From the Bench to the Boardroom:
Planning for Personalized Medicine

Managing Innovation in the Life Sciences
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Preface

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This book is the product of the Fall 2012 Managing Innovation in the Life Sciences class taught at the Zanvyl-Krieger School of Arts and Sciences of the Johns Hopkins University. Each chapter author is a candidate for a Masters Degree in the Advanced Biotechnology Program. Like others before it, this book is a class project, intended to address a lay audience about a topic of central importance in the life sciences: innovation, and how the innovation process and innovators may be managed to best achieve value. As you read these chapters, I believe that you will come to appreciate just how skillfully each author has come to terms with the key fact governing innovation in organizations: that change is difficult, and those who promote change are, at best, outliers in their environments.

To each of my student outliers: I have learned more from you, and have seen you do more than many classes do in twice the time. Congratulations on a wonderful project.

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What is Personalized Medicine

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Definition of Personalized Medicine

Personalized medicine is currently defined as the ability to “tailor” medical treatments based on the specific characteristics of the individual patient. It is a term that has been used synonymously with others such as -omics based medicine (pharmacogenomics/pharmacogenetics/pharmacoproteomics), individualized therapy, targeted therapy, and genetics based therapy. In essence, they all refer to a form of therapy that uses the patient-focused approach to treatment. This approach allows the health care provider to consider therapies based on the patient's unique clinical, genetic, genomic, and environmental information. Personalized medicine goes against conventional approaches of treating patients, which involves more than just a “one therapy treats all” strategy. There have been great advances in the field of genetics of individual diseases, as well as further understanding of the inheritance patterns of illnesses, especially cancer, cardiac disease and metabolic diseases such as diabetes. Advances in medical genetics, the development of biomarkers and their role in individualized medicine as well as the technologies involved in medical diagnostics have added great strides to the growth of personalized medicine. No other advance has been as great as the completion of the human genome project in 2003 that resulted in the mapping of the human genome, and brought forth a plethora of information. These recent discoveries have subsequently translated to the development of targeted treatments and therapies. This has allowed for a more specific drug effect that should equate to a better response as well as a safer adverse event profile. Apart from the drugs developed, personalized medicine allows for the coupling of these drugs to a patient based on their genetic profile, therefore allowing the treatment to be “personalized” to the individual patient.

Personalized medicine is a model of a system that eventually will be accepted as the norm rather than futuristic. Just as clinical information is now being kept in electronic records about each patient, we will gradually see the inclusion of the patients’ molecular and genetic profile. This will
allow the physician the appropriate amount of information to make a choice about a therapy that is tailored to the specific illness but also improves the health of the patient with minimum safety concerns. Personalized medicine will become the standard of care for patients in the near future.

Aside from playing a role in the immediate treatment of patients, personalized medicine can help in the prevention of disease. It can also indicate susceptibility to certain diseases before they manifest, allowing the physician and patient to set out a plan for monitoring and prevention. In today’s healthcare landscape, preventive medicine is emphasized. A patient's genetic blueprint may help determine their risk of developing several specific medical conditions, including cancer, cardiovascular disease, obesity, and diabetes in advance of symptoms.

There are great benefits that come with the promise of personalized medicine, apart from the patient receiving medicine that is tailored to the individual patient. The impact on the cost of healthcare is also great. With the use of targeted therapies the size of clinical trials can be reduced, therefore reducing the cost of these trials that in turn can decrease the cost of drugs and subsequently the direct cost to the healthcare system. There is also the likelihood that drugs that had “failed” in prior clinical trials might show benefit in certain subgroups of patients, therefore propelling the revival of drugs that may have been withdrawn from the market.

**Historical Events Leading to Personalized Medicine**

The mention of Personalized Medicine in literature is found much more abundantly in the last few decades. But it was not until the past few years, since the complete sequencing of the human genome in 2003, that personalized medicine has begun moving beyond the genome into the entire spectrum of molecular medicine, including the proteome, metabolome and epigenome. Prior to 1990, little information on personalized medicine is available since there was mostly only the discovery of the genetic code as well as the ability to sequence DNA. There was mention of the association of genetics and targeting treatment based on the individual patient or specific disease only a few times.

Traditional strategy for medically treating disease prevailed as drug discovery was focused more to the disease as a whole. Over 100 years ago, in 1902, Lucien Cuenot, a biologist, hypothesized that there may be genetic determinants that caused differences in the biochemical process that could be the cause of adverse reactions after ingestion of drugs. Even though this was more of a hypothesis, it did suggest that there was a beginning of understanding that genetic variations may affect the physiological processes needed for drug metabolism. It wouldn’t be till 1959 when the term “pharmacogenetics” was first coined by a German scientist/geneticist named Friedrich Vogel. Such a term provided insight to
the evolving thought that there must be an association between medical therapy and our genes. While these thoughts had a great deal of foresight, the lack of the necessary technology to prove these theories led to the eventual suppression of such ideas. The pattern that seems to have emerged was one of development followed by advancing technology that would lead to more discoveries. These advancements proved to be evolutionary rather than just a random technological boom.

**Human Genome Project**

The move to personalized medicine officially began in 1990, with the commencement of the U.S. Human Genome Project (HGP). This was a complex multidisciplinary scientific enterprise directed at mapping and sequencing all of human DNA, and determining aspects of its function. A working draft of the human genome sequence was announced in June of 2000, an initial analysis was published in February of 2001, and a high-quality, reference sequence was completed in April 2003. HGP was a 13-year effort coordinated by the U.S. Department of Energy and the National Institutes of Health and at the time led by Dr. Francis Collins, former director of the National Human Genome Research Institute (NHGRI). The project originally was planned to last 15 years, but rapid technological advances accelerated the completion date to 2003 and well under budget. The completion of the project coincided with the 50th anniversary of Watson and Crick's description of the fundamental structure of DNA, which highlighted the incredible advancement in the field of genetics in less than half a century. The goals of this project, as listed on the HGP website included:

- identify all the approximately 20,000-25,000 genes in human DNA,
- determine the sequences of the 3 billion chemical base pairs that make up human DNA,
- store this information in databases,
- improve tools for data analysis,
- transfer related technologies to the private sector, and
- address the ethical, legal, and social issues that may arise from the project.

To help achieve these goals, a control was needed so researchers also studied the genetic makeup of several nonhuman organisms. These include the common human gut bacterium Escherichia coli, the fruit fly, and the laboratory mouse.

A unique aspect of the U.S. Human Genome Project is that it was the first large scientific undertaking to address potential ethical, legal and social issues implications arising from project data,
such as patient right to privacy. Another important feature of the project was the federal government's long-standing dedication to the transfer of technology to the private sector. By licensing technologies to private companies and awarding grants for innovative research, the project catalyzed the multibillion-dollar U.S. biotechnology industry and fostered the development of new medical applications.

**How Does this “Translate”?**

Personalized medicine has altered and inevitably improved the way we treat and manage our patients today. The potential to identify the patient that will eventually need treatment, as well as the specific therapy they will need, changes the way we approach our patients. Along with patient care, the impact on clinical research will prove to be not only exciting but also much less costly. A better understanding of genetic variations could help scientists identify new disease subgroups or their associated molecular pathways, and design drugs that target them. Understanding the molecular pathways provides us insight, not limited to the efficacy of the drug but also its safety profile and also its combinability with other treatments. Molecular analysis could also help select patients for inclusion in, or exclusion from, late stage clinical trials. This ultimately abandons the large clinical trials of the past and focuses on smaller trials on specific subgroups therefore bringing the cost of the large trials to less than half. This approach also helps gain approval for drugs that might otherwise be abandoned because they appear to be ineffective in the larger patient population.

As much as there is a tremendous promise in the evolution of personalized medicine there are still many issues to be faced. Along with the genetic advancements there are still risks that have not been fully dealt with and many questions that have yet to be asked. For example, will people with certain genetic predispositions be covered by insurance companies, or determined to be too high of a risk? Therefore issues of privacy, confidentiality, and patients’ rights will need to be answered. There are also questions of reimbursements such as: will therapies be reimbursed only for those patients who are identified, using whatever tests are available at the time, as likely to respond? These are just a couple of issues that personalized medicine will need to face.

The world of personalized medicine is ever expanding. The benefits aren’t always obvious, but are being pronounced more and more as this form of medicine evolves. The topics discussed in this book deal with this evolution and touch upon the advances as well as the hurdles associated with dealing with today’s patient. Aside from the medical aspect, terms such as legal, ethics, and reimbursement become equally important when treating tomorrow’s patient.
References


Biomarkers

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Introduction

Biomarkers are historically used as a physiologic measurement to indicate the presence of a disease or the potential of developing a pathological state. Body temperature is a biomarker of fever, increased serum glucose is a biomarker for diabetes, and high blood pressure is a biomarker for cardiac infarction or a stroke. As methods in laboratory medicine progressed, biologic substances (cells, enzymes, hormones, genes) became measurable as indicators related to risk or advancement of disease or as response to a treatment. These biomarkers enabled physicians to make or confirm a diagnosis and chose a treatment.

A simple definition of a biomarker is a change in a specific molecule. Between 1986 and 2009, the National Institutes of Health (NIH) financed about 30,000 biomarker research projects. A PubMed search on the term “biomarker” for articles published between 01/01/1989 and 12/31/1999 returns 153,401 items; for the following eleven years the number more than doubles to 370,845 articles. In 2001, NIH formed the Biomarker Definition Working Group who proposed the definition of a biomarker to be: “A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”. Another definition is that of clinical response or clinical endpoint. This is a characterization of how the patient feels, functions, or if they survive. A surrogate endpoint can be used to estimate the clinical response. This is a biologic, physiologic, or molecular biomarker which is predictive of clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence. As a substitute, it may not correlate perfectly with the clinical endpoint.

Purpose of newly discovered biomarkers

Discovery of a biomarker is an initial first step but the important question to be asked is what this substance means in an illness.
- Is it linked to the pathogenesis of one disease?
- Is it present in a majority of patients with the disease?
- Is it absent in patients with similar clinical presentation who do not have the disease?
- Is its level altered by treatment of the disease?
- Is it predictive of a response to treatment?
- Is the biologic process measured by the marker affected by treatment?
- Does it provide more information than that available by current methods?

Clinical application is the ultimate goal of biomarker discovery. Diseases with the highest societal and economic burdens are the most attractive targets—malignancies, dementia, and renal and cardiac diseases. Implementation of biomarker assays into clinical practice may take years of data accumulation from numerous trials where decisions made on the basis of a biomarker can be documented with surrogate (if applicable) and clinical end points.

Since biomarkers can be used for many purposes, they can be classified into several categories which are not exclusive:

- Antecedent biomarkers indicate the risk of disease in the future
- Screening biomarkers are used to detect a subclinical form of disease
- Diagnostic biomarkers indicate a current disease state
- Staging biomarkers are used to stratify states in a progressive disease
- Prognostic biomarkers indicate the potential course of the disease which segregates patients according to outcome independent of treatment
- Predictive biomarkers are baseline results which can categorize patients according to the degree of response to a particular treatment
- Imaging biomarkers are for use in PET, CT, MRRI
- Pharmacodynamic biomarkers are affected by a drug

The clinical significance of biomarkers is independent of their categorization. It is dependent upon their sensitivity, specificity, positive and negative predictive value, accuracy, precision, and reproducibility. Ease of measurement and wide application make clinical use more likely. Biomarker results should be available quickly and show no inter-laboratory statistical differences. For use in personalized medicine, biomarkers can be distinguished between those which are disease-related and those which are drug-related. Disease-related biomarkers should be able to distinguish if a disease currently exists, whether or not a disease should be treated, or whether a disease has the ability to develop in any particular individual. Drug-related biomarkers should determine a medication’s effectiveness in an individual patient.
Early detection of disease using screening biomarkers requires the use of large populations of generally healthy people, low cost assays, and easy collectible samples such as saliva, urine, or blood. A biomarker needs to be measured in the general population as well as in the population suspected of having disease. Any biomarker to be detected in a screening assay must be of high enough concentration to be readily detectable and be able to discern between those who have the disease and those who are disease free. Variations could occur in certain demographic characteristics which may limit biomarker use in certain populations. These types of variations need to be explored during clinical studies. Screening for cancer biomarkers must take into account any age related of disease occurrence. While lesions found during an autopsy on aged patients may uncover asymptomatic cancers, two questions need to be asked: what types of cancers need to be discovered earlier for the benefit of the patient and which of those would require interventional therapy.

Biomarkers used to predict clinical response are of high benefit, both clinical and ethical. Patients which may have a positive response to chemotherapy can be selected for clinical trials thereby providing faster and potentially less costly drug efficacy trials and decreasing time to regulatory approval. However, profiling for efficacy alone neglects the fact that cancer biology is complex and may tend to lead to oversimplification of treatment regimens. Cancer consists of a heterogeneous collection of cells. Cellular biomarker analysis may not include the population resistant to the proposed treatment regimen. New collection criteria may need to be defined and subsequent samples will need to be tested to determine if a resistant subpopulation arises during treatment.

Even if a biomarker can adequately make a diagnosis, clinical use may be limited if therapeutic options are not available. This is especially true for screening biomarkers. Would you be willing to have knowledge of a probable disease if current treatment strategies do not exist? A cost-benefit analysis may also vary according to country, healthcare system, and the study approach taken by a healthcare economist. Physicians may not wish to change old habits if there are financial repercussions to their practice of medicine.

