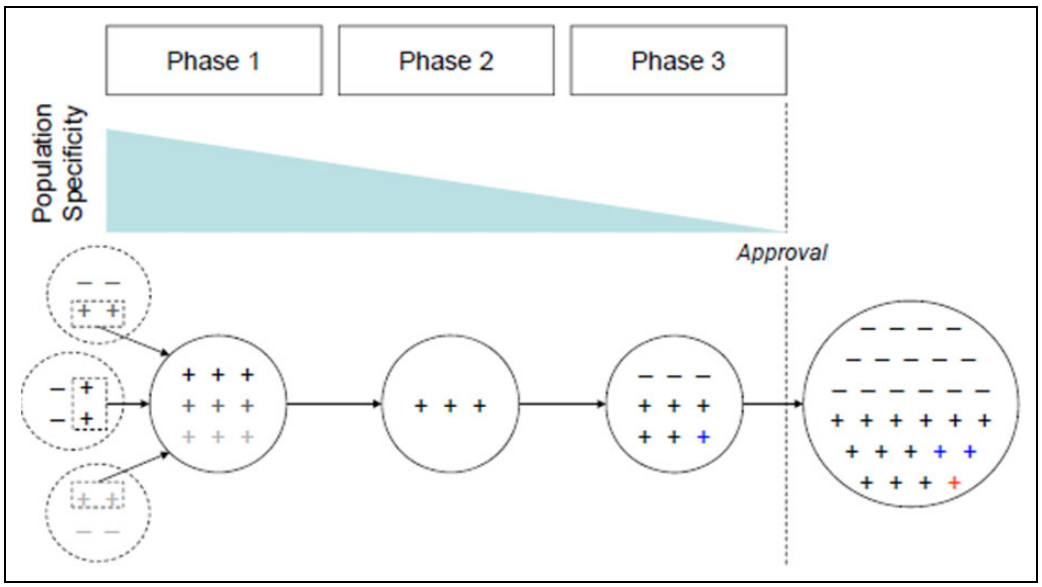


Figure 4. Alternative targeted drug development model.

In early development, one alternative to the traditional clinical trial model is to a use subgroup-driven approach employing a predictive enrichment strategy in phase 1 trials and selecting based on molecular markers (marker-positive patients) to characterize pharmacokinetics, intrinsic/extrinsic factors, and safety. Information gained in phase 1 can be used to direct more restrictive enriched phase 2 studies and prospectively stratifying in phase 3 to evaluate both marker-positive and -negative patients (Figure 4).[35]

The success of this type of enrichment design in targeted therapy development is greatly dependent on the knowledge of the drug's clinical pharmacology and disease under study. Characteristics that support biomarker-based indications and drug/CDx codevelopment include the following[5,35,48,49]:

- Confidence in the biomarker and evidence that the molecular feature is the main pathophysiological driver of the disease to be studied
- Unmet medical need (eg, serious and life threatening without adequate therapy) with biomarker-defined subpopulation homogenous and considered a rare disease
- Predictive/prognostic utility-known anticipated risks and benefits of the drug in biomarker-defined subgroups in vitro, animal models, or early phase studies
- Strong assumption marker-positive group will benefit from drug
- Intrinsic properties (variability, specificity)—preliminary evidence of harm or lack of efficacy from early phase studies in patients without biomarker

To address the issue of assessing treatment effects in various biomarker-defined subgroups, a few phase 3 trial designs can be employed that range from limiting evaluation to the biomarker-positive subgroup to sequential testing of biomarker-positive, biomarker-negative ,and overall populations. The success of these enrichment designs to provide definitive evidence for informing clinical practice is based on the level of preexisting evidence that the biomarker can successfully identify patients who will respond to investigational treatment.[50] Detailed descriptions of these clinical trial designs and considerations for selecting the appropriate phase 3 biomarker-driven strategy have been articulated in a recent review published by Freidlin and Korn.[51]

Tissue-specific and tissue-agnostic studies represent other novel biomarker-defined clinical trial designs that have the potential to speed enrollment for trials and efficiently match patients to drugs, thus speeding the development of new targeted agents. These approaches can be driven by collaborations between government, academia, and major pharmaceutical companies to quickly and efficiently test promising new therapies. These models also incorporate an adaptive trial design to rapidly eliminate ineffective treatments and build a knowledge base that can be used to inform future clinical studies.

