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Companion Diagnostics and Personalized Medicine – Part I

The New Era in Pharmacotherapeutics

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WHO SHOULD READ THIS:

Part I of this two-part series reviews how companion diagnostics and personalized medicine found their way into the mainstream pharmaceutical industry and established a foothold in a business model that was designed for products of a foregone era. Those wanting a background on the evolution of companion diagnostics and personalized medicine, and their integration into the pharmaceutical industry, may find this series of interest.

Objectives

- Review the rationale behind the evolution of the blockbuster drug era and explain how economic pressure and scientific progress work against it and contribute to the growth of personalized medicine
- Explain some of the basic drug polymorphisms and the impact they have on pharmacotherapeutics, and illustrate the potential roles that companion diagnostics and personalized medicine can play when incorporated into modern practice
- Describe the roles that personalized medicine and companion diagnostics have played in the development of well-known oncology drugs, and their roles in the treatment of breast cancer, melanoma, non–small cell lung cancer, and biomarker-directed therapeutics
- Elucidate some of the major obstacles facing the development of personalized medicines and their companion diagnostic devices, including economic and policy issues, and the opposing business models of the pharmaceutical and medical device industries

Key Points

- Based on large population statistical analyses, the blockbuster drug era targeted the largest identifiable disease-state patient population that could be positively affected by a single molecular entity
- With the failure to address the inherent heterogeneity of disease, public and regulatory pressures in response to issues of drug costs and safety encouraged the pharmaceutical industry to reduce the costs of drug development while pursuing methodologies to design more effectively targeted therapies
- Individual variability in response to drug therapy is affected by numerous physiologic and genetic factors, including drug-target polymorphisms, drug metabolizing enzyme polymorphisms, and drug transporter polymorphisms
- Variability in drug response is well recognized scientifically; however, among the forces preventing the full integration of personalized medicine into practice are the complexities of the human genome; resistance to change; and public, regulatory, and economic policies
- Together, companion diagnostics and personalized medicine have transformed the landscape of oncology practice from tissue/disease-based chemotherapy to molecularly targeted therapeutics
- Breast cancer, melanoma, and non–small cell lung cancer are among the diseases in which the most dramatic recent medical advances have been made through companion diagnostics and personalized medicine
- Biomarker-guided therapy is the hallmark of personalized medicine and companion diagnostic devices; its advent represents a major advance in medicine
- The integration of companion diagnostics and personalized medicine into clinical practice has been slow; one reason is that dosage adaptation based on pharmacogenetics is not being as readily accepted as has been dosage adjustment based on weight or renal function
- Many basic economic and regulatory policy issues entrenched in the past hinder the co-development process as well as the pharmaceutical and diagnostic device industries themselves, which are in many instances contrasting business models

PART II

Look for the upcoming *Companion Diagnostics and Personalized Medicine: The New Era in Pharmacotherapeutics, Part II*, which does the following:

- Discusses the phases of drug development and companion diagnostic device development within the context of a co-development process, and illustrates why the synchronization of these processes is so difficult
- Describes in vitro diagnostic tests relative to laboratory developed tests, the regulatory bodies, and the contexts of the regulations that govern utilization of these devices
- Reviews the regulatory roles of some of the varied agencies responsible for approving drugs and diagnostic devices, and the rationale behind classifications of these devices
- Offers expert suggestions to simplify and expedite the co-development process

CONTENTS – PART I

Overview

Companion diagnostics and personalized medicine were born of traditional medicine. In the evolution of medicine, however, these entities represent both a sweeping scientific advancement powerful enough to transform an industry and the humbling realization that, ultimately, all medicine is personal. As the pharmaceutical business evolved over the years to become an immense worldwide enterprise, the often divergent interests of science and big business were harnessed into an industrial manufacturing force whose interests were to grow through the development of products to treat disease. Philosophically, and aligned with the interests of traditional medicine, the practice of targeting the most common pathologies and the largest patient populations began. These pathologies would include cardiovascular disease and its contributing comorbid conditions such as hypercholesterolemia, hypertension, and diabetes, along with other conditions common to very large patient populations. At that time, the latter half of the twentieth century, the objective was the development of a single pharmaceutical entity for the treatment of as many patients as possible within any single given disease-state population. This was the era of the blockbuster drug.

Increasing public and regulatory scrutiny during this period, however, created pressures leading to rising manufacturing costs that eventually became unsustainable. Also, research had demonstrated that heterogeneity, not homogeneity, is the norm among patient populations, and that a patient could be treated more effectively today given state-of-the-art technologies and analyses, and given the attention to personalized therapy based on that individual's specific clinical and genetic characteristics. Inefficiencies and costs related to the development of the blockbuster drug, juxtaposed with the precision and efficacies of targeted therapies, spawned a paradigm shift toward personalized medicine.

Interindividual variability has become such an integral component of modern pharmacotherapy that drug package inserts contain specific information for prescribers concerning patients' *pharmacogenomics* (the role of genetics in drug response). Clinicians are more aware than ever that interindividual genetic differences can play a role in whether a drug is resistant to metabolism in one person (and therefore requiring a higher dose) or not resistant to metabolism in another. Individuals are also known to significantly differ in regard to how slowly or quickly they metabolize a drug, or the ways in which a specific drug may be absorbed, metabolized, and eliminated. More and more factors are known to affect interindividual variability; however, some are easier to implement into everyday practice than others. As science advances, it also becomes clear that medical practice remains an art because modern medicine is still young and much remains unknown.

The nature of chemotherapy and resistance to chemotherapy undoubtedly played a role in the development of targeted agents to treat cancer. Within a relatively short period of time, however, the advent of biomarker identification and companion diagnostics transformed oncology therapeutics from treating tissue to targeting molecules in a complementary approach to improving treatment. Companion diagnostics and personalized medicine have played major roles in advancing the treatment of breast cancer, melanoma, and non–small cell lung cancer. Research into these diseases has also yielded profound genetic insights, one example being the ability of practitioners to know whether or not certain drugs will work in certain patients with certain cancers.

The concepts of companion diagnostics and personalized medicine are not all that new, and their uptake and integration into practice have not been immediate. The newer sciences can be more complicated, laboratory logistics may present problems, cost-effectiveness may influence reimbursement, and numerous other issues that are not strictly scientific in nature impede the adoption of companion diagnostics and personalized medicine. The pharmaceutical and companion diagnostics industries themselves are different business models. Nevertheless, ample evidence demonstrates that companion diagnostics remain a growing industry, and that as the science of personalized medicine continues to evolve, these fields will contribute significantly to advances in medicine.

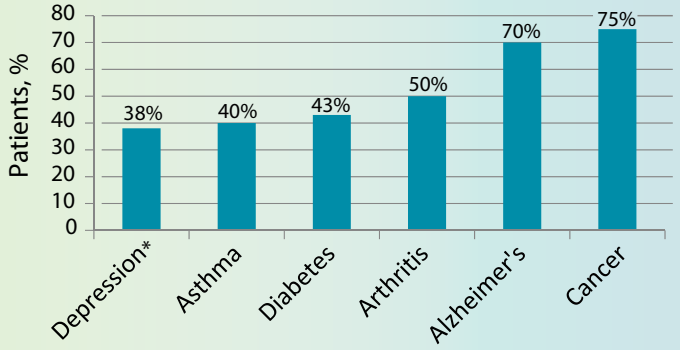
Evolution From Traditional Medicine

Throughout the twentieth century, rapid scientific advancement and tremendous growth in the pharmaceutical industry brought remarkable therapeutic advances in cardiovascular, infectious, and neoplastic diseases, and many other pathological conditions. As the pharmaceutical industry grew and both science and business became more analytical, growth focused on, and science grappled with, reaching the broadest patient population with a single agent that would effect the greatest benefit in the highest number of patients. The philosophy relied on the ability of population statistical analyses to predict individual outcomes. Dosages and therapeutic selections were derived from large population averages. Drug design and development became based on maximizing the number of therapeutic interventions, and thus, the blockbuster era was born.[1]

In time, and as these medications were introduced throughout the world, it became obvious that any given medication does not universally affect every individual in the same way. In fact, interindividual therapeutic response to any drug can vary substantially from complete cure to no therapeutic effect

Figure 1

On average patient population (%) by disease state for which a particular drug is ineffective.[2]



*Selective serotonin reuptake inhibitors.