**Validation of Biomarkers**

As indicated by the more than half million articles published on biomarkers in the last twenty plus years, development and validation of biomarkers is just beginning and much work is ahead to make them clinically useful. Disease is a complex process and medicine has yet to discover how to biologically define or manipulate diseases. Comprehensive studies of the biochemical changes during any particular disease need to be done as well as studies done during treatments.
The failure rate of biomarkers in clinical validation can be due to various problems: poor selection of patients for study inclusion; lack of adequate specimen number for statistical power; lack of quality control in specimen acquisition, processing, and storage; no standardization of preanalytical and analytical conditions; incompatible formatting for data comparison and analysis; no consensus on best practices or regulatory guidelines for the ‘–omics’ and genome sequencing.

The major portion of the published biomarker studies come from academia and lack evidence necessary to induce industry to invest in clinical trials. Detached research performed in individual laboratories using heterogeneous samples in un-standardized assays with incompatible data reporting formats does not foster comparison with other researchers working on the same problem. Single investigator-centric research may have been adequate in the past but what is needed for the future are systems-based approaches with the capacity for the integration of multidisciplinary teams. Research scientists may not be aware of all the steps to clinical application. Roadmaps are essentially non-existent and guidance may be difficult to find. Regulatory requirements may be unknown and funding to prove validation and potential utilization may be difficult to acquire.

The journey from discovery to clinical use involves a myriad of groups each approaching their part from a different aspect. Communication across these groups is of paramount importance in order to achieve the goal of better, more cost-effective patient care. Researchers, clinicians, healthcare providers, insurance companies, funding and regulatory agencies, legislative, and patient groups need to work together.

Unified approaches to the study of biomarkers have the potential to shorten the time to clinical utility and application. Standardized pre-analytical steps can provide one of the means by which studies can be combined for a retrospective analysis. Consistent specimen acquisition including selection, collection, handling, and storage has been neglected and is not always reported in journal articles. It is highly desirable to establish quality control and sample collection protocols since both can significantly impact results. There are global differences in the ways clinical observations are documented making it difficult to compare biospecimens. Standardized terminology would facilitate inter-trial comparisons. Additionally, clinical outcomes may not be consistently recorded making it hard to correlate diseases, risk, and treatment efficacy.

The medical manufacturing industry and pharmaceutical industries as partners with academia have the capacity for funding and expertise in assay validation, clinical trial design, and regulatory compliance. Regulatory approval by itself does not guarantee Medicare or health insurance reimbursement or embracement by the medical community. In order to add a biomarker to an established panel of diagnostic tests it will need to show a clear benefit. Biomarker adoption will only
be successful when health outcomes are improved or disease costs are reduced by eliminating expensive therapies of questionable efficacy.

An important aspect of biomarker development is the validity, reliability and utility of the substance being measured. For a biomarker to be useful to the diagnostician it must be a specific and reproducible measurement and it must add value over standard diagnostic and treatment measures therefore improving patient care. A specific biomarker has the ability to describe a subset of patients from within a population who have disease. The absence of a biomarker should be able to exclude a particular diagnosis (predictive value). Aside from diagnosis, biomarkers can also indicate response to therapy or carry prognostic value. When the quantitative result of a biomarker varies over time, it can be used to monitor treatment. Prognostic value is added when the biomarker can indicate the likely outcome of a patient before treatment.

The few tissue registries related to rare diseases contain small numbers of biospecimens and sharing of these specimens between researchers is limited. Acquisition of properly documented biological samples can be a major hurdle for biomarker evaluation. Creation of large biorepositories is desirable along with the abilities, policies, and procedures to facilitate collaboration with pre-approved research groups. The consent process should be simplified and each specimen should be deposited with future consent implied when used by any researcher approved by the biobank. Non-genomic data on patients may influence biomarkers and have unforeseen implications. These include such factors as gender, age, nutritional status, environmental exposure, behavioral habits, ethnicity, and geographic distribution. While it may not be possible to document every potential type of data from a patient providing a biospecimen, the inclusion of as much data as possible into the medical record is desirable.

The establishment of publically funded biobanks could provide an answer to the problem of locating a sufficient number of samples for statistically significant testing. Use of these samples could expedite the assessment of the diagnostic or predictive value of a biomarker plus help answer the question of validity and may guide future studies. The European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) has been formed and is expected to begin operating in the second half of 2013.

**Future Direction**

The path from discovery to use in clinical application should include the following stages:

1. Initial discovery and validation within defined conditions.
   a. In what group of people can the biomarker be found?
b. What does its presence mean?
c. How will current biomarkers for the disease be incorporated with this discovery in a diagnostic regime?

2. Evaluation of evidence by a multidisciplinary panel that would provide further study design criteria.
3. Obtain funding and additional specimens either from biobanks or a new sample collection.
4. Perform biomarker evaluation.
5. Return to the panel for review of the additional data and guidance on clinical trial design.
6. Obtain more funding to perform a study to determine the benefit received from implementation of the biomarker. It would be preferable to judge effectiveness using clinical endpoints. If time is critical or the biomarker provides potential life-saving qualities, surrogate endpoints could be used in the interim. Follow up by clinical endpoints should be required.
7. Have the panel review all evidence collected to date.
8. Convince the medical community to implement in limited clinical practice while continuing to gather data on endpoints.
9. Review cost-effectiveness, adoption by physicians, problems in application, and unanticipated disadvantages

The multidisciplinary panel could consist of independent subject matter experts, clinicians, statisticians, health economists, clinical societies, representatives from patient groups, health insurance, pharmaceutical and biotechnology industries, publically held biobanks, and regulatory agencies along with legal counsel. These people should evaluate the claims and utility of the proposed biomarker in an unbiased way. Evaluation should include verification of claims by independent biostatisticians with access to the raw data. Positive findings by the panel could provide the impetus for funding.

Journals can advance biomarker research by requiring the inclusion of pre-analytical data and encourage sharing of data in a publically available independently managed database. Clinical studies submitted for publication or submitted to regulatory agencies should conform to and certify compliance to guidelines such as BRISQ (The Biospecimen and Reporting for Improved Study Quality), REMARK (Reporting recommendations for tumor MARKer prognostic studies) or CONSORT (CONsolidated Standards of Reporting Trials).

The use of biomarkers as an element of personalized medicine will require the healthcare community to learn new concepts relating to disease diagnosis, pathogenesis, and treatment. Currently medical treatment begins once a disease has progressed to a symptomatic stage. Biomarkers hold the promise of very early disease detection with the potential to thwart the process thru new interventional
methods including nutrition or elimination of toxic environmental factors as well as pharmacology. Disease diagnosis will shift from symptom and histopathology based descriptions to traditional and new biomarkers and even complex molecular profile.
References


European Biobanking and Biomolecular Resources Research Infrastructure, [www.bbmri.eu](http://www.bbmri.eu)


Pharmacogenetics and the Wave of New Therapies

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Pharmacogenetics (phar-ma-co-gen-et-ics) is the branch of science that examines the inherited differences among people and the impacts those differences have on drug responses. Developing an understanding of pharmacogenetics helps to explain why some drugs or medicines are effective for some people but not others. Pharmacogenetics also explains why two people with similar weights, heights, and other physical characteristics might require different doses of the same drug. Furthermore, pharmacogenetics represents an exciting relatively new field of discovery, one that aims to provide better pharmaceutical outcomes while reducing or eliminating adverse drug reactions. In order to increase our understanding of this field, we will first examine the disadvantages of traditional, ‘one-size-fits-all’ approaches to medication before discussing the advantages of pharmacogenetics, then discuss how pharmacogenetics works, current pharmacogenetics approaches in treating breast cancer and Alzheimer’s disease, and finally explore future possibilities and current limitations of this approach.

Why One Size Fits All Doesn’t Fit All & the Benefits of Pharmacogenetics

Pharmacogenetics is built on the fact that everyone’s DNA, your so-called genetic blueprint, is unique. One of the central tenets of modern biology is that your DNA provides the instructions to make proteins and these proteins carry-out all the day to day functions of living things. Proteins are responsible for keeping your skin together, allowing your muscles to contract, digesting your breakfast, and even reading the words on this page. In essence, proteins make life possible. However if you look around a crowded room you can quickly see that no two people are exactly alike. Likewise humans are unique from all other forms of life and these differences are all due to changes in our DNA; as your DNA changes so do your proteins. Most modern medicines work by targeting common proteins deficiencies; helping to turn them on or off, marking unwanted proteins (such as those from foreign
bacteria) for destruction, or helping your body make up for missing proteins (antidepressants). However as illustrated by the example of looking at a crowded room of people – no two people make the exact same set of proteins; some people make more or less of a particular protein, others make slightly different versions of the same protein, and still others are missing a working copy. As a result people will inevitably react differently to the same medication. This is the reason certain drugs do not work, and may actually be harmful, for some people. In fact as many 4.5 million people a year suffer from adverse drug reactions with nearly 400,000 requiring hospitalization (O’Reilly, 2011), accounting for an addition $17 billion to $29 billion annually in health-care costs (Institute of Medicine, 2000). This unfortunate fact arises because the proteins many drugs interact with are slightly different in the people who the drugs do not work for. We will discuss why this is in more detail in the next section, however for now accepting that fact will help explain why this system developed in the first place.

Traditional approaches for developing pharmaceuticals focused on developing a treatment that will impact the most people possible while at the same time ensuring a broad market for the drugs being developed. Although this approach worked well for many years, providing many name-brand household staples such as Lipitor®, Flexeril®, and Prozac®, the patents on these drugs are expiring leading to a burst of generic options. Hence development of so-called ‘blockbuster drugs’ is coming to an end (Herper, 2011). Since more and more maladies are already being treated by this type of drug, there is less of a market to develop new ones. Now modern pharmaceutical companies are shifting their focus on more specific treatments for smaller percentages of the population, trying to match specific genetic differences with a specific treatment outcome by focusing on the unique differences between individuals with the same condition. In doing so, physicians and their patients can expect better options, targeted to individuals with specific genetic differences that will not only increase the results but also reduce unwanted side effects and adverse drug reaction. An example of this type of thinking will again be further explored at the end of this chapter when we discuss why some individuals taking Tamoxifen® to treat breast cancer require significantly higher doses that would have unwanted side-effects in most of the population.

Why is pharmacogenetics a better alternative? By focusing on your specific genetic differences when determining which medications to prescribe you, your doctor is better able to predict which, if any medications might trigger adverse drug reactions. Currently, there is no better way to predict this than asking about family history and even this cannot accurately predict an individual’s reaction to a specific medication. Additionally, some genetic predispositions cause people to make more or less of a particular kind of protein that may break-down the medication. In cases like this it may take months of altering dosing requirements to determine the correct dosage, however if you can determine ahead of
time whether an individual has one of these conditions the doctor could account for it from the beginning of treatment. This means a reduced chance of over or under-dosing in the first place, resulting in better treatment sooner. Finally, by developing drugs for people with specific genetic predispositions, pharmaceutical companies can pre-screen individuals at the start of pharmaceutical testing, allowing them to have smaller testing populations, more accurate results, and overall lower costs of development. This translates to reduced cost and increased delivery of pharmacogenetic drugs for consumers by lowering the cost and time of development by the pharmaceutical firms.

**How Pharmacogenetics Works**

Pharmacogenetics is the pharmaceutical arm of personalized medicine. It focuses on understanding how small differences in DNA affect whether a particular drug will be effective, ineffective, or harmful for a particular individual. In order to understand why this is we will first need to review how DNA codes for proteins and how changes in these proteins can alter drug efficacy.

In each of our DNA (collectively referred to as the genome) there are small changes. Many of these changes are benign going completely unnoticed and others account for the plethora of diversity seen in humans; some are responsible for giving people blue eyes while others have brown eyes, the same is true for hair color, the shape of your ears, whether or not you can roll your tongue, and the list goes on. However, some changes or mutations can have dramatic effects on body, such as the mutations responsible for genetic diseases. These small changes occur because one or more of the letters (or nucleotides) that make up our genetic blueprint are different. Changes in single nucleotides of DNA are referred to as single nucleotide polymorphisms and whole databases, such as the Center for Human and Clinical Genetics (http://www.humgen.nl/SNP_databases.html) and Online Mendelian Inheritance in Man (http://www.ncbi.nlm.nih.gov/omim), exist to track how these minute differences affect people. In addition to affecting drug interactions, some have been associated with diabetes (Willer et al., 2007), high blood pressure (McGreavey, 2009), and a variety of other conditions. Why is it that changes in your DNA can have such wide ranging effects on your body? The answer lies in the fact that the letters of your DNA are read and converted into proteins through two processes known as transcription and translation. Each set of three letters (nucleotides) creates a word that specifies a specific amino acid and amino acids are the building blocks of proteins. Changing the letters of your DNA, changes the amino acids that go into your proteins. At first glance this may not seem like a big problem considering that most proteins are made up of 100s or 1000s of amino acids, but some amino acids are more important than others because they are involved in making the parts of the proteins that
interact with other molecules. It’s similar to how certain parts of your house, like the doors, might be more important than other parts of the house in letting people enter and exit. Like your house, different parts of proteins do different jobs. As a result changing the instructions in the blueprint, for example replacing the ‘W’ in WALL to an ‘H’ will cause your house to look and function much differently.

Of particular interest to pharmacogenetisists are the otherwise silent changes in DNA that seem to alter how certain drugs interact with the body (Kormar, 2007). Alterations to these parts of DNA appear to be responsible for making the parts of a protein that bind to or are directly affected by certain drugs. These differences can alter the way a drug reacts in their bodies; perhaps speeding up or slowing down the amount of time a drug is effective within these individuals – thus the same drug given at the same dose can have different effects on each group. This is also the reason some people develop adverse drug reactions, their proteins don’t ‘get-along’ with the drugs. Pharmacogenetics aims to overcome this problem by determining which changes in DNA an individual has before they are given a medicine and only prescribing drugs that are known to be effective for their specific genetic profile.