Oncology Histology-Specific Trial Design: Example-Master Protocols/Umbrella Trials

Histology-based, biomarker-integrated clinical trial designs simplify oncology trials by evaluating a variety of targeted agents matched to specific molecular profiles in a tumor type. Instead of initiating multiple clinical trials in different diseases, which requires duplication of regulatory and infrastructure efforts, we can start with one trial, with multiple therapeutic

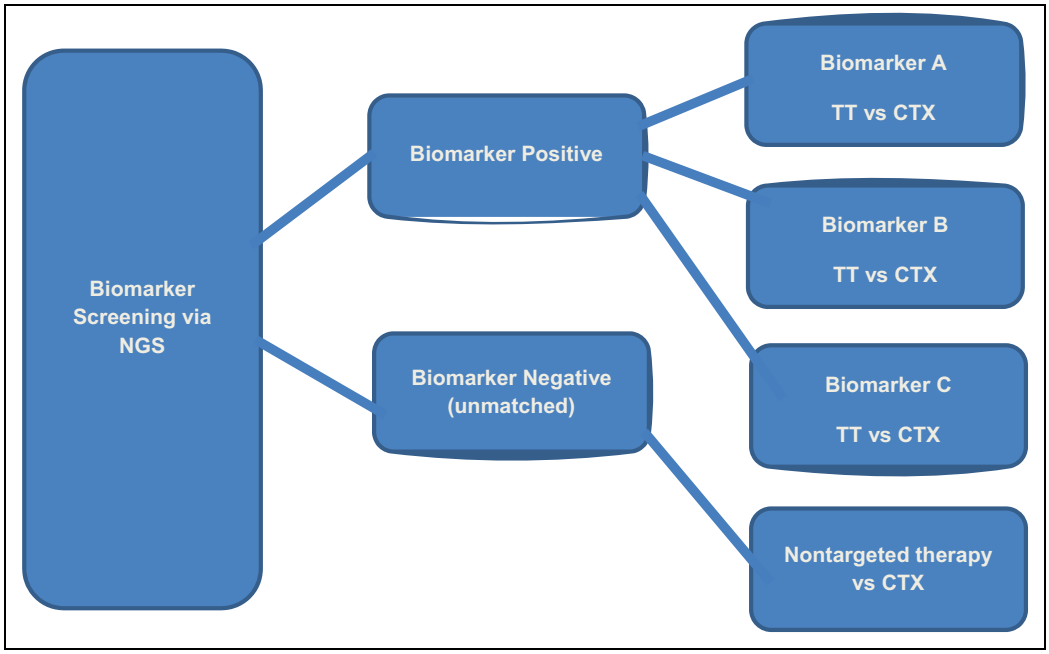


Figure 5. Histology-specific trial design: master protocols example.

molecular targets, and following molecular characterization, allow patients with multiple subsets of a single disease (eg, BRAF mutant melanoma) to enroll in treatment arms according to their molecular signature (Figure 5).[33,35]

In the initial phase of the trial, patients are randomly assigned to treatment arms (targeted therapy and chemotherapy) in equal ratios. Each treatment arm operates as its own RCT, where results for the various molecular subtypes are then used to inform the subsequent adaptive phase. If one cohort shows a clinical response, this cohort can be expanded to assess whether others could benefit from the new targeted agent.[35] If another group does not show evidence of clinical benefit, this group will be closed and the patients can move on to a different trial or consider other therapies. Using this approach, the evaluation effectiveness of targeted therapies is seamless, occurs early and rapidly, and is integrated into one trial to make drug development more efficient. Examples of clinical trials using the master protocol strategy are the BATTLE,[52] I-SPY,[53] and the recent FOCR Lung Cancer Master Protocol.[54] The challenges of the master protocol approach are often logistical in nature, as considerable planning and coordination among many pharmaceutical sponsors, drug supply vendors, and diagnostic testing sites will be required.