(Figure 1)[2] to adverse effects, including allergic reactions, anaphylactic shock, and even death. Acceptance of this new knowledge brought the first realization that, for a large percentage of patients, drug therapy was imperfect and was the first step toward pursuing optimal individualized pharmacotherapy, also called personalized medicine.[1]

One Size Does Not Fit All

Over more recent decades, hard and significant evidence emerged indicating that a great deal of variability in response to therapy is dependent on interindividual differences in genetics, age, nutrition, health status, environmental exposures, and concomitant drug therapy.[1] Interindividual variability in response to drugs led to a new discipline that came to be known as pharmacogenetics, a blend of genetics, biochemistry, and pharmacology focused on drug response variability among individuals based on genetic differences. Even more recently, pharmacogenomics integrated pharmacogenetic study with genomics, enabling utilization of an individual's unique genetic profile to predict response to drugs and risk of disease. The result will have profound effects on disease pathogenesis and treatment, and may allow for truly personalized medicine.[1]

The initial observations of interindividual variability in response to drugs were made in the 1950s,[1,3] the first of which involved the prolonged effect of the muscle relaxant succinylcholine.[1,3] The duration of action of succinylcholine is determined by its hydrolysis; thus, those enzymes mediating its hydrolysis also play a role in its duration of action. It was observed that patients homozygous for an atypical form of the enzyme that mediates its hydrolysis had a prolonged drug-induced muscle paralysis. In a second observation, isoniazid, a tuberculostatic drug, was known to be metabolized by *N*-acetylation. It was observed that side effects attributed to isoniazid were common to those in whom its metabolism was prolonged. This metabolic defect in *N*-acetylation was soon identified and shown to be hereditary.[3] Later, it became clear that not only do genetic defects that impair metabolism and other functions exist but genetic duplications also exist that can have the effect of enhancing or speeding up metabolism and other functions. The consequences of these anomalies for drug therapy are obvious. In patients who are "poor metabolizers," for example, relevant drug dosages should be titrated down. In gene-amplified or "rapid metabolizers," relevant drug dosages should be titrated up.[3]

Targeted therapies are being seen as the wave of the future, with an inevitable shift away from the blockbuster model.[4]

These observations beg the inference that ultimately all therapy should be personalized. After the early observations of the drug isoniazid in which "slow acetylators" were identified, it was later discovered that these individuals, in varying frequency, occupy defined geographic locations and distributions in ethnic populations. The "slow-acetylator" phenotype characterizes 40% to 60% of the Caucasian population. This phenotype is also known to result in prolonged clearance and the potential for associated toxicities of drugs such as procainamide and phenelzine (Nardil®).[1] These observations are clinically significant, given that adverse drug reactions are reputed to be the fifth leading cause of death in the United States.[1]

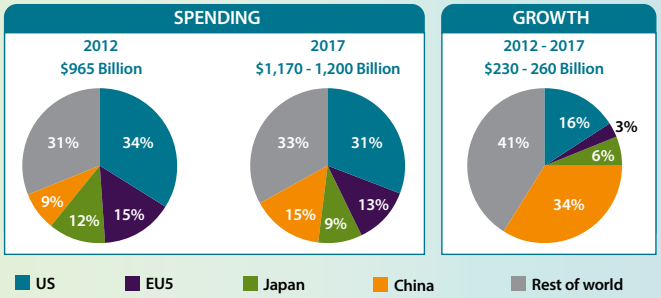
For decades it has been known that individuals' responses to a single drug are not homogeneous. However, it has only been within the recent past that specific genomic and protein biomarkers have been identified that are capable of distinguishing us as individuals. These and other factors have had an impact on the pharmaceutical industry, and over the past 5 to 10 years the industry has gone through radical changes in how it conducts research and drug development, and how it addresses the market. Targeted therapies are being seen as the wave of the future, with an inevitable shift away from the blockbuster model.[4]

Decline of the Blockbuster: A Confluence of Economic Pressures and Scientific Progress

Recent years have brought pressures to weigh both heavily and simultaneously on the pharmaceutical industry, forcing it to change in order to adapt. With rising healthcare expenditures and global prescription expenditures **(Figure 2)**,[1,2,5] the industry is facing cost-containment pressures

Figure 2

Figure 2. Geographic distribution of spending on medications: almost 70% of total global spending on medication is by the United States, the European Union Five (EU5: France, Germany, Italy, Spain, and the United Kingdom), Japan, and China.[5]



from government regulatory agencies, private insurers, and patients.[6] The industry is also facing an innovation gap: although it is required to make larger financial investments in product research and development, these investments are resulting in fewer therapeutic products that reach the market. Regulatory demands and societal expectations have also increased and have cultivated an intolerance to new drugs that provide only little or minimally incremental improvement over their predecessors.[6]

Coupled with growing public unwillingness to endure side effects, regulatory pressures for longer, larger clinical trials have also increased costs to the pharmaceutical industry. According to industry groups, the cost of bringing a new drug to market in 1987 was $230 million and by 2003 that cost had almost quadrupled to $900 million. By 2005 the projected cost of bringing a new drug to market in 2010 was $2 billion, which in 2005 was seen as unsustainable.[7] *Forbes* reported in 2013 that the cost of developing a new drug to a major pharmaceutical manufacturer had reached $5 billion, a cost that is truly unsustainable.[8]

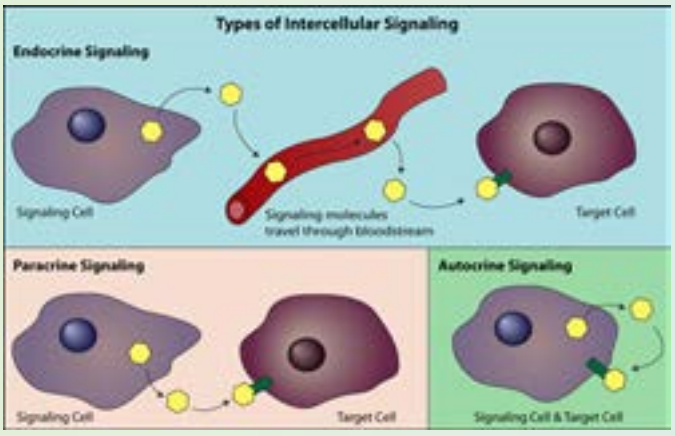
In 25 years, the cost of bringing a new drug to market increased from $230 million to $5 billion.[7,8]

The greatest expenses incurred in drug development do not occur in early-stage research but, rather, after the drug leaves the laboratory to be tested in human subjects. Clinical trial failures incur the greatest costs. Even when a drug has reached the first stage of testing in humans, it has only about an 8% chance of making it to market. Even in late-stage human trials, approximately 50% of drugs fail, often because they offer little or no value over existing treatments.[7]

A Vision of Reduced Drug Development Costs

The unsustainable costs of drug development under the blockbuster model drove industry to embrace the economic elements of genetic/genomic drug development. The pharmaceutical industry began using biomarkers—which are genes, proteins, or other cellular signals (the hallmarks of personalized medicine) that indicate which patients are likely to respond to which drugs, and in what ways **(Figure 3)**. Employing these aspects of personalized medicine has enabled greater efficacy in drug utilization and has reduced side effects, and has allowed industry to learn whether or not a drug works much earlier in the development process. Personalized medicine has enabled the specific identification of disease populations who will respond to a therapy; the development of fewer drugs that fail in clinical trials; and smaller, shorter clinical trials to demonstrate efficacy. Some pharmaceutical executives believe that $700 million per drug can be saved in development costs through incorporating the techniques of personalized medicine into the process.[7]

Figure 3



***Inter*cellular signaling is communication between cells that can occur at a distance (endocrine), in the local cellular environment (paracrine), or at the same cell (autocrine). In *intra*cellular signaling (not shown), a vast array of cellular responses can be set in motion by signaling molecules, including metabolic changes in the cell receiving the signal or a change in gene expression within the nucleus of that cell. (Reproduced with permission from Hartnell College, Biology Department, Salinas, CA. Signal Transduction Tutorial.)**