Although this may seem like science fiction, the tools already exist to allow scientists and doctors the means to scan an individual’s DNA for as many as 10,000 small nucleotide polymorphisms at a time. Using a technique known as micro-array analysis an individual’s DNA is analyzed to see which specific genetic traits they have. The results can then be compared to a database of known adverse drug effects with specific DNA sequences and the doctor can alter their medication, its dosing, or other factors associated with their patient’s treatment. Unfortunately, widespread development of these tools is currently limited due to the cost of running and analyzing these tests.

**Pharmacogenetics in Treating Breast Cancer**

The treatment of breast cancer provides a unique opportunity to observe current development and thinking around a pharmacogenetic treatment plan. The high prevalence of breast cancer has provided scientists with a wealth of knowledge regarding its development including the genes and proteins involved. In addition, years of research have provided several effective treatment options including Tamoxifen and Herceptin® both of which exhibit gene-dependent effects. In this section we will examine some of the research related to the genetic-dependent effects of these drugs and how understanding these interactions is leading to better care for individuals with breast cancer.

Tamoxifen (Nolvadex®) is in a family of medications known as antiestrogens that block the activity of estrogen within the breast tissue preventing growth of certain types of breast cancer tumors.
After oral ingestion tamoxifen gets absorbed into the blood where it travels to the breast tissue. In order to become active in the body it must get converted into another molecule. This conversion is accomplished by an enzyme (protein) known as CYP2D6. There are currently 63 different known versions of the CYP2D6 enzyme in the human body (Beverage et al., 2007), most of which function normally. One variant in particular known as CYP2D6*4 is relatively common (found in ~10% of the population) and results in non-function of the enzyme (Goetz, 2007; Bijl et al., 2009). This means that while tamoxifen is normally an effective treatment option for breast cancer – individuals with two copies (one from their mother and one from their father) of the CYP2D6*4 gene will not be able to use tamoxifen as a treatment option. As mentioned previously there are many other versions of the CYP2D6 gene. Table 1 below shows several different versions and whether or not they are effective in tamoxifen treatments. Careful inspection of this table reveals that in addition to the non-functional version CYP2D6*4 other versions, such as CYP2D6*2 have increased activity while others still, like CYP2D6*9-11 all have decreased activity. This means that individuals with the CYP2D6*2 version require increased doses of tamoxifen because it gets used more rapidly than normal and individuals with the CYP2D6*9 version will require reduced doses of tamoxifen because they process it more slowly than normal. Due to the fact that these variations have been known for several years, commercially tested products already exist of the CYP2D6 gene (http://molecular.roche.com/assays/Pages/AmpliChipCYP450Test.aspx), making this the first microarray specifically designed to assess a person’s genetic predisposition to a specific treatment option (Table 1).

In addition to the gene-dependent effects of tamoxifen, breast cancer treatment also provides another example of the role of pharmacogenetics in modern medicine. Herceptin® is used to treat metastatic (spreading) breast cancer and works by interacting with a protein on the outside of cells called HER2, marking these cells for destruction by the immune system (http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001048/). HER2 is produced by a gene with a similar name; her2. The her2 gene is overactive in 20-30% of individuals with metastatic breast cancer, causing above-normal levels of the HER2 protein to exist on their cells. Herceptin® has been shown effective in treating HER2-overexpression in metastatic breast cancer, resulting in the destruction of these tumor cells. Unfortunately individuals with normal HER2 levels do not respond to Herceptin® treatments because their bodies are unable to distinguish between normal and HER2-expressing cancer cells. Thus Herceptin® represents one example of how an overactive gene can be specifically targeted to aid in treatment.
Table 1. CYP2D6 allele and enzyme activity (Droll et al., 2012)

<table>
<thead>
<tr>
<th>Allele</th>
<th>CYP2D6 activity/Tamoxifen activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6*1</td>
<td>normal</td>
</tr>
<tr>
<td>CYP2D6*2</td>
<td>increased</td>
</tr>
<tr>
<td>CYP2D6*3</td>
<td>none</td>
</tr>
<tr>
<td>CYP2D6*4</td>
<td>none</td>
</tr>
<tr>
<td>CYP2D6*5</td>
<td>none</td>
</tr>
<tr>
<td>CYP2D6*9</td>
<td>decreased</td>
</tr>
<tr>
<td>CYP2D6*10</td>
<td>decreased</td>
</tr>
<tr>
<td>CYP2D6*17</td>
<td>decreased</td>
</tr>
</tbody>
</table>

These two examples, CYP2D6 variation in tamoxifen treatment and her2 activity in Herceptin® treatment illustrate the dramatic effects small changes in DNA can have on the outcome of a given cancer treatment. Building on advances like these will help to make a pharmacogenetic approach to medicine more common in the coming years.

**Pharmacogenetics: A Look Forward**

Incorporation of pharmacogenetics into the everyday practice of medicine will require several key developments. The first is to develop a low-cost way of providing on-site genetic screens that can detect differences in our DNA. Advancing technology and smaller analytic tools are already making this possible, however it will probably be years before doctor’s offices are equipped with tools like this. As the availability of the tools for analyzing our genetic differences increases, so too will the need to train physicians in interpreting these results in order to provide the best care available for their patients. A shift is already occurring to standardized medical information, and practice including the rise of genetic counselors. However, new standards of care will need to develop that include information pertaining to genetic screening and drug interactions. Finally the future of pharmacogenetics will invariably bring with it new ethical considerations including but not limited to the use of genetic screening in determining insurance premiums, as well as avoiding ethnic and racial genetic profiling as these tools become more commonplace. Despite these current limitations, pharmacogenetics offers a promising step forward in our understanding of how each individual’s unique genetic differences can alter the success or failure of a given pharmacological treatment. Pharmacogenetics offers the hope of reduced adverse drug reactions, time of development, and cost; all of which serve to improve the standard of care of patients receive across the board. In addition to the developments already being made in breast cancer treatment, other diseases, such as identification of the APOE4-variant in Alzheimer’s disease, are already benefiting from a pharmacogenetic approach and undoubtedly more
advances will continue to develop as we increase our understanding of the role genes play in pharmaceutical outcomes.

**Additional Reading**

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Introduction: From Genomics to Proteomics

The completion of the Human Genome Project created a great deal of fanfare in the field of genomics and has facilitated the development of modern Proteomics. Since then, we have seen the development of comprehensive protein databases generated from the theoretical translation of the collection of genes from human DNA databases into their corresponding primary protein structure (Rahbar et al., 2011). Where Genomics can be defined as the study of the DNA sequences that make up an organism’s genome (Rahbar et al., 2011); Proteomics is the systematic or large-scale study of all protein molecules in a cell (Ornes, 2010).

There are approximately 20,000 – 25,000 genes in the human genome that are thought to encode for tens of thousands to over several million different proteins (Rahbar et al., 2011; Ornes, 2010). These proteins are the workers of the body’s cells. They assemble themselves into complex networks that construct, maintain and repair cells. In addition to acting as enzymes, hormones and transporters; they also regulate genes and act as antibodies (Ornes, 2010).

Most human diseases are caused by the functional dysregulation of protein interactions. In diseased cells, the protein network is disrupted, deranged or locally hyperactive compared to that of normal cells (Liotta, Kohn, & Petricoin, 2001). There is no denying that Genomic sequencing and mRNA-based analysis of gene expression has provided important information. However, this purely gene-based expression data is not enough to analyze the physical manifestation of disease at the molecular level mainly because there is no strict correlation between the gene expression and the actual protein expression (Jain, 2004). And while the cause of the deregulated process may be at the genetic level, as in the case of mutations, it manifests as defective, overabundant, or absent protein expression that prevents maintenance of normal cellular function (Liotta, 2001).

In short, DNA sequence information provides a static snapshot of the various ways in which the cell might use its proteins, whereas the life of the cell is a dynamic process (Jain, 2004). The proteome,
unlike the genome, reflects this dynamic nature and can vary widely at different points in time depending on internal and external stimuli, both between and even within specific individuals (Rahbar et al., 2011; Ornes, 2010]. The analysis of different levels of gene expression in healthy and diseased tissues by proteomic approaches is as important as the detection of mutations and polymorphisms at the genomic level, and may be of more value in developing biomarkers for personalized medicine (Jain, 2004).

**Diagnostics**

Diagnostic screens utilizing biomarkers that indicate the presence of disease can potentially increase the early identification of the disease in patients (Sikora, 2007). Conventional proteomic technologies focus on identifying disease-specific biomarkers, while Serum Proteomics Pattern Analysis, a relatively new technique, offers better diagnostic possibilities over the use of a single biomarker. Serum displays a protein content reflecting homeostasis of circulating blood and perfused tissues, including tumors (Goncalves, Borg & Pouyssegur, 2004). By comparing the overall pattern of proteins, one can discriminate cancer from non-cancer samples and thus diagnose disease states without the need to identify any of the individual components (Jain, 2004). The most advanced technology for looking for protein patterns or fingerprints specific to a tumor at the serum level is Surface-Enhanced Laser Desorption/Ionization Time of Flight Mass Spectrometry (SELDI-TOF MS); which couples chromatographic separation of samples using reactive surfaces and high-throughput mass spectrometry analyses, with the added advantage of limited processing steps (Goncalves et al., 2004).

The first published study using this method showed the great potential for this technology for early diagnosis of ovarian cancer (Goncalves et al., 2004). This method accurately identified cases of ovarian cancer with 100% sensitivity and 95% specificity (Jain, 2004). All that was required was a small serum sample that was be obtained by a finger prick and less than 30 minutes to generate the mass spec results (Jain, 2004). This proteomic technique is cost-effective, and may have applications in high-throughput screening as well as in medical screening clinics as a supplement to diagnostic work-up and assessment (Jain, 2004).

Profiling proteins on biochips is another useful way to distinguish proteins of normal cells from early-stage cancer cells and from malignant metastatic cancer cells (Jain, 2004). These protein chips or protein microarrays offer the possibility of developing a rapid global analysis of the entire proteome leading to protein-based diagnostics (Jain, 2004).
Therapy Selection & Monitoring

Proteomic techniques and biomarkers can play a huge role in therapy selection. Biomarkers used in pre-disposition screens would identify cancer patients for chemo-prevention while pharmacodynamic biomarkers can determine and establish pharmacological doses as well as predict patient-specific toxicities (PMC, 2011). This would greatly reduce the occurrence of adverse events by allowing for dose adjustments according to the individual (Sikora, 2007). Additionally, biomarkers that allow predictive reclassification of disease would help target therapies to those patients who are likely to respond; and biomarkers used as early response surrogates will help identify those patients who should stop treatments that are proving to be ineffective (Sikora, 2007).

One of the most common applications of proteomics-based molecular screening is seen in women with breast cancer (PMC, 2011). About 30% of breast cancer cases are characterized by over-expression of a cell surface protein called human epidermal growth factor receptor (HER2) (PMC, 2011). For these patients, standard therapy is ineffective. Instead, molecular screening tests for HER2 are used to identify patients who will benefit from receiving an antibody drug called Herceptin which was shown to reduce the recurrence of a tumor by 52% in combination with chemotherapy (PMC, 2011).

In another study, published in a 2007 issue of the *Journal of the National Cancer Institute*, imaging mass spectrometry was used to test blood samples from non-small-cell lung cancer patients before they were given a drug that targets a particular protein found in tumors. This technique correctly predicted the cancer patients who would respond well to the treatment (Ornes, 2010). With proteomics tests like these, researchers and clinicians may be able to identify in advance which patients are most likely to respond to a particular therapy, and which patients should move on to other treatment options (Ornes, 2010).

Beyond selecting the best therapies, proteomics has important applications in monitoring the effects of treatment. Essentially, careful observation of the changes in the different proteins related to the development of the disease tells you whether your therapy has been working or not. In a Phase II study of a combined therapy for women with ovarian cancer, blood samples were taken to monitor changes in the concentration of cytokines associated with the growth of cancer (Ornes, 2010). From this kind of data, it may be possible to determine the precise concentrations and combinations of proteins in the blood that indicate a treatment is working or not with the ultimate goal of developing systems to allow doctors to monitor patients responses to therapy, thus approaching disease as a dynamic and customizable process rather than a single prescription (Ornes, 2010).
Prognosis

Once a disease has been diagnosed, the next difficult task is to correctly identify patients who have aggressive disease from those who do not. This is especially important in the case of cancers like prostate cancer where, in some cases, patients are diagnosed and treated for slow growing, non-problematic tumors that would not have significantly affected the patient; and for which treatment may not have been necessary and may or may not have aggravated or exacerbated the condition.

Proteins released or displayed by growing tumors may convey identifying information about the disease; and it is these proteins that are the focus of proteomic efforts to distinguish between subtypes of cancers (Ornes, 2010). Techniques similar to Serum Pattern Proteomics Analysis may be helpful in distinguishing between outwardly similar tumors by considering a pattern of proteins, and not a unique protein, as a biomarker (Goncalves et al., 2004). Using a variation of protein pattern MS, it may be possible to uncover information on a tumor’s size or aggressiveness based on protein patterns which could then be used to make decisions on the best treatment (Ornes, 2010). This kind of protein fingerprint analysis has already been used successfully on whole pieces of tumor biopsies thanks to Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOF MS). Researchers were able to correctly identify different histological types of lung and brain tumors (Goncalves et al., 2004).