Genotype-Focused Oncology Histology-Agnostic Trial Design: Example-Basket Studies

Researchers have also recognized that single genomic alterations or pathways may occur too infrequently to perform clinical trials but still might have clinical relevance across clinical indications.[55] In this context, the concept of a "basket study" can be applied when the functionality of genetic variants have been determined to be clinically relevant by preclinical studies or other means.[56] These exploratory, or "signal-seeking" studies are organized around cancer mutations rather than cancer type and are typically conducted when either the cancer type or mutation is rare. This approach is particularly useful when an RCT is not feasible because very few patients fit the profile of the disease in question or in metastatic diseases where the tumor site of origin is unknown. Rather than search for new oncogenic targets, existing targets can be exploited using this design to help provide insight into the molecular mechanisms of the same genomic aberration across different tumor types. In this clinical trial design, patients of most any clinical classification whose tumor contains the molecular alteration may be eligible. Trial designs based on this strategy may generate increasingly larger numbers of biomarker-based indications, better resolve molecular aberrations, and potentially uncover mechanisms of resistance that would form the basis for further investigation.

An adaptive strategy may be employed such that if early signals of antitumor activity are seen in particular tumor types harboring the relevant mutation, then accrual of more patients with these tumor types can occur while excluding nonresponsive subgroups.[55] In the BRF117019 BRAF mutant trial, the groups that achieved at least a 50% response rate were deemed successful, ensuing in future discussions around the development and regulatory pathway forward with the FDA (Figure 6).[56]

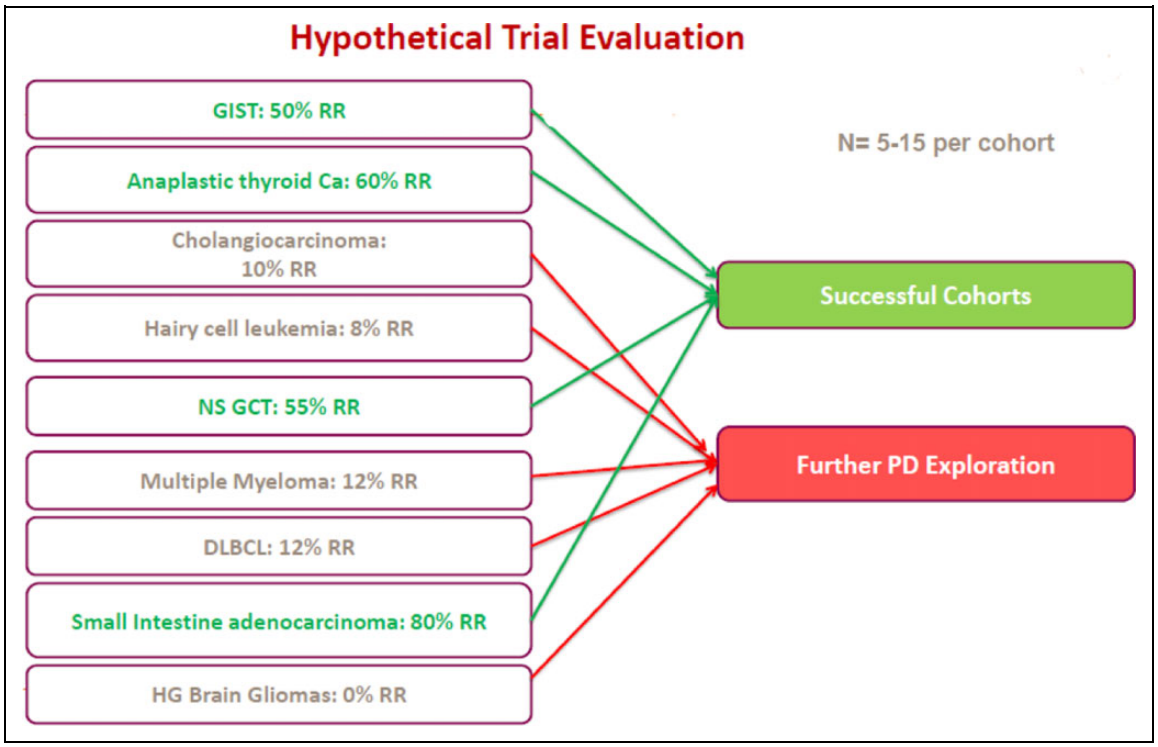


Figure 6. Trial evaluation of histology-agnostic BRF117019 BRAF mutant trial.