Advances in genomics have contributed greatly to the economics of personalized medicine. Our understanding of DNA sequencing has expanded at an extraordinary rate. Sequencing the first draft of the human genome required 13 years and cost more than $1 billion.[2] During that time the cost of sequencing declined at a rate comparable to the increase in computer performance over the last 40 years. From 2001 to 2007 whole-genome sequencing costs fell from up to $300 million to about $10 million. By 2009 the cost required to sequence an entire genome had decreased even more, to $50,000, and the time involved declined to only 2 months. In fact, costs associated with whole-genome sequencing have decreased so dramatically that in an increasing number of cases insurers have paid for genome sequencing to resolve difficult diagnoses. In January 2014, Illumina introduced a new instrument capable of sequencing a human genome for $1,000.[2] It is expected that in the not too distant future sequencing improvement will allow everyone to carry his or her personal genome on a small portable device.[3]

In 14 years, the cost of sequencing the human genome decreased from up to $300 million to $1,000.[2]

Incorporating personalized medicine into healthcare is predicted to resolve inefficiencies such as late diagnoses, therapeutic selection by reaction, dosing by best guess, and hospitalizations from adverse drug reactions. For example, a genetic testing model of warfarin dosing in 3,600 patients reduced hospitalizations by 30% in heart patients when their genetic information was given to their warfarin prescribers.[2]

Pharmacogenomics focuses on drug response as a function of interindividual genetic heterogeneity. Understanding how these individual distinctions relate specifically to drug metabolism and manifestations of adverse events can reduce incidences of drug toxicity and increase rates of effective treatment. Based on 1999 data, of 3.1 billion prescriptions written approximately 2.1 million result in adverse reactions. Of these 2.1 million adverse reactions 1 million may result in hospitalization, and of these more than 100,000 patients may die.[1] In 2011, the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality reported that drug-related adverse events were found in 1.87 million hospital inpatient stays, which is 4.7% of all stays. A total of 838,000 treat-and-release emergency department visits, that is, 0.8% of all visits, resulted from drug-related adverse events.[9] The ultimate vision of pharmacogenomics enables foreknowledge of which drugs will prove the safest and most effective in patients based on their genetic profiles.[1]

TABLES TO REVIEW:

1. **A table of pharmacogenomic markers specifically mentioned in labels of drugs approved by the FDA can be found at: www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm.**
2. **A table of companion diagnostic devices and the drugs with which their use is indicated by the FDA can be found at: www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm.**

Roots of Companion Diagnostics and Personalized Medicine

The concept of combining a diagnostic and a therapy as part of a package is typically perceived as a recent development in pharmacotherapy. However, if this concept is broadened to consider any drug with an indication requiring diagnostic testing before it is prescribed, then more than 50 drugs across multiple disease states qualify as of 2009. Approximately 60% of these drugs were launched without the requirement of pretreatment diagnostic testing; however, as new data emerged, the testing requirement was added to the corresponding drug labels.[10] A table of pharmacogenomic markers specifically mentioned in labels of drugs approved by the Food and Drug Administration (FDA) can be found at: www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm. The labeling for some of the drugs in this table includes specific actions that should be taken based on the relevant biomarker information.[11] The concept of variability, along with its importance, has become an accepted component of medical practice; testing for manifestations of variability has become standard of care in major treatment centers.

For many medications, interindividual differences are partly due to *genetic polymorphisms*, which are variations in the DNA sequence that are common in the population.[12] (Note that if the frequency of a variation is <1%, this variation is regarded as a mutation rather than a polymorphism.[13]) These genetic polymorphisms encode drug targets (eg, enzymes, receptors), drug metabolizing enzymes, and drug transporters.[12] These major categories of genetic polymorphisms responsible for interindividual variability and their affects are reviewed next.[12]

Drug-Target Polymorphisms

Response to therapy can be profoundly affected by drug-target genetic polymorphisms either through direct effects on drug-target function or drug-target interactions. As a result of these effects, increased or decreased dosing may be needed to achieve the desired therapeutic concentration of drug.

Worldwide, warfarin remains the most widely used anticoagulant. The enzyme vitamin K epoxide reductase (VKOR) was determined to be the target protein of warfarin 36 years ago; however, VKOR complex subunit 1 (C1), the direct target protein of warfarin, was not identified until 2004. VKOR catalyzes conversion of vitamin K epoxide to reduced vitamin K, which is required for the synthesis of clotting factors II, VII, IX, and X, and the anticoagulant proteins C, S, and Z. Warfarin-mediated inhibition of VKORC1 results in depletion of reduced vitamin K, which in turn leads to anticoagulation. At least five genetic mutations in the coding region of *VKORC1* have been identified. In humans these mutations occur only rarely (<0.1%). When they do occur, however, these mutations endow the VKORC1 protein with warfarin resistance, requiring administration of warfarin dosages greater than 15 mg a day.[12] Mutations in other genes result in a requirement for lower warfarin dosing (discussed below).

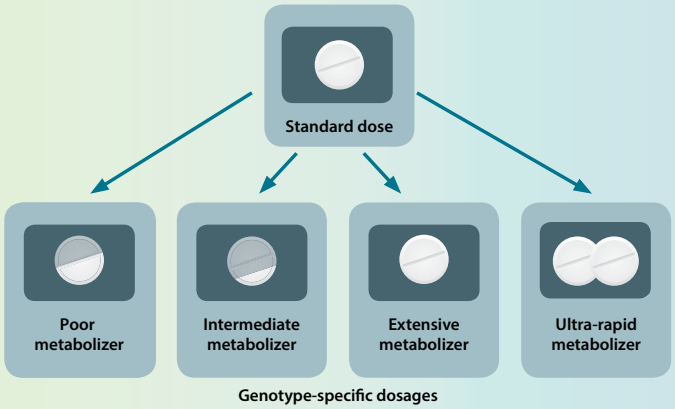
Encoded by the angiotensin-converting enzyme (*ACE*) gene, ACE-I catalyzes decapeptide ACE-I conversion to the vasoconstrictor octapeptide ACE-II and degradation of the vasodilator bradykinin. ACE inhibition is a primary strategy, and ACE is the target protein, in the treatment of hypertension, heart failure, type 2 diabetes, and diabetic nephropathy. An insertion (I)/ deletion (D) polymorphism of *ACE* has an impact on ACE inhibition in some patients with these conditions. Patients carrying the homozygous I/I genotype who have high blood pressure, albuminuria, or insulin-dependent diabetes do well on ACE inhibition therapy. Those with a heterozygous genotype (I/D), and especially those homozygous for the D/D genotype, are at an increased risk of accelerated loss of kidney function that reduces the long-term benefits of ACE inhibition on the progression of kidney disease. Patients with the D/D genotype are also less likely to experience regression of left ventricular hypertrophy than those with other *ACE* genotypes.[12]

Drug Metabolizing Enzyme Polymorphisms

One or more members of the cytochrome P450 family of enzymes are responsible for the metabolism of most or all drugs. Polymorphisms of P450 enzymes are well-known major variables in drug plasma levels, drug detoxification, and the activation of prodrugs. Of the P450 enzymes, CYP2D6 by itself is responsible for the metabolism of approximately 20% to 25% of all marketed therapeutic entities. The polymorphisms of CYP2D6 are among the most studied of the P450 enzymes. CYP2D6 is highly polymorphic. The variants of CYP2D6 are classified based on their enzymatic activities, and the frequency and genetics of the major CYP2D6 variants are well documented. Rapid and effective methods of clinical testing for the variants of CYP2D6 are also available, which means that if CYP2D6 is the primary metabolic enzyme responsible for drug blood level, and genetic polymorphism of the drug target is not at issue, knowing the patient's CYP2D6 phenotype would enable clinicians to prescribe safe and effective doses on an individualized basis **(Figure 4)**.[12]

Figure 4

Knowing the CYP2D6 phenotype of a patient could enable individualized dosing based on the genetically predisposed metabolic functioning of that patient.[12]