Drug Development & Clinical Trials

The drug discovery & development process utilizes clinical samples throughout all of the stages from the earliest investigations into target expression, to the studies used to validate the target expression in the context of disease, to the identifications of biomarkers that can be used to monitor either disease development or the pharmacological effect of compounds on targeted pathways (Feniger, Laurel and Marko-Varga, 2005). A 2010 survey conducted by the Tufts Center for the Study of Drug Development found that 50% of clinical trials are collecting samples from patients to aid in the discovery of drug-related safety and efficacy biomarkers; and 30% of the companies surveyed require all compounds in development to have a biomarker (PMC, 2011).

The role of proteomics in drug discovery and development is known as ‘pharmacoproteomics’ and may accelerate the drug development process by classifying patients as responders and nonresponders (Jain, 2004). In addition, biomarkers acting as surrogate markers of clinical efficacy would provide early indication of proof of concept for clinical trials (Sikora, 2007).
Expression proteomics and functional proteomics have been applied to pharmacology, toxicology and the development of drugs, particularly in cancer drugs. Normal cells, precancerous cells and tumor cells from an individual can be isolated from a patient using tools that maintain the original protein pattern of the cells. Analysis of the protein patterns of patient tumor cells taken after treatment shows how a particular therapy affects the protein pattern of a cell. This approach facilitates development of individualized therapies that are optimal for a particular patient rather than to a population and can also provide information regarding the effects, both toxic and beneficial, of a therapy (Jain, 2004). The ability to establish relationships between toxic effects and protein markers could allow new compounds to be screened for toxicity using panels of predictive biomarkers. Proteomics can provide valuable information on the biochemical consequences of various drugs on the liver, kidney, and cardiovascular system. Furthermore, identifying toxicity markers raises the possibility of monitoring the onset of toxicity before cellular damage is evident (Jain, 2004).

Several other approaches to developing personalized therapies are underway. One method for cancer is to study the signal pathway activation within a patient's tumor using reverse phase protein microarrays from biopsy tissues; the effect of treatment on the pathway containing the target can be studied before during and after therapy (Jain, 2004). In the general approach to drug discovery, Affinity–Based Biosensor technology is being investigated to profile lead compound-protein interactions; and Immobilized artificial membrane chromatography is being evaluated to predict oral compound absorption. These tools will provide valuable measures of absorption, distribution, metabolism, excretion and toxicity (ADME-Tox) characteristics for annotating screening libraries, to evaluating hits and ultimately leads; which can then be related to their performance in actual clinical trials (Jain, 2004).

Technology

In the past, proteomic technologies were not well suited for application to human clinical trial specimens (Liotta, 2001). Traditional protein analytical methods such as 1-D and 2-D gel electrophoresis and mass spectrometry required large amounts of input material and complex sample preparation. As a result, researchers attempted to modify these traditional technologies or develop innovative technologies to bring proteomics from the laboratory to the clinic (Liotta, 2001).

Significant advances have been made in broad categories of proteomics technologies; many of which are used to survey and discovery proteins that change under various conditions (Liotta, 2001). Efforts by the National Cancer Institute to standardize existing proteomic technologies such as Mass
Spectrometry are leading to more robust identification of protein biomarkers which indicate the presence or absence of disease apart from the risk prediction of genetic analysis (PMC, 2011). In addition, there are entirely new approaches to protein biomarker detection that are promising to make proteomics as “simple” as genetic analysis, which would allow diseases to be diagnosed and treated in their earliest stages (PMC, 2011). There are three main classes of proteomics technologies that are amenable for use in the clinic; Antibody-based, Array-based and Mass Spectrometry (MS)-based (Rahbar et al., 2011).

Antibody-based technologies like enzyme-linked immunosorbent assay (ELISA) and Immunohistochemistry (IHC) are commonly used in proteomics. The ELISA is the ‘gold-standard’ used for protein-based testing in clinical laboratories around the world. IHC is used in the clinic by pathologists for cancer diagnosis, tumor type differentiation and the determination of patient prognosis. Bead-based immunoassays are being used with increasing frequency to develop multiplex diagnostic tests for use in the early detection and differentiation of disease. While these methods may have high sensitivity and specificity, they are limited to previously identified targets and they rely on the availability of high-quality antibodies which can be expensive and time-consuming if there are no antibodies and reagents commercially available for the targets of interest (Rahbar et al., 2011).

Array-based Technologies like Forward-Phase, Reverse-Phase and Peptide microarrays are not as commonly used in the clinic as their nucleic acid-based counterparts; but they are used in research to look for protein-protein interactions or autoantibodies for biomarker, signatures that indicate specific diseases or infections. If successfully transferred to the clinic, these methods offer many advantages namely; their high-throughput nature, and simple sample preparation steps. Array-based methods offer the ability to multiplex, have relatively limited sample preparation and are compatible for high-throughput screening; however they share the same limitations as those of the Antibody-based technologies (Rahbar et al., 2011).

Mass Spectrometry-based Technologies are used in proteomics to identify, quantify and characterize the structure of proteins and other biomolecules from complex biological systems. Unlike the other methods described above, MS-based technologies do not require antibodies, and are relatively unbiased, making them well suited for discovery experiments. Multiple Reaction Monitoring (MRM) provides targeted multiplex analysis of complex mixtures like plasma and serum. Matrix-Assisted Laser Desorption Ionization (MALDI) Spectrometry has several applications and can be relatively high throughput. MALDI Imaging in particular for example, is used to analyze tissue samples. It correlates the location of proteins to sections of tissue to obtain information about the cell and tissue type based on protein expression and localization patterns. Electrospray Ionization (ESI) is
used for discovery proteomics. A method called Tandem MS is particularly useful for obtaining peptide sequence information and analyzing thousands of proteins from complex mixtures (Rahbar et al., 2011). Despite the advantages of MS-based technologies, there are disadvantages as well. MS technologies are generally low-throughput with a limited dynamic range, and they require a high level of expertise to operate the equipment (Rahbar et al., 2011).

**Challenges & Future Prospects**

Through the use of protein biomarkers, it will be possible to analyze the state of proteins and signal pathways in the disease altered cells before, during and after therapy (Liotta, 2001). The potential impact of proteomics on diseases is not limited to the identification of new biomarkers for early detection and new targets; these tools and methods will be used to design rational drugs based on the molecular profile of the protein circuitry of the diseased cell (Jain, 2004). By combining pharmacoproteomics and pharmacogenomics, it will be possible to define smaller, more rapidly responsive trial populations and to monitor drug responses more effectively. This will lead to a reduction in trial time and cost of drug development. Proteomics will facilitate mass screening at the protein level to supplement the genetic screening and fill a gap in molecular medicine leading to greater advances in personalized medicine (Jain, 2004). However, in order to reap these benefits, and to bring proteomic technologies like MS to the clinic, several factors will need to be addressed (Rahbar et al., 2011).

The development of clinically useful protein biomarkers has been progressing at a relatively slow rate with an average of only one and a half FDA-approved protein-based biomarkers introduced per year over the last 15 years due to a variety of reasons including a number of biological and technical barriers (Rahbar et al., 2011);

- Low reproducibility and repeatability of proteomic measurements; including sample collection, storage and analytical factors related to the workflow
- Low throughput of proteomics technologies
- Poor sample availability
- Poor availability of reagents and resources for protein-based assays

The US NCI’s Clinical Proteomic Technologies for Cancer initiative (CPTC) and the NCI Office of Biorepositories and Biospecimen Research have been working to address many of these issues through the introduction of standard operating procedures (SOPs) and Best Practice Guides
(Rahbar et al., 2011). In addition to the technological barriers, there is somewhat of a disconnect between the proteomics research laboratories and the clinical laboratories. What may seem practical in the research lab may not be feasible at the clinical level. In response to this, the CPTC has begun working with the American Association for Clinical Chemistry to coordinate the training and education of the clinical community in proteomics standards and advances in the technologies used in the research field (Rahbar et al., 2011). Addressing the technical issues and facilitating concerted efforts between members of the research, clinical, advocacy and the regulatory community will facilitate the transition of proteomic technologies from the laboratory to routine clinical use (Rahbar et al., 2011).
References


An Introduction: Nutrigenomics vs. Nutrigenetics

An impressive new frontier of the 21st century in biomedical and clinical research has arisen, and it is known as nutrigenomics. Through the recognition that nutrients have the ability to interact and modulate molecular mechanisms underlying an organism’s physiological functions, the nutrition field has capitalized on technologies of the post-genomic era to study the relationships between genes and diet. In doing so, the fields of nutrigenomics and nutrigenetics were created. These fields are often used interchangeably, but actually represent two different approaches to study the underlying mechanisms of gene-diet interaction. Nutrigenomics aims to identify how food affects our genes and how individual genetic factors affect our body's response to nutrition. Meanwhile, as nutrigenomics takes a more micro scale approach to understanding the effects of food, nutrigenetics takes a more macro scale approach and aims to identify genetic susceptibility to disease through food intake by studying the genetic variations between certain population subgroups based on diet and health. Using these approaches, researchers hope to devise powerful methods to decipher the complex relationship between nutritional molecules, genetic polymorphisms, and the biological system as a whole. The related research that is underway may pave the way for optimizing an individual’s health by means of nutritional intervention.

The segment of personalized medicine incorporating nutrigenomics and nutrigenetics harnesses multiple disciplines, which includes studying the dietary effects on genomics, transcriptomics, proteomics and metabolomics. Research in this field has enabled a more rapid and comprehensive understanding of how bioactive compounds affect human health. By analyzing genome stability (DNA damage at the molecular level), epigenome alterations (DNA methylation), RNA and micro-RNA expression (transcriptomics), protein expression (proteomics) and metabolite changes (metabolomics), researchers can diagnose health status and disease progression. The genetic variations that cause differences between individuals is complex but is mainly known to be attributed to single nucleotide
polymorphisms (SNPs) which are the most common form of sequence variation in the human genome, due to the vast number of SNPs (over 10 million) that have been identified. Another suspected genetic variant is copy number variants of genes, or whole chromosomes, both of which can provide a greater source of genetic variation. Nucleotide repeats, insertions, and deletions are other types of variations that can also modify an individual's response to diet. Different experimental approaches can be used to identify genetic variants that are responsible for modifying the effects of dietary factors.

The Experimental Approach

A candidate gene approach is the most common method in this field, whereby a gene is selected based on its putative function, and functional effect analyses are performed. Other techniques designed to unearth individual genes associated with a trait of interest, include genetic engineering and mouse knockout systems that can be used to identify the functional effect of gene targets. An alternative approach is one called systems-genetics, which is a novel population-based approach for identifying the genetic architecture of complex traits and gene-environment interactions. By observing populations with a certain disease and performing genome-wide association studies, researchers can identify numerous gene polymorphisms associated with quantitative traits such as body weight. The connections from genetic variants can be created in gene networks through where intermediate phenotypes can be overlayed with systems level phenotypes. Because of this, all of these disciplines can be used to identify biologically meaningful gene networks. An additional method, proteomics, may also be exercised to study protein structures and functions. Proteins are key actors in all biological processes and by examining the way our genome responds to certain diets, we may identify which proteins are produced and modified post-translationally. Through this multi-faceted approach, researchers in the field of nutrition are making breakthrough correlations between diet and health.

Dietary reference values, often referred to as recommended dietary allowance (RDA) represent the safe upper limits of dietary intake for the general population. RDA is based on a variety of metabolic outcomes but is not optimized for genetic subgroups, which, for example, may be representative of populations who may express differences in transport protein activity for a micronutrient or in enzymes that require specific micronutrients, such as a cofactor. It has been shown that by matching a personalized nutriome (nutrient intake combination) with that same individual’s current genome status, genome maintenance, gene expression, metabolism and cell function, people can live healthier lives. However, all of these studies rely on three fundamental assumptions about nutrition. The first is the hypothesis that nutrition can influence health outcomes by altering gene
expression in critical metabolic pathways. Research also assumes that the nutritional content of food has health benefits that depend on inherited genetic variants, which alter the uptake and metabolism of nutrients. Lastly, it is assumed that health advantages can be achieved if nutritional requirements are customized for each individual by taking their inherited and acquired genetic characteristics depending on life stage, dietary preferences and health status, into consideration.

Preliminary research indicates that it is possible to personalize diets in order to target specific health benefits by studying the biological effects of nutrients and food bioactives. The nutrients and bioactives found in food are dependent on a series of physiological processes, including absorption of nutrients in the stomach and intestine, transport of nutrients to different parts of the body, biotransformation of nutrients through digestion, binding of nutrients by proteins, storage and excretion of nutrients, and cellular mechanisms of action. Establishing a genetic basis for food preferences, such as predisposition from taste, could lead to the development of novel food products. These food products could then be used to target genotypes of certain ethnic populations that don’t typically consume certain food products which could help explain some of the inconsistencies among studies relating foods to risks of chronic diseases.

**In application: Disease Prevention**

“*Let thy food be thy medicine and thy medicine be thy food*” - Hippocrates

Celiac disease (inability to tolerate gluten-containing foods) is an example of a disease currently under investigation, and can presently only be attended to with a lifelong gluten-free diet that avoids wheat, rye, barley and related food groups. In an effort to relieve sufferers of celiac disease, the food industry has developed a range of gluten-free products, but meanwhile on the medical front, genetic screening for this disease is continues to be unavailable. Current research has determined that the disease is associated with serious inflammatory symptoms, including changes in the colonic villi, and is hereditary with 75% concordance of disease development. Carrying the genes may not tell the whole story, but can be a helpful route in revealing genetic predisposition. Certain genetic variants in the HLA-DQ (DQ2 and/or DQ8) genes indicate high levels of risk and could potentially be used in a screening test to help diagnose the disease. It is the hope of the medical community that screening for predisposition will alleviate the unnecessary suffering of individuals affected by the disease.