Groups achieving less than a 50% response rate will undergo further pharmacodynamic exploration to further investigate biomarkers implicated in the corresponding tumor types.

Examples of trials using a histology-agnostic approach are the National Cancer Institute's NCI MATCH, the Novartis *Signature* protocols, and the GlaxoSmithKline BRF117019 BRAF mutant trial.[56,57] Similar to the master protocol approach, logistical challenges also exist in designing histology-independent, marker-specific studies since success may be contingent on administrative support, patient resources, and partnership among many pharmaceutical sponsors.

Regulatory Challenges in Drug/Diagnostic Codevelopment

Although personalized medicine offers tremendous potential to improve patient outcomes, several regulatory and review management challenges are inherent in synchronizing the development of molecularly targeted therapies with in vitro CDx for use in in rare, biomarker-defined populations. As scientific knowledge in our understanding of molecular levels of disease improves, more prospective biomarker-defined indications will be studied in clinical trials, with the development and approval of more drugs guided by biomarker use. In the premarket setting, biomarker-based strategies, evaluating genetically defined patients, select a much smaller subset of the overall population (via inclusion/exclusion criteria and diagnostic testing of predictive marker) than unselected trials to identify patients who will most likely benefit from the investigational treatment. By design, these populations are generally not representative of the overall population, and the exact clinical utility of the biomarkers is often not completely understood. Many of these biomarker-based programs are built around the drug as emerging data become available during the development program, often with limited scientific understanding of the disease and endpoints clinically meaningful to the outcome of the disease in the early stages of development. In addition, many of the tools or instruments produced for use in clinical trials are usually lacking or not well developed for the intended purpose (eg, "to be marketed"), with no regulatory precedent for review and approval.[18] As a result, there can be a much greater degree of uncertainty and available information for regulatory or clinical decision making. Many of these programs have limited to no information in the marker-negative subgroup obtained throughout the drug development process. In the US, drugs developed for orphan populations are held to the same statutory standards as nonorphan drugs, requiring demonstration of substantial evidence of efficacy, safety, and quality (21 CFR 314.50) assessed by adequate and well-controlled clinical trials conducted in the relevant patient population.[18]

The FDA has issued a number of guidances to provide clarity, predictability, and guidance for sponsors to encourage development in the rapidly evolving field of personalized

medicine. These guidances were developed to outline major principles affecting targeted therapies throughout clinical development for a broad range of topics, which include incorporating genetic and other biomarker information in drug development programs, designing clinical trials to incorporate biomarker data, coordinating cross-labeling activities, evaluating pharmacogenomics data, and demonstrating companion diagnostic test performance.[1] An overview of the guidance documents related to personalized medicine has been described in a recent FDA report, "Paving the Way for Personalized Medicine,"[1] and is also available on the FDA Personalized Medicine website.[58] Since targeted therapy codevelopment has many intricacies, it has been difficult for the Agency to develop policies and evidentiary standards that are broadly applicable. To minimize uncertainty and improve exchange of regulatory advice, the Agency highly encourages sponsor engagement early and often throughout the clinical development program.[18]

Codeveloped personalized medicines also raise logistical challenges to the Agency, since expertise from and careful coordination between the FDA centers is required to ensure consistent reviews and simultaneous approval of the drug and CDx.[1] The typical individual regulatory challenges of targeted therapies and diagnostics is further compounded by the coordination between the drug and diagnostic sponsors and the regulatory oversight and coordination of multiple FDA centers, as each center operates under different laws, regulations, review cycles, and timelines.[1]

As the science and diagnostic technologies continue to evolve with biomarkers increasingly being incorporated in targeted therapy clinical trial design, all FDA centers see the need for collaboration to address the complexities that continue to arise with the current regulatory framework. Major challenges faced across FDA centers in drug/diagnostic application reviews include aligning drug and CDx timelines, regulatory decision making, IDE and IND requirements, and timing the review of Pre Market Applications (PMAs) alongside new drug applications.