As an example of CYP2D6-dependent metabolism, tamoxifen (Nolvadex®) is a prodrug that requires activation to its metabolites 4-hydroxytamoxifen and endoxifen. Both metabolites have significantly greater affinity for the estrogen receptor (their target) than their parent, tamoxifen. Patients with multiple copies of *CYP2D6* (UM) alleles achieve higher mean blood levels of endoxifen than those without a UM allele. On the opposite end of this spectrum, *CYP2D6*4* is the most common null allele contributing (in white persons) to the CYP2D6*4/*4 genotype (PM). Patients with the PM genotype have demonstrated shorter relapse-free time and less disease-free survival time than patients with either only one or no *4 alleles. The differences in CYP2D6-mediated metabolite formation in these instances have been attributed to these specific allelic differences observed in these cohorts.[12]

Another cytochrome P450 enzyme, CYP2C9, is responsible for the metabolism of approximately 15% of drugs, including warfarin, which was discussed previously herein. The highly polymorphic *CYP2C9* gene has more than 35 known variant

alleles, including several that reduce its enzymatic activity, thereby decreasing the metabolism and clearance of warfarin. Individuals with these *CYP2C* polymorphisms have increased exposure to, and require reduced dosing of, warfarin, in contrast to individuals with mutations in the *VKORC1* gene.[14]

Drug Transporter Polymorphisms

Drug transporters modulate the absorption, distribution, and elimination of drugs through control of the influx and efflux of drugs from cells. The impact that transporters potentially have on the safety, efficacy, and disposition of drugs within the body is profound, as recent evidence indicates.

The *ABCB1* gene encodes P-glycoprotein ABCB1 (multidrug resistance 1), a transporter P-glycoprotein responsible for the efflux of many important drugs from cells. *ABCB1* is highly polymorphic. Some of the allelic variants of *ABCB1* exhibit preferential ethnic-dependent distribution. The C3435T single-nucleotide polymorphism of *ABCB1* occurs with incidences of 20% to 60% in some populations. Digoxin, well known to have a narrow therapeutic window, is a substrate of P-glycoprotein *ABCB1*, and conflicting results have been reported concerning its disposition in patients with the C3435T single-nucleotide polymorphism. In one study, this polymorphism was associated with higher digoxin serum levels in patients; in another study, it was associated with lower digoxin serum levels in patients. Explanations for these contradictory results include the existence of other genetic traits that influence the function and expression of the ABCB1 protein and the existence of polymorphisms other than C3435T.[12]

Breast cancer resistance protein (BCRP) is an important ABCG2 transporter in intestinal absorption and biliary excretion of drugs and their metabolites. A variant of the *ABCG2* gene, *C421A*, causes a mutation in the BCRP protein and is present in frequencies of 30% to 60% in Asians and 5% to 10% in whites and African Americans. Upon intravenous administration of diflomotecan, an anticancer therapy, patients heterozygous for the *ABCG2 C421A* genotype exhibit plasma levels 300% higher than normal.[12]

The pharmacokinetic and therapeutic effects of the antihypercholesterolemia drug rosuvastatin (Crestor®) are also affected by the *ABCG2 C421A* polymorphism in Chinese and white patients. In a dose-dependent manner, in a study of 305 Chinese patients with high cholesterol levels, reductions in low-density lipoprotein cholesterol levels were significantly greater in those with the *C421A* variant than in those without it.[12]

Genetic Testing and Enzyme Analysis Incorporated Into Practice?

Severe hematologic reactions and death can result from administering 6-mercaptopurine (Purinethol®), 6-thioguanine, or azathioprine (Imuran®) to patients with acute lymphocytic leukemia who have nonfunctioning thiopurine S-methyltransferase (TPMT) variants. This enzyme, TPMT, must be functional in order to metabolize these drugs. Patients homozygous for the alleles encoding nonfunctioning variants of the enzyme can be treated safely with dosages of 10 to 15 times less than those typically administered. Conversely, patients homozygous for the alleles encoding nonfunctioning variants of the enzyme that go undetected and who are administered standard doses of azathioprine are at risk of overdose. Thus, genotyping or functional enzyme analysis for these patients is standard practice at major cancer treatment centers.[1]

Personalized Medicine Achieved?

Clearly, individual examples exist of relatively sophisticated pharmacotherapeutics that can be characterized as personalized medicine and implemented in practice. But does this mean a revolution in medical practice has occurred? Consider the previous example relative to warfarin therapy. A substantial amount of high-quality research has been conducted on warfarin due to its clinical importance. Still, accurate therapeutic dosing can be predicted for only about 25% to 50% of patients given warfarin based on genetic and clinical information. Therefore, up to 50% of warfarin dosing remains empiric and 50% of the factors responsible for variability to warfarin response remain unknown.[12] The question of whether personalized medicine will ever truly be incorporated into clinical practice varies from optimism to pessimism depending on the individual practitioner, patient, drug, and disease.

When variables affecting the efficacy, toxicity, and side effects are simple and well defined, personalized medicine can be practiced readily. For example, because many psychiatric drugs are metabolized by the CYP2D6 enzyme, and metabolism of these drugs is the key factor affecting drug response and safety, genotyping for dose selection in these patients is practical. Patients who carry CYP2D6*3, -*4, -*5, or -*6 variants should receive reduced antidepressant dosages to avoid or minimize side effects. At the Mayo Clinic, psychiatrists are requesting that patients' CYP2D6 genotyping information be made available to them before prescribing psychiatric therapy.[12] This is a simple example of how personalized medicine can work in practice.

Variability of drug response, however, quickly becomes very complicated. Multiple factors may be interrelated, including a clear understanding of the disease pathogenesis and the gene(s) involved, along with the roles of drug-target polymorphisms, drug metabolizing enzyme polymorphisms, and drug-transporter polymorphisms. When genes that cause disease remain unidentified, achieving any degree of personalized medicine becomes particularly challenging. Through genetic testing that reveals predispositions to drug toxicities or diseases, one major goal today is to establish phenotype–genotype associations between the manifestations of certain toxicities or diseases and specific genes. A degree of success has been achieved in establishing such associations relative to monogenetic (single-gene) disorders; for the most part, however, the complexity of the human genome has made defining such associations problematic. Researchers have argued that based on today's literature it would be extremely difficult to unequivocally determine an exact phenotype or genotype for complex diseases involving multiple genes. Whether or not individualized therapy can ever be achieved through DNA testing alone is also questionable because many factors that influence variability in efficacy and toxicity are not reflected in genetic information.[12] Despite all of these considered complications, companion diagnostics and personalized medicine have synergistically brought a profound change to our therapeutic approach toward disease, particularly cancer.

Companion Diagnostics in Oncology

Resistance to targeted anticancer therapy develops rapidly resulting from frequent mutations in drug-target cancer cells.[12] Nevertheless, oncology remains the most active therapeutic area in the development of companion diagnostic tests.[14] In some tumors where chemotherapy demonstrates little or no benefit, targeted therapies prove more effective.[15] Targeted therapies, however, are typically only capable of providing partial responses or disease stability; full remissions are few and usually not curative. Despite these shortcomings, targeted therapy and companion diagnostics are changing the cancer treatment paradigm from tissue/disease-based chemotherapy to molecularly targeted therapeutics.[16] The advent of companion diagnostics (biomarker technology coupled with diagnostic devices) marks a new standard of care, and the use of companion diagnostics is expected by many to grow significantly, providing greater efficiency, value, and cost savings.[16,17]