As the average lifespan increases, researchers have acknowledged the deterioration present in aging populations in cognition and neural control of motion, from, for example, Alzheimer’s and Parkinson's diseases. Recent research is examining the role of specific gene variants involved in lipid
metabolism, in patients suffering from such neurodegenerative diseases. For example genetic variation in the genes apolipoprotein E (principal cholesterol carrier protein in the brain) and apolipoprotein E4, are significant biomarkers with high risk for Alzheimer's disease. On the other hand, Parkinson's disease is partly caused by lipid peroxidation due to activation of phospholipases. Preventative strategies are being designed for these diseases including dietary supplements that inhibit these lipid activities. While there is much anticipation in the progress of these nutrigenomic-based strategies, none are currently available.

The optimization of one’s diet can also provide an approach for cardiovascular medicine, with the potential to prevent and treat cardiovascular diseases (CVD). Recent research has characterized multiple intermediate phenotypes correlated with CVD, such as elevated plasma lipid concentrations, plasma glucose, markers of inflammation and endothelial damage, oxidative stress, blood pressure, anthropometric measurements and down to characterizing the intima-media thickness of artery walls. However, despite considerable research, there is a lack of fundamental evidence to validate that the theories are effective enough to move into clinical experiments. Diet has traditionally been considered one of the main risk factors for CVD, as research has traced affected populations to certain diets and geographical areas. Despite national programs designed to improve nutritional awareness, few real improvements have been observed. New research is encouraging, and it is my hope that it can serve as the basis for future research in providing the justification for dietary personalization to optimize CVD treatment and prevention.

Obesity is another disease that’s prevention rate can be improved using nutrigenetic knowledge. A recent experiment devised a personalized calorie-controlled diet based on the identification of 24 variants in 19 genes for 50 people. The findings showed that utilizing both exercise and the specialized diet resulted in more weight loss and greater weight loss retention than in control group with no personalized diet. These biomarkers for obesity can also be associated with increased risk for developing type 2 diabetes in multiple populations. It was found that individuals with this genetic variant would consume more food than those without it if placed inside similar environments. Detecting the genetic variant through a test could be the first step in preventative treatments.

Global cancer rates are predicted to increase by about 50% by 2020, which stresses the need for the development of appropriate prevention strategies for both developing and developed countries. One finding shows that populations living in lower latitudes had a lower incidence of colon cancer due to increased sunlight exposure. Increased sunlight exposure resulted in ultraviolet radiation that can lead to vitamin D formation in the skin. This resulted in the connection that vitamin D is linked to cancer prevention, which ultimately prompted the recommendation that increased sunlight exposure, vitamin
D rich foods and dietary supplements can optimize one's vitamin D status and prevent cancer. However despite numerous experiments and studies between vitamin D status and breast cancer risk, limited associations could be made and in fact DNA damage can occur from excessive sunlight exposure. It is possible that vitamin D from sun exposure could be more harmful in terms of cancer progression than for retarding the incidence but more research still needs to be done.

These are significant observations that sub-populations have variable responses to diet; this is most highly evident in countries that have diverse ethnic backgrounds and have undergone rapid socio-economic development, such as in Singapore. The population of Singapore is very diverse, consisting of three main ethnic groups Chinese, Malays, and Asian Indians, all of whom live in integrated, urbanized communities. Increases in life expectancy due to benefits of modern medicine have given rise to an epidemiologic transition, such that mortality from infection and malnutrition have been replaced by chronic non-communicable diseases; for example, cardiovascular disease and cancer are now the top two causes of death in Singapore. However, not all ethnic groups were equally affected by this transition. For instance, it was found that Asian Indians are at higher risk for developing cardiovascular disease; and additionally, they have a higher risk than the Chinese of developing myocardial infarction, by threefold! It was also found that obesity is more common for Malays, for whom the distribution of fat is localized peripherally, whereas Asian Indians were found to have larger waist circumferences. Given that these diverse populations live in integrated environments, how can one explain the differences seen here to be from differences in insulin resistance, diabetes, high cholesterol, or hypertension? The most likely answer is from food consumption and by finding the genetic variants correlated to these differences can explain how the subpopulation interacts with its environment.

Considering these observations, it is becoming increasingly evident that the study of nutrigenetics and nutrigenomics will take center stage in the investigation of the effect of nutrition on health outcomes. The studies done through a multitude of ‘omic’ technologies and biomarkers can have helped evaluate the impact of nutrients and correlated it with genetic backgrounds such as gender and life stage. The translation of findings from preclinical to clinical domains requires more time, yet current research is providing a plethora of new knowledge making it clearer which genetic factors are key contributors for formulating dietary recommendations for different population subgroups. The combination of genetic tests using biomarkers, with nutrigenetic-based advice, will allow for personalized dietary recommendations with evidence-supported health benefits; despite the hurdles, the public health implications are enormous.
References


Introduction to P4

Globally, the prevailing trend is customization; in fashion, construction, and in automobile features, the concept is widespread, but what about in healthcare? If patients seek more customized services, are genetics, biomarkers and proteomics clinically applicable?

As the scientific community works to unravel the features "driving inter-individual variability" (Issa, 2007) of human conditions, customization may be possible. In fact, it's desirability urges individualized medical science, founded in pharmacogenetics and pharmacogenomics, to venture towards clinical application (Paul & Fangerau, 2006). It looks like “one-size-fits-all” is no longer in vogue.

An appreciation of the comprehensive scientific background of personalized medicine offered in the previous chapters is undoubtedly essential, so long as the science is effective in application. Personalizing medicine from a clinical approach is based on the premise - "the right treatment for the right patient at the right time" (Steele, 2009), which is hard to come by; however, its value is tremendous.

Imagine tailoring a therapy to fit a person's genome, or eliminating trial-and-error treatments by screening cancer patients to classify exact receptors on tumor cells. Although personalized medicine is largely regarded as a phenomenon of the future, it is slowly but surely revolutionizing the model of healthcare to one that is personalized, predictive, preventive and participatory (P4), from a current model that is, to a great extent, reactive and responsive.

It may be years before we see the full potential of the "P4 model", as its success depends on the translation of pharmacogenomics into clinical practice; yet the integration of some personalized practices into mainstream healthcare are within reach, for good reason. On the horizon are three main clinical benefits of integration: better diagnoses, earlier interventions and optimal therapies. This
chapter provides an overview of these benefits, and documents a case in point to illustrate the value of each, ranging from cancer to cardiology, and everything in between.

A Proactive Pursuit

"It's far more important to know what person the disease has than what disease the person has"

- Hippocrates

The proactive pursuit of personalized medicine is to exercise pharmacogenomic strategies in concert with family and clinical histories to improve medicine threefold, by diagnosis, intervention and treatment. Traditionally the diagnosis of a disease is based on a series of manifesting symptoms that may be representative of several diseases, a patient history, and laboratory and imaging data. The nature of some diseases, however, is that they can be determined more accurately, and more cost-effectively via genetic tests and molecular diagnostics - although the development of these tests demand a large-scale undertaking. Advancements such as biomarkers have the potential to detect residing disease or risk of development, as well as how an individual's body might react to a certain treatment based on genetic variations.

Research tells us that personalized technologies will be a way, if not the way of future medicine. Doctors will be able to tailor medical/treatment strategies to the patient by using molecular assays that determine concentrations of proteins, genes or specific mutations (Wikipedia, 2009). Imagine that! Be that as it may, without becoming entwined in the basic science, which is the focus of several other chapters, I'd like to delve into the concept of clinical utility and validity. Together, the two are crucial to both the advancement and adoption of improved diagnostics, interventions and therapies, as only their efficacy encourages incorporation of the tests mentioned, into clinical guidelines and practices.

Validity, to start with, refers to the predictive potential of the actual test, or "a test's ability to detect and predict the outcome associated with the biomarker" (Trakas, n.d.). Utility, on the other hand, is defined as "the value of information to the person being tested" (“Secretary’s Advisory Committee”, 2009). To be adopted as a routine measure in healthcare, validity and utility must be provided for a companion diagnostic. "However, of the roughly 1,000 to 1,300 newer and more complex tests, only a minority have demonstrated clinical utility so far" (“Trends and Prospects”, 2012). Though there is a shift towards proactivity, there is a sizable bottleneck for clinical validation of biomarkers that researchers have developed; so while the scientific community is optimistic, personalized medicine can only take full effect with further preclinical work to authenticate these tests.
In addition, preclinical work needs to "determine which genetic variants regulate which explicit pharmacological effects" (Anonymous & Issa, 2009), not to mention the need for additional clinical trials and randomized control trials to show improved health outcomes. There has been a flood of research in recent years on personalized medicine, but it is the translation from the lab-bench to bedside that is essential to truly adapting personalized initiatives. Then as always there are the socioeconomic issues at stake — as seen later in Chapter 10 - and to put it simply, means, "who's paying"?

How it works, clinically

From a basic description of personalized medicine, one might perceive a model of totally individualized pharmacotherapy (target drugs for each unique genetic profile), but this is not the case. The clinical model categorizes patients into subpopulations that are varied in their predisposition to a particular disease or their response to a specific treatment (Lee, Flammer, Lerman & Lerman, 2012). So while one-size-fits-all is not all too trendy, one-size-fits-sub-population is making headway.

In his paper, "The Application of Personalized Medicine," (2011) otolaryngologist Robert Ruben designed a prototype checklist to better organize personalized care. He created his 4-point checklist based on treatment for an ear infection, but in many ways his management applies across the board. His practical patient/disease assessment is framed as follows: 1. patient's intrinsic susceptibility, including "genetic makeup, family history" (Lee, Flammer, Lerman & Lerman, 2012), and 2. intrinsic morbidity, which explains "the effect of the disease on the individual". He also lists 3. extrinsic susceptibility, which includes external features that may make an individual more prone to disease, and 4. extrinsic morbidity, including "deprived environments" such as "poverty or inadequate medical care" (Ruben, 2011). The importance of taking these features into account demonstrates a need for a multidisciplinary approach to a patient's healthcare, an approach that can work cohesively with the scientific breakthroughs for medical treatments and diagnostic tools designed for treating and detecting certain subpopulations.

Better Diagnoses

Per usual, this is easier said than done. The landscape of a disease varies greatly due to the many variables that play a role in disease. People are unique - whether it’s the food they eat, the environmental factors they are exposed to, their stressors or their DNA. To achieve a better diagnosis,
personalized medicine most famously utilizes techniques of molecular and genetic analysis that take some of these variants into account.

A case in point is reported by Dauber, et al. (2012), in which a patient exhibits a growth disorder. Multiple tests (routine karyotyping, chromosomal microarray, and individual gene sequencing) at a sizable cost, were performed on the patient, but were unsuccessful in determining diagnosis. Exome sequencing was elected upon for further investigation. Remarkably, exome sequencing enabled the detection of an uncommon homozygous frameshift mutation in the CUL7 gene of the patient. Human CUL7 gene is one of the causative genes of a rare primordial growth recessive disorder, 3-M syndrome (Dauber, 2012). At the cost of all these other tests, exome sequencing brought forth results that led to a better diagnosis.

"This report signifies the impact of exome sequencing in reaching genetic diagnosis for cases with inconclusive clinical diagnosis" (Hedge, 2012). It is not to be assumed however that personalized medicine is only applicable in "House, M.D."-like, atypical cases, but rather it is just as applicable in common diseases and cancers, such as breast cancer. For example, one of the first examples of personalized medicine impacting patient care was in a treatment called Herceptin (trastuzumab) for breast cancer. Approximately 30% of patients that have breast cancer, have a class of the disease that "over-expresses a protein called HER2" ("The Age of Personalized Medicine", 2011). This form of breast cancer was unresponsive to the standard therapy provided to patients; thus the development of Herceptin, designed specifically for individuals who exhibited HER2 positive tumors, was enormously successful.

Herceptin was approved in 1998, but since then scientists in the field think that even this is an oversimplification of the complex mutations occurring in breast cancer. Despite their prevalence, cancers are complex diseases that require thorough profiling constructed from genetic mapping and matching to a clinical cohort; in cancers, subpopulations may be divided based on tumor-type, or tumors that bear select molecular alterations. One approach in the works is the actual targeting of the tumor mutations to further personalize "standard therapy" for a certain cohort.

Cancer is not one disease, nor is one cancer the only type of "that cancer". Rather, cancer patients have a host of cell types, which vary by location. Personalized medicine aims to "a. understand pathogenesis, b. look for markers of prognosis, [and] c. identify novel mechanisms to target treatment" (Thompson, Drew & Thomas, 2012). There is a lot of trust being put into personalized medicine techniques. Per-patient sequencing may pave the path for better disease models, and allow medical professionals to better affiliate novel phenotypes with certain genes and mutations. This can, in effect,
broaden the "clinical spectrum, genetic heterogeneity and pleiotropy of diseases" (Hedge, 2012) to solidify more valuable and more specific diagnoses to guide eventual treatment.

**Earlier Interventions**

An important aspect of obtaining a better diagnosis is determining increased risk of disease susceptibility, hopefully in order to prevent the onset of disease, or at least enable more effective treatments or options. One of the hottest topics under discussion is identifying increased risk for Alzheimer's. Fast growing, and debilitating for individuals affected, Alzheimer's is a complex disease for which scientists have made little progress in attacking the "underlying progression of the disease" (Huang, 2006), rather their efforts have lead to improving the cognitive symptoms that manifest. While testing has been used at the population level to detect a population level risk, less accuracy has been determined for predicting individual risk. "Identifying an increased risk allows [for] early intervention and planning" (“Clinical Utility”, n.d.), which, and is extremely powerful in the handling of disease.