The FDA's regulatory oversight activities for personalized medicine products include the 3 medical product review centers: the Center for Devices and Radiological Health, the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER).[42] Each of these centers has different statutory authorities while applying specific sets of regulations. Thus, it is not surprising that the existing regulations for drugs, biologics, and medical devices do not currently address the current practice of drug/diagnostic codevelopment in personalized medicine. This has led to some inconsistencies in regulating personalized medicine products. The Agency has identified these gaps and is establishing regulatory processes and implementing policies to clearly describe the responsibilities of the different centers in the oversight of drugs and diagnostics when their safety and efficacy are intimately tied to one another.[59] These initiatives are intended to help coordinate premarket reviews for the different drugs and CDx to provide consistency and timeliness in regulatory decision making for these products.

As a result of the enhancement proposals included in the recent Prescription Drug User Fee Act V reauthorization, CDER was provided increased staff to support the review process and guidance development for personalized medicines.[60] In addition, the FDA Office of In Vitro Diagnostics added a cross-cutting personalized medicine staff that is charged with addressing the unique regulatory and policy issues around use of CDxs to specifically guide therapy and to promote the use of novel technologies as clinical diagnostics.[61] The personalized medicine staff is currently working on developing regulatory approaches for codevelopment and recommendations for FDA intercenter collaboration for more efficient product reviews and is helping to guide the appropriate balance of regulatory oversight between centers for personalized medicine products.[61]

To make the review process as efficient as possible for PMAs alongside NDAs, particularly with compressed drug development programs, the personalized medicine staff works with medical officers and scientific reviewers across centers, including molecular diagnostic expertise to facilitate intercenter consultations and alert the appropriate FDA center of anticipated issues and questions.

The process of translating new scientific findings into safe and effective use of personalized medicine remains a major challenge. Significant progress has been made in understanding how genomic variations affect an individual's response to treatments, enabling potential improvements in the clinical use of existing therapeutics and opening up the possibility of codeveloping drugs and diagnostic tests that can be used to tailor targeted treatment to individual patients. Clinical development programs to evaluate personalized therapies can be lengthy and expensive with uncertain outcomes. It is imperative that new and forward-thinking tools and approaches be developed to speed efficacious medical products to patients by modernizing the conduct of clinical trials. We have explored several key scientific, developmental and regulatory challenges facing the future of personalized medicine. To keep pace with the extraordinary advances in science and to build on the promise that personalized medicine holds for new and better therapies, the FDA is attempting to develop policies and flexible regulatory approaches to support codevelopment and expeditious product reviews.[41] The Agency has been working among its centers to develop infrastructure programs and to review capacity to optimize the integration of genomic sciences into regulatory review and drug development. New clinical trial paradigms, incorporating public-private partnerships, are being developed for

translational and confirmatory clinical trials to catalyze personalized medicine, drive efficiency, speed patient access, and allow for the simultaneous testing of matched diagnostics and therapeutics to important targeted therapies. These changes result from the recent surge in high-throughput sequencing, supporting that many diseases, especially cancer, are genomically heterogeneous and that these differences in molecular signature have major influences on the disease and responsiveness to treatment. As we move out of the basic and translational research environment with an ever-increasing array of targeted therapies and approved NGS-based tests and platforms, there will be a greater interest in evaluating and resolving these multimarker complexities within the context of drug/CDx codevelopment. Finally, the promise of NGS and other multimarker strategies has brought personalized medicine to exciting crossroads, where there is tremendous opportunity for biomarker-defined trials to support research and drug/CDx codevelopment. To ensure the safety and effectiveness of these personalized technologies and to advance the personalized medicine field, early engagement and collaboration with the Agency is essential. The opportunities and risks at this juncture are noteworthy. Therefore, collaboration among industry, academia, government, provider, advocacy, and patient stakeholders will become increasingly important in clarifying the opportunities and challenges that will define future efforts in this area.

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