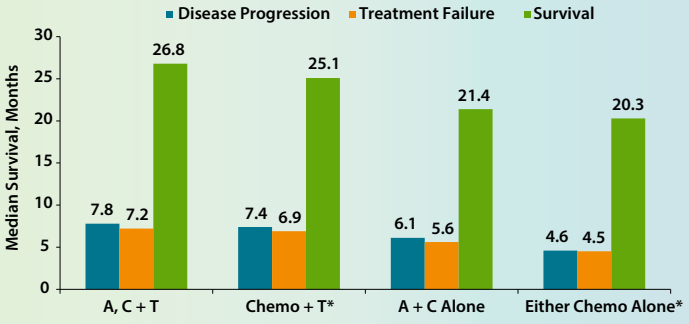
Breast Cancer

Amplification of the *HER2* gene or overexpression of its proteins occurs in approximately 20% to 25% of all breast cancers.[18] The enhanced cell signaling resultant from this overexpression produces stronger responsiveness to growth factors and malignant growth, explaining why HER2 overexpression is associated with a poor prognosis, tumor recurrence, and shorter survival. In the 1990s it was learned that overexpression of HER2 plays a direct role in an aggressive form of breast cancer,[19] and in September 1998 the FDA approved trastuzumab (Herceptin®), a targeted therapy for HER2-positive metastatic breast cancer, as a first-line agent with paclitaxel (Taxol®), docetaxel (Taxotere®), or aromatase inhibitors, and as a single agent in second-line and third-line therapy.[18-21] The approval of trastuzumab was based on a landmark phase 3 trial that enrolled 469 patients. The primary endpoint of the study was time to progression in patients treated with chemotherapy versus those treated with trastuzumab plus chemotherapy.[20,21] Few studies on metastatic breast cancer have ever demonstrated a greater survival benefit associated with a single agent as did the study on which the trastuzumab approval was based (7.4 vs 4.6 months, respectively) **(Figure 5)**.[21]

The trastuzumab label indicates its use only in breast cancer with HER2 overexpression.[22] The label also clearly states that the detection of HER2 overexpression is necessary to select patients appropriate for trastuzumab therapy, and that only FDA-approved tests for the specific tumor type to assess HER2 protein overexpression and *HER2* gene amplification should be used. In 1998, DakoCytomation developed and introduced the HercepTest, a first-in-class companion diagnostic tool

Figure 5

Trastuzumab targeted therapy of HER2 overexpression in metastatic breast cancer has resulted in one of the greatest survival benefits ever attributable to a single agent.[21]



Time to disease progression, treatment failure, and survival are medians in months. A = an anthracycline, C = cyclophosphamide, T = trastuzumab. Differences in the median times to disease progression and treatment failure between the Chemo + T group vs the Either Chemo Alone group were statistically significant ($P < 0.001$) as was the difference in median survival ($P = 0.046$).*

developed to identify patients eligible to receive trastuzumab. The companion diagnostics era began with the introduction of this test, a proof of concept that companion diagnostic tests can guide personalized medicine.[19] The FDA now recognizes several approved assays to select patients eligible for trastuzumab therapy and suggests that clinicians refer to the labeling of specific diagnostic kits for information on their validation.[22] Prior to the introduction of trastuzumab and its companion diagnostic, HER2-positive breast cancer was associated with a high rate of relapse and poor prognosis. In combination with standard adjuvant chemotherapy, trastuzumab is now credited with reducing the risk of recurrence of HER2-positive breast cancer by more than 50%.[18]

The companion diagnostics era began with the introduction of the HercepTest, (a test developed to identify patients with HER2 overexpression eligible to receive trastuzumab) a proof of concept that companion diagnostic tests can guide personalized medicine.[19,22]

Melanoma

For patients with metastatic melanoma, no therapeutic agent extending life had ever been available until 2011 when ipilimumab (Yervoy®) and vemurafenib (Zelboraf®), two targeted therapies, were introduced. Ipilimumab is a first-in-class immunostimulatory drug. Vemurafenib is indicated in patients with late-stage melanoma who have the *BRAF* V600E mutation and was granted FDA fast-track approval after its sponsor (Roche-Genentech) halted its clinical trial in which 675 patients had been randomized to either vemurafenib or dacarbazine. When the trial was halted, 77% of patients given vemurafenib were still alive (median survival time had not yet been reached), whereas only 64% of patients given dacarbazine were still living and had reached an 8-month median survival time.[23]

The development of vemurafenib followed the new paradigm of targeted drug development in oncology, which is to develop agents that inhibit specifically recurring genetic lesions in tumors. A critical component in this drug development paradigm is the simultaneous development of an accurate and robust in vitro companion diagnostic assay that will detect these specific recurring genetic lesions, and thus identify patients who are likely to respond positively to treatment. The cobas® 4800 BRAF V600 Mutation Test [real-time polymerase chain reaction (RT-PCR) test] is such a test that was developed in tandem with vemurafenib as a companion diagnostic.[24] Co-development of the RT-PCR test and vemurafenib resulted in FDA approval of vemurafenib in less than 5 years after submission of the Investigational New Drug Application.[25] The RT-PCR test was used to screen all patients who enrolled in the clinical trial and was approved to simultaneously select all patients for vemurafenib therapy.[24] Key factors in the successful co-development of this drug and its companion diagnostic test were early identification of the BRAFV600E biomarker; early development of the diagnostic test; and early, close, focused, and integrated collaboration and communication between the pharmaceutical and diagnostic device development teams.[25]

Both dabrafenib (Tafinlar®) and trametinib (Mekinist®) were approved individually for metastatic or unresectable melanoma in May of 2013. Dabrafenib (a *BRAF* inhibitor) was approved to treat patients with the *BRAF* V600E mutation, and trametinib (a MEK inhibitor) was approved to treat patients with either the *BRAF* V600E or the *BRAF* V600K mutation.[26] Both drugs block cellular signals at different sites along the same molecular pathway that promotes the growth of cancer cells. Dabrafenib and trametinib combination therapy was then approved in January 2014.[27] These drugs are specifically indicated in combination for patients whose tumors express *BRAF* V600E or *BRAF* V600K mutations, representing approximately half of all melanomas arising in skin.

Both dabrafenib and trametinib were approved with the THxID® BRAF companion diagnostic that detects V600E or V600K mutations in the *BRAF* gene. FDA approval of this test was based on clinical study data that supported the approval of both dabrafenib and trametinib.[26] Patients receiving dabrafenib experienced tumor growth that was 2.4 months delayed compared with patients receiving dacarbazine. Patients receiving trametinib experienced tumor growth that was 3.3 months delayed compared with patients receiving chemotherapy. Tissue samples of patients with melanoma were collected to test for the mutations. The THxID BRAF test is the second companion diagnostic approved to detect *BRAF* mutations in patients with melanoma. Concerning approval of the THxID BRAF test, Alberto Gutierrez, PhD, Director of the Office of In Vitro Diagnostic Devices and Radiological Health in the Center for Devices and Radiological Health of the FDA said that the approval, "Demonstrates the commitment of pharmaceutical and diagnostic partners to develop products that detect and target the molecular drivers of cancer."[26]

Non–Small Cell Lung Cancer

In 2011, crizotinib (Xalkori®) became the first FDA-approved targeted agent for non–small cell lung cancer (NSCLC) available with a concurrently approved companion diagnostic

test.[23,28,29] Crizotinib was approved for advanced-stage NSCLC positive for the anaplastic lymphoma kinase (*ALK*) fusion gene, which represents about 1% to 7% of the NSCLC patient population.[23] The concurrently approved companion diagnostic, the Vysis ALK Break Apart FISH (fluorescence in situ hybridization) Probe Kit, is a qualitative test to detect rearrangements involving the *ALK* gene via FISH in formalin-fixed, paraffin-embedded NSCLC tissue specimens.[30] The August 26, 2011, approval states that crizotinib is a kinase inhibitor indicated for treating locally advanced or metastatic NSCLC that is *ALK*-positive as detected by an FDA-approved test.[29] Approval was based on response rates of 50% and 61% from the first 136 and 119 patients, respectively, in two key clinical trials (PROFILE 1005 and 1001, respectively).[29] Research surrounding crizotinib in NSCLC made obvious the requirement for a validated companion diagnostic to evaluate molecular alterations in a small subgroup of patients. Such tests should be sensitive, specific, relatively inexpensive, and universally feasible for adoption by diagnostic laboratories worldwide.[29]

The approval of the THxID BRAF test, "demonstrates the commitment of pharmaceutical and diagnostic partners to develop products that detect and target the molecular drivers of cancer."