Type II diabetes, a disease that results from gene-environment interactions, also has widespread recurrence in our population, but may manifest differently in different patients and subpopulations. Screening genetic tests that "can test for the presence of up to 40 implicated gene mutations"(“Clinical Utility”, n.d.), and identifying biomarkers, can pinpoint patients with high risk of developing diabetes, and may detect whether a patient would benefit from a particular intervention or dosing regimen. An adequate response from the get-go, often before the disease even develops, can be crucial to the outcome.

One syndrome in which intervention has really made strides is Lynch Syndrome. "Detection of mutations in the MLH1, MSH2, MSH6 and PMS2 genes, allows for surveillance, which includes a colonoscopy and removal of precancerous polyps every one to two years starting at age 25" (“Clinical Utility”, n.d.). While this successful detection model is for a disease that seems to be based on single genes, rather than the interactive causes for the complex diseases above; as a whole there is great promise in this predictive practice that is intrinsic to personalized medicine.

**Optimal Therapies**

The idea behind personalized medicine is to enhance therapeutic efficacy - by ensuring that appropriate drug use and dosing regimen takes into consideration any genetic variants which might influence the metabolism of the drug. Personalized medicine also has capacity to avoid preventable
drug related complications and side effects, and steer clear of trial-and-error practices. By tailoring drugs to fit the individual genetic/molecular profile, better outcomes can be expected.

By demarcating sub-cohorts of patients based on "specific genetic, 'druggable' alterations (i.e., genetic alterations for which therapies exist)" (Trakas, n.d.), personalized medicine conveys its superiority. One example of its effect on optimizing therapies is in cardiovascular disease. Coumadin, or warfarin, which is prescribed to patients in order to inhibit blood clots from occurring, is a medication that relies on trial-and-error procedures for determining appropriate dose per patient. Due to the nature of the medication, rounds of trial and error dosing could be detrimental to the patient, in increasing "risk of excessive bleeding or further blood clots" ("The Age of Personalized Medicine", 2011). In the vein of personalized medicine, genetic tests have been developed that spare already sick patients from accumulated risk. "Genetic tests detecting variations in the way individuals metabolize the drug can help predetermine the right dose for a patient for the first time" ("The Age of Personalized Medicine", 2011). In fact, on the Coumadin sticker lists a recommendation for considering a patient's genetic makeup before administering a certain dosage. Just within the cardiovascular arena, there are a multitude of tests and biomarkers, in addition to that testing for warfarin metabolism, that have extremely valuable clinical application.

Similarly, a medication used to treat HIV infection can cause a life threatening allergic reaction in a certain percentage of patients. Susceptibility to this complexity in administration of medicine was shown to be affiliated with a certain allele (the HLA-B*5701 allele in Caucasians). DNA testing devised to detect the presence of this allele can, and does, prevent complications and averts putting lives in jeopardy.

What's in store for the future? "In what could be the ultimate in personalized medicine, animals bearing your disease, or part of your anatomy, can serve as your personal guinea pig, so to speak" (Pollack, 2012). For now, the hope is that progress can be made threefold - in diagnoses, interventions, and therapies, based on simpler genetic analyses, and techniques that will be examined in the following chapters.
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Academia vs. Industry

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Introduction

In the last few decades, there have been two major trends in the research and development (R&D) of new medical products. The first trend has been for academia to commercialize discoveries. The second trend has been for the pharmaceutical industry to externalize innovative R&D approaches in order to expand the ability to address complex and unmet medical needs (such as Alzheimer’s and Parkinson’s disease). The United States Bayh-Dole Act of 1980, also known as the Patent and Trademark Law Amendments Act, granted universities the ability to retain ownership of patents that were generated via federally funded research. Since then, both industry and academia have sought to profit from the more “commercialized” university research.

The global R&D landscape is constantly adapting to the ever-changing advances and changes in healthcare. In the past, the public sector (i.e. academia) has greatly contributed the basic science of drugs and biologics through research, while the private sector (i.e. industry) was responsible for the development and testing (from preclinical/clinical testing to approval and marketing). Due to the ever-rising cost of development, today’s industry is constantly seeking new ways to improve productivity, increase efficiency and decrease attrition. Many corporations have expanded R&D collaboration vertically with grants, licensing, and acquisitions, as well as horizontally with private-public partnerships and pre-competitive collaborations. Academia, on the other hand, has suffered from the flat or decreased funding via National Institutes of Health (NIH), with no increase of funding in sight. The proposed federal funding for research in 2013 matches the amount provided in 2012 (about $31 billion) and there are also talks in US Congress of decreasing this amount to aid in trimming the national deficit. Thus it becomes clear that both industry and academia must work together to meet their individual needs.

Academic Contribution to Personalized Medicine
Pharmaceutical drug development is a huge risk due to the large percentage of failure at the clinical stages. Only five to ten percent of clinical trials succeed. Moreover, to take a drug into late stage development and not have the ability to obtain approval for marketing is an enormous expense. According to Forbes, the average cost of bringing a drug to market is $1.3 billion. For major pharmaceutical companies the lowest cost for development is $4 billion and as high as a staggering $11 billion. Although industry offers the tools and information to translate research discoveries into practical applications for patients, academia offers a thorough understanding of the mechanisms of disease as well as expertise of patient care and clinical practice. In addition to identifying new uses for existing drugs, academic research has developed novel compounds for use against targets that the pharmaceutical industry has presumptively exhausted. Such is the case for HIV protease inhibitors. HIV patients previously treated with antiretroviral were given a combination treatment of Norvir (ritonavir) along with the protease inhibitor drug Prezista (darunavir). The pathway to this treatment was initiated by the research at Purdue University, where a nonpeptide protease inhibitor was discovered. This inhibitor was shown to have superior activity against a number of mutants that were resistant to all previously approved HIV protease inhibitors. Tibotec Therapeutics, now called Janssen Therapeutics (a division under Johnson & Johnson) was able to obtain US marketing approval in 2006. In the third quarter of 2012, the sales figures for Prezista were at $364 million and the US Food & Drug Administration (FDA) recently approved a new dosage (800 mg) that is projected to push annual sales above $2 billion in 2015. Academia’s initial role in the development of Prezista not only brought an immense profit to Johnson and Johnson, but more importantly, it ultimately helped to provide personalized treatments of many desperately ill patients.

Is the Industry Collaborating with Academia?

As patents on many of the current blockbuster drugs will continue to expire in the next several years, the pharmaceutical industry will have to look for innovative ways to develop novel therapies. Increases in industrial and commercial R&D expenditure have not translated into new approvals. An array of recent mergers and acquisitions signifies that the industry must seek more cost effective ways to deliver new drugs - Enter academia. Some major pharmaceutical companies have certainly taken a hint and began looking into new collaborations. For instance, Pfizer recently partnered with seven New York medical institutes to research biological drugs. In 2008, Pfizer entered a three-year partnership with a physiological modeling company and four major research universities to study insulin signaling in adipose cells with the goal of developing new treatments for diabetes and obesity.
Similarly, Sanofi collaborated with the University of California, San Francisco, to study aging, diabetes and inflammation; and Gilead is working with Yale University to research cancer. If Gilead’s collaboration with Yale is extended for the full 10 years, then Gilead will have contributed $100 million, the largest private contribution in the school’s history.

In March 2011, GlaxoSmithKline along with AstraZeneca (AZ) entered into a joint venture with the University of Manchester (UK) to study inflammation. Each partner will contribute $5 million dollars over three years and aim to translate the research, university expertise and resources into a medically usable drug. AZ, on its own, has collaborated with the French National Institute of Health and Medical Research to study cancer, inflammation and respiratory diseases. And finally, Takeda entered into an agreement with Kyoto University (Japan) to research obesity and schizophrenia. Fortunately for all involved, these are but a few examples and many more partnerships have been and will continue to be formed.

A great deal of inventions for molecularly targeted anticancer therapeutics have been driven by collaborative efforts between the pharmaceutical industry and academia. Historically, cancer target identification was the expertise of academic institutions; drug discovery, development, and diagnostics were the domain of the industry. Recently, the industry has taken a larger role in target identification and development, such as in the case of Herceptin (trastuzumab), which was discovered and developed by researchers at Genentech (now part of Roche). On the other hand, academia has shown that it can effectively develop drugs, as in the case of Erbitux (cetuximab). Collaborations between the industry and academia are evolving in the era of biomarker diversity and validation to support the development of personalized therapies. The discovery and development of breakpoint cluster region (BCR)-ABL kinase inhibitors like Sprycel (dasatinib) meant potential relief for patients suffering from chronic myelogenous leukemia who did not have a positive result from traditional treatment by Gleevec (imatinib). The industry provided important know-how in high-throughput screening and medicinal chemistry to generate drug candidates, while academic laboratories, with expertise in kinase structure and function, provided important insights into structural mechanisms for resistance. The combined efforts led to the development of next-generation inhibitors with improved resistance profiles.

Academic drug discovery can benefit from early intervention and collaboration with the industry. Today, pharmaceutical companies more readily take strategies that focus on open innovation. In 2009, Eli Lilly introduced the Phenotypic Drug Discovery Initiative, which makes their assays and expertise available to academic institutions. That same year, GSK created a patent pool, which attempts to remove intellectual property as a barrier to research for treatments of neglected diseases, such as malaria. A great deal of scientists in academic settings have molecules they would like to
explore as potential medicines, but for a number of reasons, such as insufficient funding or obstacles in
the drug discovery and development process, they are unable to pursue their ideas further. This vast
body of free knowledge creates an environment where academia can thrive in finding new personalized
solutions and treatments at minimal expense for the industry.

Despite the recent increase in industry-academia partnerships, several important barriers must
be overcome to ensure success for both sides. First and foremost, academic institutions should seek
partnerships that are heavily supported by faculty. Second, a transparent structure for corporate
arrangements must be present. Confidentiality, intellectual property, financing (including indirect
costs), and conflict resolution should all be clearly defined in these arrangements. Third, projects must
have well defined objectives and timelines. Fourth, academic leadership must be fully onboard with
being sponsored by the industry. Fifth, the industry must have a definite internal champion of the
proposed agreement. And last but not least, in order to have the formation of personal connections and
mutual trust, the partnership should be of a sufficient duration.

Conclusion

Personalized medicine attempts to discover gene variants associated with a certain drug class,
disease predisposition or subclass. It then tries to divide the patient population into subgroups on the
basis of biomarkers and ultimately, it determines the optimal treatment of each subgroup. Despite all
the knowledge that the pharmaceutical industry possesses, it is not an expert in personalized medicine.
In order to realize the full financial potential (and return on investment) of personalized medicine, the
industry must continue to form partnerships with various biotechnological companies (genomic and
diagnostic) as well as with academia. This model has worked well in the development of small
molecules, vaccines, and biologics; and it would foster innovations in medicine as it becomes more
personalized. A close and synergistic relationship between the industry and academia is crucial to
having a vibrant biomedical research capacity. With the emergence of several open innovation models,
mentioned previously, and the growing recognition by the industry for a need to change their R&D
operating model, the time has never been better for academia to take their place on the drug discovery
stage.
References


R&D productivity what does it mean?

R&D productivity is the relationship between the value created by a new product (output or outcome) and the investment needed to create it (input). Inputs can be measured in personnel, facilities, new technology and methods, funds needed … and outputs range from processes to patents, products, cost savings and therapies whose outcome are beneficial to customers (patients) and provide return on investment for the sponsors. Organizations that invest in R&D, whether in the biotech/pharmaceutical field or not, need to measure this success and track the impacts of different strategies and changes in research dollars spent. As much as these measurements of performance have been blamed for lack of creativity, innovation and motivation, it is important for management to understand where the value in putting money into R&D is. A breakdown of R&D productivity reveals two dimensions, efficiency and effectiveness that are necessary when aiming for at increasing productivity as a whole.

Dimensions of R&D Productivity (Paul et al., 2010)
“An effective R&D must encompass both of these components” so focusing on this model we will show how the Personalized Medicine approach could improve the declining biopharmaceutical R&D productivity.

**What is the problem at hand?**

For some time now, analysts have been predicting a problem with the biotech and pharmaceutical industry which may affect the sustainability of these organizations. Already facing patent cliffs and growing generic competition, the industry is also seeing a shrinking drug pipeline fueled by high failure to deliver positive results in the clinic; the number of new drugs approved by the FDA has been steadily decreasing over the years and, down 71% from 1996 to 2010 although biologics approvals remained constant.

**FDA drug approvals per year (Allison, 2012)**

![FDA drug approvals per year](image)

This decline can be attributed to many factors such as rising costs of R&D keeping investments at bay, more complex targets being prosecuted, tougher regulatory environment creating higher hurdles before approval to market and, constant organizational changes, clinical trial design failures, all of which reduce chances of success. Companies are beginning to learn that the older blockbuster drug development model may no longer be viable.

Take for example the clinical studies that led to the marketing of Gefitinib and Erlotinib, inhibitor of epidermal growth factor receptor (EGFR) for non-small-cell lung cancer (National Research Council, 2011). The early trials of these drugs only saw efficacy in 10% of the subjects and
although they received FDA approval, investigators had failed at the time to recognize the biological diversity in the patients as distinct subsets, namely between those that responded well to the drug and those that did not. This led to large, expensive and unsuccessful trials to some extent on a broad range of individuals which only contributed to increasing costs (bad for R&D efficiency) and pick-up side effects without adding any value to those who did not respond (bad for R&D effectiveness). Today we know that a natural mutation occurring in about 10% of the population is responsible for the increased sensitivity to these drugs (Morita et al., 2009) and that patients with the mutation enjoyed longer progression-free survival.