Alberto Gutierrez, PhD

The KRAS *Gene in Colorectal Cancer*

Among the RAS family of proto-oncogenes, *KRAS* is the most commonly mutated member in colorectal cancer (CRC). The *KRAS* gene encodes a protein in the epidermal growth factor receptor (EGFR) pathway that is required for the differentiation and proliferation of cancer. It is estimated that 30% to 40% of CRCs harbor *KRAS* mutations.[31] The clinical ramifications of KRAS status in CRC are that patients who carry the *KRAS* mutation do not benefit from first-, second-, or third-line treatment with EGFR-inhibiting monoclonal antibodies.[32] Thus, agents such as cetuximab (Erbitux®) and panitumumab (Vectibix®) are restricted to use in patients with *KRAS* wild-type (nonmutated) CRC.[31] The significance of KRAS status is so great that prior to prescribing therapy the KRAS status of all patients with CRC should be established.[32] This practice became mandatory in Europe in 2008.[31] A table of companion diagnostic devices and the drugs with which their use is indicated by the FDA can be found at: www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm.

Gaps in the Implementation of Companion Diagnostics and Personalized Medicine

If the introduction of a new clinical entity to the market were not in itself complicated, the additional challenges related to biomarkers and simultaneously developing and bringing to market a companion diagnostic device multiplies the complexity of the approval process.

Integration of the 'New' Science Into Practice Is Lagging

Pharmacogenetics, on which companion diagnostics and personalized medicine are based, has not achieved broad acceptance into medical practice. Typically, traditional medicine readily adapts to advances in science as demonstrated through evidence-based medicine. For example, dosage adjustments based on age, body weight, and renal or hepatic function are accepted common medical practice. Pharmacogenetic studies have also clearly shown the need for dosage adjustment based on DNA sequence variations; however, dosage adaptation based on pharmacogenetic studies has not been accepted into practice with the enthusiasm that dosage adaptation has been accepted based on age, renal, hepatic, and other clinical findings.[33]

The antidepressant nortriptyline is a classic example. Interpatient serum levels of the same dose of nortriptyline may vary as much as 10-fold based on interpatient CYP2D6 allelic variations. Nevertheless, it is accepted practice to prescribe the same dose regardless of whether patients are ultrarapid, intermediate, or slow CYP2D6 metabolizers. The same dose of nortriptyline is not bioequivalent between these three groups of patients, which means that the prescribing practice is not evidence-based. Regulatory authorities allow the practice, although they would not grant a generic nortriptyline bioequivalence to a reference drug with the same disparities in area under the curve.[33]

Genotyping has potential far beyond its uses today in diagnostics, with a primary focus on the prevention of adverse events in individual patients. Treatment optimization and the prevention of toxicity through prospective screening remain far from common practice.[33]

Resistance on Many Fronts Confounds Co-development

A coordinated integration of the companion diagnostics/personalized medicine paradigm into medical practice presents complicated issues on all levels that have interconnected implications. Public policy issues must be

addressed. Payer and reimbursement issues, physicians' incentives, medical records privacy, and clinical trial ethics are just the beginning of a list of issues on which agreement must be reached. Considering only the mechanics of co-development, an integrated policy framework is needed that requires clear communication and cooperation between pharmaceutical and biotechnology companies, diagnostics companies, researchers, medical educators, information technology managers, healthcare providers, laboratories, patient advocates, policymakers, payers, and other stakeholders.[34]

Economic and Policy Issues and a Lack of Demonstrated Cost-effectiveness Exist

The medical-industrial complex must change in order to integrate the companion diagnostics/personalized medicine paradigm into practice. However, the existing healthcare infrastructure presents major challenges. In July of 2013 the Personalized Medicine Coalition (PMC), an education and advocacy organization, held a briefing in the Senate Visitor Center in Washington, DC. The briefing was attended by more than 100 people, a third of whom were congressional staff members. The cost-effectiveness of the new paradigm versus the one-size-fits-all blockbuster paradigm was explained, noting that advancement in the new era of diagnosis and therapy depends on our ability to aggregate data and effectively use informatics. PMC also unveiled its Cost-containment and Deficit Reduction Policy Principles, and noted how such policies can effectively and efficiently meet unmet patient needs by enabling the provision of novel targeted therapies. The ways in which progress in medicine occurs was also explained, and the ways in which policymakers can either help or hinder such progress was illustrated.[35]

For example, laboratory reimbursement rates for processing diagnostic tests in 2014 were established in 2013, and some went up dramatically (EGFR testing at $332.50 increased by 114%) but others went down (KRAS testing at $198.97 decreased by 15%).[36] The critical role that companion diagnostic devices play in facilitating targeted therapeutics was explained. It also was pointed out how the future of companion diagnostics may be threatened by proposed cuts in Centers for Medicare and Medicaid Services payment schedules for devices. These proposed cost cuts are often below the cost of conducting the test, not to mention the research and development costs of creating the devices.[35]

Cohen et al recently studied the clinical and economic challenges facing developers of and payers for companion diagnostics and personalized medicines. Specifically, these authors studied eight high-profile personalized medicines and their companion diagnostics: trastuzumab, cetuximab (Erbitux®), imatinib (Gleevec®), abacavir (Ziagen®), erlotinib (Tarceva®), gefitinib (Iressa®), warfarin, and irinotecan. Overall these researchers concluded that a comprehensive lack of reimbursement for companion diagnostic tests exists. This refusal to reimburse occurred even when these devices were specifically identified, recommended, and even required in the FDA drug label.[37] Insurance companies refused to pay for the tests not because they failed to accurately identify a patient subpopulation with a specific genetic mutation but because existing clinical evidence is not sufficient to link the diagnostic tests to improved health outcomes.[37]

Health economists can contribute to this type of translational research that would link diagnostic tests to outcomes. However, obstacles exist to conducting high-quality studies of this kind. For example, genomic tests can have multiple applications in varied contexts and often it is not possible to synthesize the results of economic evaluations conducted in varied contexts. Uncertainty also exists about which costs should be collected and when, and how these costs may vary between laboratories and countries. New methodologies may be required to resolve these issues.[38] It has been suggested that an increase in comparative effectiveness research may contribute to closing this evidence gap.[37]

Opposing Business Models Require Realignment

Many of the co-development conflicts revolve around regulatory and reimbursement issues. Both the drug and diagnostic device industries are well developed; however, each is representative of an entrenched healthcare infrastructure. Traditionally pharmaceutical manufacturers have completely controlled product development, marketing, and sales of their drugs. Developers of diagnostics require pharmaceutical manufacturers to be dependent on their diagnostic for the sale of their drug. In contrast, developers of diagnostics require partnerships. Partnerships are complicated by different cultures, different business models, and different approaches to product development.[6]

For example, the pricing of companion diagnostics can be perceived as obstructive to drug sales. Simply to maintain drug sales momentum, biopharmaceutical organizations have been known to completely absorb the cost of a companion diagnostic.[39] The drug development business is associated with long development timelines, high research and development costs, a complicated regulatory process, and high drug product prices. The diagnostic device business is associated with short lead times, low research and

development costs, comparatively minimal regulation, and low product prices. Pharmaceutical manufacturers also calculate return on investment completely differently than diagnostics companies. Mutual education is required to understand the interdependent roles and responsibilities of each partner. When these two seemingly diametrically opposed organizations do initiate talks about a co-development project, it is imperative that each is appreciative of the other's position and understands how they must work together carefully to achieve mutual benefit.[39]

In its report, "The Case for Personalized Medicine, 4th Edition," published in 2014, the PMC provides two tables listing numerous personalized medicine drugs, relevant genes, and indications, and numerous personalized medicine genetic tests regarding drugs and or diseases, including the name of the test kit and the indication.[2] These resources are available online at www.personalizedmedicinecoalition.org/Resources/Publications.

Few case studies on companion diagnostics/personalized medicine collaborations exist; however, obviously, some have come to fruition. For example, see Cheng et al, "Co-development of a companion diagnostic for targeted cancer therapy," for the full story about the successful collaborative development of vemurafenib, the first-in-class selective BRAF kinase inhibitor and its companion diagnostic, the cobas® 4800 BRAF V600 Mutation Test.[25] Further evidence that companion diagnostics and personalized medicine are playing a role in development pipelines comes from the Tufts Center for the Study of Drug Development Impact Report, which surveyed 16 pharmaceutical companies and found the following[39]:

- Targeted therapies, biomarkers, or both are used by all 16 companies in their research
- Most activity in companion diagnostics and personalized medicine occurs in oncology
- The personalized medicine/companion diagnostics paradigm is apparent in approximately 13% to 50% of clinical development pipelines

In its report, "The Case for Personalized Medicine, 4th Edition," published in 2014, the PMC provides two tables listing numerous personalized medicine drugs, relevant genes, and indications, and numerous personalized medicine genetic tests regarding drugs and or diseases, including the name of the test kit and the indication.[2] These resources are available online at www.personalizedmedicinecoalition.org/Resources/Publications.

Different scenarios have been suggested to more closely integrate and balance the financial interests of drug and diagnostics companies. For example, one scenario suggests that pharmaceutical manufacturers assume financial responsibility for diagnostic test development. Test developers would be fully compensated by pharmaceutical companies for their initial investments in early test development. Another scenario, which suggests revenue-sharing, is a partnership model in which a percentage of drug revenue is generated from sales attributed to diagnostic test–based prescribing decisions.[40] It is hoped that these two constituencies will find a mutually agreeable and speedy path forward to implement co-development of personalized drugs and companion diagnostics—for the benefit of the largest possible population of patients.

On May 5, 2015, IBM Watson Health announced a collaboration with 14 leading cancer institutes to better understand a patient's full genetic profile in order to apply personalized treatment. Genetic sequencing is becoming increasingly accessible and affordable, and patients with cancer are beginning to benefit from treatments that target their specific cancer-causing mutations. However, genetic sequencing requires a great deal of time and effort on the part of clinicians to sift through and reconcile the 100 GB of data for each individual with journal publications, clinical trial information, and personal health information. This initiative will make use of the advanced cognitive abilities of the Watson computer to greatly reduce the time needed—from weeks to minutes—to sequence an individual's genome and tailor treatment.[41]

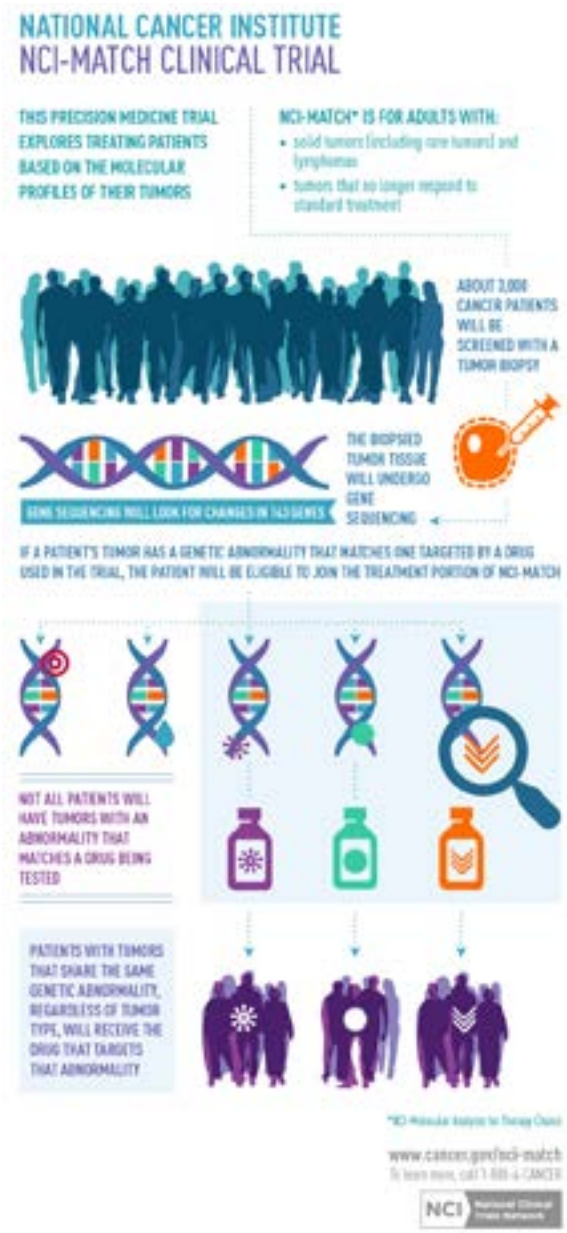
National Cancer Institute (NCI)–Molecular Analysis for Therapy Choice Program (NCI-MATCH) Opens in July 2015 to Study Whether Treating Cancers According to Their Molecular Abnormalities Will Be Effective

In the NCI-MATCH clinical trial, the tumors of patients will be analyzed to determine whether they contain genetic abnormalities for which a targeted drug exists and treatment will be assigned based on the abnormality. The trial will open with 10 arms in adults at least 18 years of age who have advanced solid tumors and lymphomas that are no longer responding to, or have never responded to, standard therapy and that have begun to grow. A goal for NCI-MATCH is for at least 25% of the approximately 1000 patients enrolled to have rare cancers. Rare cancers include those classified as rare because of an undetermined primary site at the time of diagnosis and cancers at locations where they rarely occur such as the ureter, pituitary gland, and eye.

Investigators for the NCI-MATCH clinical trial plan to obtain tumor biopsy specimens from 3000 patients initially for DNA sequencing to identify those with genetic abnormalities that may respond to the select targeted drugs. The genetic test will assess 10 molecular abnormalities with estimated mutation prevalence of 1% to 7% at the start of the trial in July 2015; additional mutations and treatments are expected to be added soon thereafter. Ultimately 20 to 25 drugs will be tested, each in a different arm of the trial.

Because the NCI-MATCH clinical trial will be open at up to 2400 clinical sites across the United States, including those that participate in the NCI National Clinical Trials Network, patients may not need to travel to participate.

www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match



connexion healthcare

ABOUT CONNEXION HEALTHCARE

Connexion Healthcare provides medical and scientific communications for pharmaceutical companies. Connexion is composed of two Centers of Excellence—Oncology and Rare Disease. Our philosophy focuses on these specific therapeutic areas to allow for a deeper understanding of the science so that it can be translated into meaningful medical communications.

Each Center of Excellence consists of highly skilled communications experts who develop, plan, and execute strategic communications based on their scientific training, knowledge, market insights, and professional relationships with key opinion leaders and related scientists, clinical practitioners, allied healthcare professionals, patients, and industry professionals within Oncology and Rare Disease. In addition to strategic planning, all Connexion Healthcare staff members are committed to continuous learning, educating physicians and pharmaceutical partners, and patient advocacy.

Brand Adoption Accelerator Program

All Connexion Healthcare programs are based on achieving simple objectives through the design and execution of key components defined by the given product milieu:

Objectives:

- Build a powerful and pertinent value proposition
- Express the value proposition clearly
- Engage all external stakeholders effectively
- Align internal stakeholders and prepare the organization
- Mitigate competitive forces

Key components:

- **Competitive strategy:**
  - Predict competitive agent strategies and prepare a defensive plan to mitigate impact on priority patient segments
  - Identify true points of leverage that enhance the value proposition and clinical utility and that provide laser focus on attributes differentiating and boosting physician uptake
- **Communication strategy:**
  - Provide an evidence-based strategic communications plan that drives medical, commercial, and publication scientific messaging in an aligned and integrated fashion
  - Mitigate the influence of current and emerging treatment options by pinpointing key value drivers that withstand counter-communications from competing therapies
- **Segmentation:**
  - Develop, delineate, and prioritize patient or market segments to form the foundation of a strategy that meets the needs of each heterogeneous group
  - Decipher clinical drivers for each segment to determine persuasive attributes that lead to greater uptake versus alternative treatment options
- **Positioning:**
  - Provide multifaceted identification of differentiate brand attributes in which the product outperforms the competitive set and is of high importance to physicians
  - Ensure that the product occupies a unique, distinctive, and relevant place in the minds of the target audience; create a shift in treatment patterns
- **Asset Prioritization/Life-cycle Management:**
  - Optimize pipeline effectiveness by identifying gaps between research and development operational performance and strategic importance, resulting in enhanced pipeline value
  - Comprehensively assess viable clinical development paths that balance the need to deliver brands with high clinical utility and the need to maximize return on investment
- **Core Claims Directive:**
  - Develop asset core claims that form the basis of scientific messaging for scientific, publications, and commercial communications channels
  - Ensure internal stakeholder communications alignment of factual statements regarding efficacy, safety, tolerability, and other important elements

Developing the key components of a brand strategy is, of course, more complicated than illustrated here. Brand strategies involve participation in selected congresses and professional and educational events, as well as the design of strategic publication plans. Connect with us for guidance in launching your diagnostic device or therapeutic product, regardless of its position in product life span.