As evidenced above, this approach to designing clinical studies by recruiting subjects putting emphasis on the complexity of questions inherent to individuals’ genotype and phenotypes is problematic and conducive to failure. They require very large sample sizes which contribute to high costs on a per subjects basis, dilute out specific drug effect which may be present only in smaller but specific population subset. The challenge for biopharmaceutical companies is how to increase R&D efficiency by reducing cost per drug without affecting effectiveness (quality of the product) and one way to do this is via personalized medicine approaches.

**Why personalized medicine is important for drug R&D?**

Looking for new ways to design and run more successful clinical studies is a key strategy to any drug developer. According to Dimasi’s (2007) estimates out of pocket costs for the clinical period were $361 million versus $198 million for the preclinical period and when combined with the industry’s current 85% clinical failures for new therapies (Ledford, 2011), there is a crucial need to reinvent the drug development process. Companies have begun adapting technology to allow for electronic patient monitoring as a way to reduce costs from clinic visits and adaptive study designs are being adopted where the investigation starts out with a smaller cohorts with flexible protocols allowing for changes to the number of study arms, doses, and other parameters as the study progresses. This is a great opportunity for the industry to become creative in that space with their R&D approaches since many regulatory agencies that often required rigid study designs with large one size fits all trials understand that they are expensive and inefficient. This is the time for predictive, preventive patient-centric (personalized) medicine.

**Personalized medicine applied to R&D**
The personalized medicine approach to drug R&D relies on developing the right drug for the right target in the right patient population. This will increase the chances of success in the clinic, but also working backwards by starting with the patient, it can have a positive impact on productivity by dictating how to approach new drug programs based on the therapeutic needs of a particular individual or group of individuals. By integrating clinical information from patients’ medical diagnoses with molecular information obtained from the various diagnostic biomarker tools available, it promises to deliver greater outcomes for patients with clinically significant therapeutic effects and with favorable safety profiles. Personalized medicine when applied to R&D is expected to allow scientific insights early on that should facilitate the development of more therapeutics with a more pronounced effect in their target population. This will eventually lead to lower attrition rates and lower clinical trial costs.

**Impacts on R&D productivity:**
Better understanding of a disease that is not gained by traditional methods of running empirical trials on a large sample size in order to make out a small statistically significant effect.

Investigators will look at genetic, molecular and phenotypic data before identifying pathways that are most critical driver of a given human disease. In the laboratory this translates into better selection of targets.

Gain better understanding of clinical outcomes in relationship to a compound’s ability to affect a disease pathway.

More efficient clinical trials resulting from the use of biomarkers to select appropriate subpopulations of patients with distinct biological causes of disease.

Quick an early decision to terminate a study if a specific group is not responsive without disrupting the study progress in other groups that do respond well.

Lower costs due to smaller trials. A study by Cutting Edge Info (2011) found that Phase I clinical trials cost upwards of $21,000 per patient while Phase II and III were about $36,000 and $47,000 respectively. The Gefitinib study example we used earlier illustrates this well. 90% of its costs went to patients that never had the chance of seeing any benefit.

A poster child for R&D applications of personalized medicine

According to a transcript of a Pfizer presentation at Barclays Capital Global Healthcare Conference Pfizer’s Worldwide R&D president Michael Dolstein presented their efforts to develop a new generation of lipid lowering drug targeting PCSK9 as a poster child for personalized medicine applications for R&D. This insight came when, thanks to high throughput genetics screening, people with a rare mutation in PCSK9 gene had very low lower LDL levels compared to others and were also living a normal life. This information was then fed back to the labs with companies now developing drugs (both small molecules and antibodies) aimed at reducing function of PCSK9 protein eventually leading to lower LDL levels. These products once marketed will be target individuals that do not currently benefit fully from conventional statin therapy like Lipitor, Crestor and the likes.

In Summary

Changing drug R&D from a “lottery model”, the more you play (the more projects or the more people you recruit for clinical trials) the higher your chances at winning to this Precision Medicine model thus offers the opportunity to impact the two dimensions of R&D productivity, efficiency and
effectiveness, with more affordable and innovative drugs carrying high quality information via less costly R&D, in the end more value to the patient.
References

Introduction

The rise of personalized medicine creates vast opportunities in healthcare. The development of companion diagnostics allows medical professionals to tailor disease treatment for optimal safety and efficacy using a patient’s genetic profile or related information. This partnership between the (bio)pharmaceutical (pharma) and diagnostics industries will increase the quality of healthcare, improve productivities in research and development (R&D), and improve the cost of healthcare, in some cases. Entering its second decade, personalized medicine has been slow to take off. This is not for a lack of science or technology. The recent advances in the ‘–omics’ sciences (proteomics, genomics, pharmacogenomics, etc.) have allowed drugs to be designed such that they are complementary to the proteins, genes, and metabolites of the patient on a molecular level.

It is becoming apparent that the barrier rests on the economics side and the poor alignment of incentives between key stakeholders. The challenge to pharma is determining how to structure their current business framework to stimulate development in this innovative period of patient care. How does personalized medicine fit with the traditional business models and what are the value systems that will encourage research and development? There are questions surrounding drivers of return on investment (ROI), leaving investors and industry leaders to exercise caution surrounding the excitement.

With its new markets and new value networks, successful implementation of personalized medicine represents a disruptive innovation which has the potential to overtake the traditional establishment of the healthcare industry. Clayton Christensen, author of ‘The Innovator’s Dilemma,’ finds that such innovations are often slow to develop and, because they initially appeal to niche markets, established industries may fail to recognize their significance. The rapid rate of improvement
in these emerging technologies is often greater than the sustaining improvements of the established firms and will eventually disrupt their market position. This appears to be the case for personalized medicine, as its gradual emergence into mainstream healthcare is forcing pharma to rethink their current business practices and charter into unfamiliar territory. Within the labyrinth of uncertainties, trial and error, there will be winners and there will be losers but companies that wait for sound market research and planning are destined to fall behind, sacrificing their first mover advantage to this inevitable reality in the future of healthcare.

**Business models for personalized medicine**

*Traditional business model of the pharmaceutical industry*

Of the many stakeholders in the healthcare industry, pharma faces the greatest dilemma in the emergence of personalized medicine. The traditional business model of the pharmaceutical industry is often termed the blockbuster or one-size-fits-all (OSFA) model. Blockbuster drugs are those therapies used to treat large disease markets and bring in at least $1 billion in annual revenue. While this model has created significant financial success for the pharmaceutical industry, the need to address its shortcomings is becoming apparent. In 2006, only 2 out of 10 approved drugs were able to recoup their cost of development (Newman, 2010). Thus, even when an approved drug is earning money for the company, it is often not enough to recover the cost for the roughly 15 years it took to get to market. Additionally, focusing R&D efforts on a small group of large disease markets, where the drug is applicable to the greatest proportion of the target population, has led to smaller product portfolios and reduced innovation. Failing to address the genetic variation of the disease population requires much larger, longer, and expensive clinical trials to analyze the safety and efficacy on a large and varied group. Rather than treating an entire disease population, personalized medicine seeks to identify key biomarkers allowing specific patient profiles to be targeted. This narrows the patient pool for any given drug but increases the likelihood of treatment success.

Pharma will be forced to transition its business model from the philosophy that a drug should be used broadly by as many patients as possible to one that addresses segmentation of the patient pool where treatment regimens will be applied to smaller, well-defined target populations. Medium-sized firms that depend heavily on a few blockbuster drugs are the most vulnerable as they will see their market share fragmented. The industry as a whole will need to respond by expanding their capabilities, creating large, diverse product portfolios that address multiple small- to moderately-sized disease
markets rather than a few blockbusters. Change to established practices will be required in all stages from R&D, to commercialization, manufacturing, and marketing and sales (Figure 1).

In spite of these barriers, most companies are making progress towards integrating personalized medicine into their organizational structures. From 2006 to 2010, investment in personalized medicine increased 30% even in a down economic climate. This growth is expected to continue over the next five-year interval (Milne & Zuckerman, 2011). Those that work towards adoption of personalized medicine are poised to achieve the competitive advantage that will emerge from a stratified target population, increased efficiencies in clinical development, greater patient safety, and improved treatment success.

Figure 1. Comparison of traditional and personalized medicine business models
Rx: drug; Dx: diagnostic; FDA: Food and Drug Administration

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<th>Blockbuster/OSFA Model</th>
<th>Personalized Medicine</th>
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<td>Large, extended duration</td>
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<td>Broad disease population</td>
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Pharma and Diagnostics
There is an unavoidable connection between pharma and diagnostics in personalized medicine and the business practices of these two industries could not be more different. Pharma is characterized by long timelines, huge R&D costs, long and complex regulatory processes, and high product prices. For diagnostics, lead times are short, R&D costs are low, there is less regulation, and the product price
is low, relatively speaking (Carlson, 2012). As a result, methods for calculating net present value (NPV) and ROI from either a drug or a diagnostic lack agreement also.

However, there is a way for these two industries to work together. We have already witnessed many successes in companion diagnostics. Take Genentech’s breast cancer drug, Herceptin, considered to be the poster-child for personalized medicine. Normally, the FDA would reject approval of a drug that was effective in only 25% of breast cancer patients. However, the diagnostics company Dako AS developed an assay that identified elevated levels of the protein marker HER-2 in patients who were responsive to treatment. The FDA approved the drug for only those patients exhibiting overexpression of HER-2. Annual sales of Herceptin now top $6 billion (Kulkarni & McGreevy, 2012). The relationship between Genentech and Dako AS proves that a value chain incorporating these two business models is feasible; the complexity arises in how to develop and sustain it.

Many leading pharmaceutical companies are responding to the demand for personalized medicine by building up their diagnostics assets. Last year, Novartis acquired Genoptix for $470 million. This year, GlaxoSmithKline acquired Human Genome Sciences for $3.6 billion. Given the distinct business environments of pharma and diagnostics, analysts caution against incorporating combined diagnostics capabilities under the framework of the mainstream business. The reason is not that pharma’s senior management does not trust the technology, but the business model is beyond their expertise of traditional drug development and commercialization. Primary concerns are the small margins, short market cycles, and uncertainty surrounding diagnostics reimbursement policies. For the company who still prefers developing in-house diagnostics capabilities, look toward companies holding impressive innovation portfolios to consider how this can be accomplished. IBM, Unilever, Cisco, and Procter & Gamble had innovation arms that functioned independently of the mainstream business. These units were responsible for the development and commercialization of the technology up to a stage where the organization would decide how to proceed, whether to stop funding, continue development, integrate into the existing business, or spin-off (Lester, 2009).

**Co-development of a drug and diagnostic**

Most pharmaceutical companies are choosing to partner with diagnostics companies for co-development of the drug and diagnostic. Timing is a crucial factor in maximizing the benefit for both partners. There are two main convergence scenarios for co-development:

1. Early convergence - at the beginning of the R&D process
2. Late convergence - beyond Phase II or Phase III clinical trials.
Early convergence (Scenario 1) is most beneficial to pharma. Use of a novel biomarker could aid in confirming the drugs mode of action. Access to the biomarker early in development also allows the development team to ‘kill it early’ in which development is stopped as soon as success is looking less likely, saving the expense of entering more expensive stages of development. Benefits also include smaller, better-defined clinical trials and decreased risk of failure in Phase I and Phase II.

For the diagnostics company, Scenario 1 bears the greatest risk. This early commitment ties the fate of the diagnostic to that of the drug. Considering that most drugs fail in Phases I and II, the probability of investing resources into a companion diagnostic that may never be commercialized is high. Late convergence (Scenario 2) is more favorable for the diagnostics company. By converging business models later in development (beyond Phase II), the probability of FDA approval is greatly increased. Regardless of early or late convergence, the uncertainties surrounding reimbursement strategies make it difficult for a diagnostics company to justify input of substantial resources into developing a companion test when the risks of failure of the therapeutic are so high. The diagnostics firm could still consider alternate markets for the test, but it then becomes a matter of how much time, money, and other resources were invested before this was realized.

This lack of incentive for the diagnostics company is the reason many industry analysts propose that the pharmaceutical company assume responsibility for the costs to develop the companion test, yet the diagnostics company will retain rights to the test. In the instance that the therapeutic fails in development, the diagnostics company may still pursue development in other, related pipeline products with the same pharmaceutical company (Lester, 2009). Risks are shared and investment in not completely lost, creating additional opportunities for both players. Such a business model is certainly complex, but could provide the stimulus for diagnostics companies to find co-development more attractive.

**Box 1: NPV and ROI**

**Net present value (NPV)** compares the value of a dollar today to the value of that same dollar in the future, taking inflation and returns into account.

**Return on investment (ROI)** measures the efficiency of an investment by calculating the return that an investment produces.

*Source: Investopedia*
Drivers for optimizing ROI

Significant resources have been poured into researching and understanding what drives development and commercial success of targeted therapies. A 2007 McKinsey report of the top pharmaceutical and biotechnology companies found that as many as 50% of drugs in development had an associated biomarker, yet less than 10% of those drugs were expected to be launched with a companion diagnostic (Davis, et al., 2009). Such statistics highlight the lack of incentive, fueled by a lack of overall understanding. What is required for commercial success is not merely a combination of drivers for a stand-alone diagnostic and a stand-alone drug, nor is it simply good science and a viable market. Although the current blockbuster model has proven to be less productive of late, without a model specifically designed for personalized medicine, the industry naturally falls back on historical practices. Using the blockbuster model results in an overestimation of the resources required in the more efficient development process of a targeted therapy, while underestimating the proactive approach necessary to encourage adoption of the companion test. When applying the blockbuster model to personalized medicine, it is no wonder that investors are slow to move. Targeted therapies require different resources, different inputs, and market success is dependent on a different set of drivers. Diaceutics, the leading personalized medicine consulting firm, has identified ten drivers to optimizing returns in personalized medicine (Table 1).