For additional information, contact Connexion Healthcare through the company Web site at www.connexionhealthcare.com and follow us on Facebook and Twitter.

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APPENDICES

Appendix A. Companion Diagnostics/Personalized Medicine Advocacy Organizations

Organization	Description	Contact Information
AdvaMed	AdvaMed promotes policies to establish high ethical standards, rapid product approvals and appropriate reimbursement, and international market access to treatment. AdvaMed is a trade association that represents 80% of the medical technology firms in the United States.	AdvaMed 701 Pennsylvania Avenue, NW, Suite 800 Washington, DC 20004-2654 Phone: 202-783-8700 Fax: 202-783-8750 Email: info@advamed.org Web site: http://Advamed.org
Biotechnology Industry Organization (BIO)	BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the United States and in more than 30 other nations. Among the priority issues of BIO are matters affecting the healthcare-related regulatory and reimbursement climate, pandemic and biodefense preparedness, publicly funded scientific research, and personalized medicine.	Biotechnology Industry Organization 1201 Maryland Avenue, SW, Suite 900 Washington, DC 20024 Phone: 202-962-9200; 888-246-1728 Fax: 202-488-6301 Email: info@bio.org Web site: https:/bio.org/
Coalition for Genetic Fairness (CGF)	CGF is a public interest group concerned about genetic discrimination. The group was founded in 1997 by several organizations. Much of the work of the CGF has surrounded the Genetic Information Nondiscrimination Act (GINA).	Coalition for Genetic Fairness 4301 Connecticut Avenue, NW, #404 Washington, DC 20008-2369 Phone: 202-966-5557 Fax: 202-966-8553 Web site: http://www.geneticfairness.org/index.html
The Coalition for 21st Century Medicine	The mission of the coalition is to improve the quality of healthcare by encouraging research, development, and commercialization of innovative diagnostic technologies that will personalize patient care, improve patient outcomes, and substantially reduce healthcare costs. The coalition represents more than two dozen of the world's most well-known diagnostic technology companies, clinical laboratories, researchers, physicians, venture capitalists, and patient advocacy groups. They work to ensure that high-quality, innovative diagnostic tests—necessary to ensure that timely and accurate information is available when diagnosis, prognosis, and therapy decisions need to be made—are available to patients and their physicians.	The Coalition for 21st Century Medicine PO Box 15519 Arlington, VA 22215-0519 Web site: http://www.twentyfirstcenturymedicine.org/ For more information, contact Jordan Butz at jordan.butz@deweysquare.com, or Hathaway Russell at hrussell@foleyhoag.com
Colorectal Cancer Alliance	The mission of the Colon Cancer Alliance is to remove colon cancer from the list as one of the top-three cancer killers. The alliance is achieving this mission by championing prevention, funding cutting-edge research, and providing high-quality patient support services. Goals include advancing biomarker research, learning why individuals younger than 50 years of age are increasingly being diagnosed with colon cancer, decreasing late-state diagnosis in high-risk populations, closing the referral gap for screening and diagnostic testing, and advancing long-term survivorship psychosocial concerns.	Colorectal Cancer Alliance 1025 Vermont Avenue, NW, Suite 1066 Washington, DC 20005 Toll-free Helpline: 877-422-2030 Phone: 202-628-0123 Fax: 866-304-9075 Clinical Trial Matching Service: 866-278-0392 Web site: http://www.ccalliance.org/index.html

Appendix A. Companion Diagnostics/Personalized Medicine Advocacy Organizations (cont'd)

Organization	Description	Contact Information
European Diagnostic Manufacturers Association (EDMA)	EDMA is an international nonprofit organization representing the interests of the medical in vitro diagnostics (IVDs) industry in Europe. Its mission is to promote the value of IVDs in delivering sustainable and effective public health systems, and provide technical, regulatory, and market research information to its members.	European Diagnostic Manufacturers Association Rue Joseph II - 40 1000 Brussels Belgium Phone: +32-2-772-2225 Fax: +32-2-772-2329 Email: edma@edma-ivd.eu Web site: http://www.edma-ivd.be/
The European Personalised Medicine Association (EPEMED)	The EPEMED is an independent voice and catalyst acting for the advancement of personalized medicine in Europe and the breakthrough role of diagnostics and co-dependent drug-companion diagnostics technologies in improving patient outcomes. The EPEMED is a nonprofit organization founded in 2009 by European leaders with extensive expertise in stratified medicine and diagnostic tools. It is the first European association to address exclusively European issues in personalized medicine that confront industry, regulators, payers, and government.	The European Personalised Medicine Association 59 rue de X Octobre L-7243 Bereldange Luxembourg Email: contact@epemed.org Web site: http://www.epemed.org/online/www/content/ENG/index.html
Friends of Cancer Research (FOCR)	The FOCR advocates for policies and solutions that connect treatments to patients in the safest, fastest way. The FOCR works closely with government agencies (Food and Drug Administration, National Cancer Institute, National Institutes of Health, and Health and Human Services) and congressional leadership to create educational, policy, and scientific approaches to improve health outcomes and cancer care.	Friends of Cancer Research 1800 M Street, NW Suite 1050 South Washington, DC 20036 Phone: 202-944-6700 Web site: http://www.focr.org
Personalized Medicine Coalition (PMC)	The mission of the PMC is to build the foundation that advances personalized medicine as a solution to the challenges of efficacy, safety, and cost. PMC represents a broad spectrum of more than 225 innovator, academic, industry, patient, provider, and payer communities.	Personalized Medicine Coalition 1710 Rhode Island Avenue, NW, Suite 700 Washington, DC 20036 Email: pmc@PersonalizedMedicineCoalition.org Web site: http://www.personalizedmedicinecoalition.org/
Personalized Medicine World Conference (PMWC)	Launched by Silicon Valley investors and entrepreneurs in 2009, PMWC International has held several conferences in the United States and abroad to forge connections and drive innovation. PMWC International is dedicated to transforming healthcare through the global adoption of personalized medicine, molecularly targeted therapies, and companion diagnostics.	Personalized Medicine World Conference 1456 Fowler Lane Los Altos, CA 94024 Phone: 650-924-2341 Email: pmwcintl.com Web site: http://pmwcintl.com/contact.php

Appendix B. Publications of Related Interest

Publication and Web Site	Description
Medical Device and Diagnostic Industry (MDDI) **http://www.mddionline.com/ivd**	*MDDI* is a trade journal designed exclusively for manufacturers of in vitro diagnostic products. Articles contain authoritative information on all aspects of manufacturing immunoassays, nucleic-acid-based diagnostics, clinical chemistry tests, and related instrumentation. Issues cover applied technology such as antibody development, substrate selection, purification, lyophilization, filtration, quality assurance and quality control, raw materials specification, clinical testing, and research and development. MDDI also analyzes critical business and marketing issues such as product liability, emerging markets, and other key trends.
Qmed **http://www.qmed.com/**	*Qmed* is an online directory of suppliers to the medical device and in vitro diagnostics (IVDs) industry. Categories of products and services included in the directory comprise the following: adhesives and adhesive products; clean rooms and environmental control; components; computing and software; consultants; contract manufacturing services; electronic components; filters and intravenous products; IVDs; manufacturing equipment; materials; molding services and equipment; motors and motion control; packaging and sterilization; printing, labeling and barcoding; pumps and valves; research and development and design services; surface treatment; testing metrology, and inspection; and tubing and extrusion. White papers, reports, and other services are also available.
Personalized Medicine Bulletin **www.personalizedmedicinebulletin.com/**	*Personalized Medicine Bulletin* is a free resource covering the legal, ethical, and business issues that have an impact on the evolution of personalized medicine. Its editor, Antoinette F. Konski, is a partner and intellectual property lawyer with Foley & Lardner LLP. Ms. Konski works with life science clients, creating and optimizing value in intellectual property portfolios encompassing technologies that include personalized medicine, regenerative and stem cell biology, antibodies, immunology, gene therapy, nanotechnology, diagnostics, small molecules, and drug delivery.

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