Table 1. Ten financial drivers in personalized medicine
Rx: drug; Dx: diagnostic; OSFA: one-size-fits-all

<table>
<thead>
<tr>
<th></th>
<th>Financial Driver</th>
<th></th>
<th>Financial Driver</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Optimize R&amp;D investment</td>
<td>6</td>
<td>Higher propensity to prescribe</td>
</tr>
<tr>
<td>2</td>
<td>Rx pricing</td>
<td>7</td>
<td>Improved Rx compliance</td>
</tr>
<tr>
<td>3</td>
<td>Earlier Rx market revenue</td>
<td>8</td>
<td>Extend Rx life-cycle</td>
</tr>
<tr>
<td>4</td>
<td>Faster Rx adoption</td>
<td>9</td>
<td>Optimize Dx adoption</td>
</tr>
<tr>
<td>5</td>
<td>Better Rx differentiation</td>
<td>10</td>
<td>Adjust for OSFA tax/bonus</td>
</tr>
</tbody>
</table>

Source: Diaceutics (Roth, Keeling, & Smart, 2010)

The firm that takes these drivers into account and allocates the necessary resources to them will see a substantial increase in the net present value (NPV) of these therapies. As the adoption and sales curve shifts earlier in time, the firm captures the market share sooner, leading to an overall increase in the ROI. Remember the success story of Herceptin discussed earlier? Incorporating the Diaceutics
CBR Financial Benchmarking Model finds that the Herceptin franchise lost an estimated $3 billion in additional revenue as a result of a poorly executed strategy (Roth, Keeling, & Smart, 2010).

**Optimize research and development investment**

Personalized medicine is heralded by many as the savior of R&D productivities, but there is little consensus about how this will play out. It is generally accepted that companion diagnostics will lead to smaller Phase III clinical trials, but whether this will result in shorter development times and overall lower R&D costs has been debated. While it would seem intuitive that the outcome of smaller Phase III trials would be shortened development times, one must consider the complexities of recruiting patients with a defined genetic profile to participate. The potential for lag time in diagnostic development and the uncertainties with the current US regulatory environment must also be considered. Some suggest that the inclusion of biomarkers, pharmacogenetics and diagnostics will require additional investment than what is typical with a stand-alone drug. Others argue that having a better-defined patient population will reduce the overall failure rate in development and allow R&D budgets to decline. Despite how costs at this particular stage will be affected by targeted therapies, it is safe to assume that while investment is likely to increase, there is great probability that it can be recaptured later in the value chain.

**Revenue strategies**

A widely held assumption is that targeted therapies will never generate the revenue that is possible with blockbuster drugs, but there are conflicting reports based on what drivers and assumptions are applied to the economic model. An MIT study found that the NPV of a targeted therapy for a large indication such as lung, breast, or prostate cancer, is significantly lower than that predicted for the blockbuster model (Trusheim & Berndt, 2012). Even maintaining a substantially large market share, the NPV still drops from $1166 million to $484 million (Table 2).

With the anticipated increase in patient response, there is an opportunity for payers to support pricing premiums in the future. The MIT study argues that the increase in revenue per patient could shorten but not surpass the gap between blockbuster and targeted therapies. Raising reimbursement costs seems counterintuitive to the goals of personalized medicine but one must take into account the overall net reduction in treatment costs that is likely to occur with more effective treatment regimens (better patient response, shortened duration of treatment, less trial-and-error).

**Table 2. Economic model defining feasible development space for private sector innovators**
### Model parameters

<table>
<thead>
<tr>
<th>Blockbuster drug, large cancer</th>
<th>Stratified population, large cancer, high share</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost of development (US$ million)</strong></td>
<td>400</td>
</tr>
<tr>
<td><strong>Years of development</strong></td>
<td>7</td>
</tr>
<tr>
<td><strong>Net patent life (years)</strong></td>
<td>13</td>
</tr>
<tr>
<td><strong>Number of eligible patients/year</strong></td>
<td>200,000</td>
</tr>
<tr>
<td><strong>Revenue per patient (US$)</strong></td>
<td>20,000</td>
</tr>
<tr>
<td><strong>Peak market share (of eligible) (5%)</strong></td>
<td>40</td>
</tr>
<tr>
<td><strong>Peak patients treated</strong></td>
<td>80,000</td>
</tr>
<tr>
<td><strong>Peak revenue (US$ million)</strong></td>
<td>1600</td>
</tr>
<tr>
<td><strong>Years to reach peak</strong></td>
<td>6</td>
</tr>
<tr>
<td><strong>Costs of revenue (%)</strong></td>
<td>40</td>
</tr>
<tr>
<td><strong>Taxes (%)</strong></td>
<td>35</td>
</tr>
<tr>
<td><strong>After tax margin (%)</strong></td>
<td>39</td>
</tr>
<tr>
<td><strong>Peak year net income (US$ million)</strong></td>
<td>624</td>
</tr>
<tr>
<td><strong>Discount rate (%)</strong></td>
<td>11</td>
</tr>
<tr>
<td><strong>NPV (US$ million)</strong></td>
<td><strong>1166</strong></td>
</tr>
</tbody>
</table>

*Source: Trusheim & Berndt, 2012*

Another factor that must be considered is what some in the industry refer to as the OSFA tax. This ‘tax’ is factored into the costs of drug development to account for the millions of dollars in annual litigation expenses that may be brought against the drug developer in response to adverse events. With the anticipated increase in drug safety that comes with a better-defined, well-matched patient population, this OSFA tax can be considered a bonus (Roth, Keeling, & Smart, 2010). The impact that avoiding this significant revenue loss would have on pricing strategies may reduce or eliminate the need for higher price points.

These two opportunities for cost savings highlight the ultimate goal of personalized medicine to streamline the overall R&D process. By reducing the trial-and-error nature of healthcare, companies
are wasting fewer resources. In turn, the value chain is more efficient, more sustainable, and the value proposition grows (Lechleiter, 2007). In the emergence of personalized medicine, there are a multitude of barriers, accompanying opportunities, and knowledge gaps. The MIT study highlighted additional economic barriers to development of personalized medicine and potential policy actions to challenge these barriers and you are encouraged to read it.

The Diaceutics PM Financial Benchmarking Model sharply contrasts the predictions of the MIT study and illustrates the potential for personalized medicine to exceed the return seen by blockbuster models. What they found was that applying the drivers to adoption (Table 1) and allocating resources appropriately delivered a positive NPV in the range of $57 million to $311 million over the base case of $195 million for a stand-alone therapy (Keeling, Roth, & Zietlow, 2012). Effective planning was the key factor in determining where a company would fall in this range. Even taking the most conservative outcome where the company took the least proactive approach in planning, the consideration of these drivers still generated an additional NPV reservoir of $57 million over that of a stand-alone drug. Acknowledging the sensitivity of such analyses to the cost of capital and discount rate assumptions, Diaceutics reports that “estimates of the market impact of all drivers would need to overestimated by 33% before our NPV would become negative” (Keeling, Roth, & Zietlow, 2012).

**Market diffusion and adoption**

Any practice that moves a product to market faster will shift the sales and adoption curve to generate a faster ROI. Shorter clinical trials and reforms to improve efficiencies in the US regulatory approval process would aid this early-to-market opportunity. Another key factor is market adoption. Diaceutics states that the average time for a drug to reach peak sales is 4.5 years. The MIT economic model above lists this sales peak at 6 years. Regardless of the estimate you use for drugs, the market diffusion and adoption of diagnostics is much slower, spanning approximately 15 years (Keeling, Roth, & Zietlow, 2012). For pharmaceutical management teams who are expecting the companion diagnostic to drive drug adoption, this time span will clearly destroy the value of the drug. This paper will not delve into the details of diagnostics development and adoption, but one key driver to test adoption is test availability, from the physician’s point of view. Test availability includes:

- How accessible is the test when the physician requires it?
- Technical complexity of the test
- Turnaround time for results
Ease of interpreting the results

These factors should be considered by the diagnostics company during development phases. The pharmaceutical company must also consider these factors. In selecting a diagnostics partner for a companion test, the pharmaceutical team must be sure to choose the technology that will encourage adoption. Consider the software industry many years ago. Too often, the manuals that accompanied the software technologies were so complex and full of computer jargon that a user would need to be a software engineer themselves to understand them. For the diagnostics developer, be sure to avoid this tendency and design the test to be interpreted by a variety of users in the healthcare community.

Closely related to test availability is the physician’s propensity to prescribe (P2P), the likelihood that a physician will prescribe the drug in response to a positive test result. The safety and efficacy of a targeted therapy will not create value for stakeholders if the physician is either unaware or apprehensive about the treatment. There is a danger in assuming that simply informing the physician about a drug will automatically lead them to its prescription. Going back to Herceptin; research shows that even after seven years of this drug being on the market, 20% of physicians did not understand how to correctly interpret the results of the test. In 2007, only 40% of early-stage and 70% of advanced stage breast cancer patients exhibiting HER-2 overexpression were prescribed Herceptin, despite being ideal candidates for this targeted therapy (Roth, Keeling, & Smart, 2010).

Overcoming such obstacles is the responsibility of those commercializing the drug. For physicians to adopt targeted therapies there needs to be great effort invested toward ensuring that perceived complexities of the test do not pose a barrier for entry in use of the drug. Equally important is communication of the value and significance of the drug itself. Producing the best therapy for any given disease returns no value to any of the stakeholders if it never reaches the patient. Healthcare providers are one of those central stakeholders in personalized medicine and investment in educating them on the goals and benefits of targeted therapies is essential to ensure commercial success.

**Market share and product differentiation**

Providing product differentiation is vital to acquiring a competitive advantage for your company. In the market, what unique features of your product distinguish it from the competition? Does this feature appeal to a specific or niche market where consumers place greater value on this distinction? The traditional business model of pharma has placed greater emphasis on appealing to the masses rather than meeting the diverse needs of target customers. Evidenced by the ballooning R&D budgets and dwindling output of this sector, the blockbuster strategy is plagued by a focus on market
share rather than a focus on profit. By differentiating itself from the competition, a personalized therapeutic has the opportunity to realize “monopolistic benefits” by serving a specific customer (Roth, Keeling, & Smart, 2010).

Let’s consider the argument that segmentation creates smaller markets. Across all categories, the average response rate for drugs is 50% (Kulkarni & McGreevy, 2012). If a company commercialized a drug for a patient population of 1000 but the treatment is only effective in 500, then this drug is for a patient population of 500, not 1000 (Roth, Keeling, & Smart, 2010). The half of the patient population that received no benefit from the drug is likely to discontinue its use. In this way, targeted therapies do not represent smaller markets, only better-defined markets.

The case of Actos (Takeda), a peroxisome proliferator-activated receptor (PPAR) agonist, shows how segmentation can actually result in larger markets. Actos is used in the management of diabetes. In 2005, it was estimated to have a 50% market share with a total patient population believed to be around 3 million diabetics (Roth, Keeling, & Smart, 2010). As it turns out, there were approximately 9 million in the US with insulin-resistant diabetes. By underestimating its market 3-fold, Actos missed an opportunity to appeal to a much larger patient pool. A companion test could have helped Actos accurately identify and market to those patients that could benefit from the drug. Through increased safety and efficacy, personalized medicine allows product differentiation in a crowded marketplace. This ability to better define exactly who your best patients are can lead to patient pools and revenue streams comparable to that of the blockbuster model.

**Conclusion**

Companion diagnostics represents a new business model for both the pharmaceutical and diagnostics companies. For pharmaceutical companies who have little experience in the discovery and development of biomarkers or diagnostics, the learning curve will be steep. However, this need to adapt is supported by the declining productivity within the pharmaceutical and biopharmaceutical R&D sectors. Drugs launched in 2012 were starting discovery in 1997. Half of this time was spent in clinical development. The average cost for pharma to develop a new drug can start at $5 billion and top $10 billion. When R&D spending accounts for approximately 20% of the total sales, it is evident that the current business model is unsustainable from both ends of the stakeholder spectrum. Pharma will be unable to continue recouping the cost of development for only 2 out of 10 approved drugs. Passing down these incurred costs to the payer is not a feasible long-term strategy, especially considering a lackluster average patient response rate of only 50% for many of these drugs. New practices that increase efficiency are welcome, but sustaining improvements are unlikely to bring the
necessary overhaul required to reform the current system. In the ongoing theme of disruption, the well-established organizations are often left bruised and battered by the rise of new entrants. But industry leaders can take comfort in Christensen’s proposal that “today’s healthcare leaders can educate themselves and play a major role in disrupting their own business, as IBM did when it introduced the personal computer” (Kulkarni & McGreevy, 2012). Established norms are slow to change and new capabilities take time to cultivate, but companies that can make the leap will be better off than they were before.
References


Insuring Diagnostic Testing: Coverage & Ethical Concerns

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Introduction

As advances in biotechnology pave the way toward personalized medicine in the form of diagnostic test kits, these new product tools face significant barriers before adoption of personalized diagnostic testing becomes a mainstream clinical practice. One of these barriers is the uncertainty surrounding reimbursement for diagnostic tests. Each diagnostic test may involve a myriad of coding, coverage, and payment policy assessments prior to insurance conclusions (Cohen, 2012). Although insurers are actively revising protocols and policies in order to adapt to the increasing number of laboratory tests, the existing systems for reimbursement did not anticipate a need for test-specific coverage/payment (Cohen, 2012).

Diagnostic Reimbursement

Insurance Company & Payee Standpoint

Personalized medicine is not truly personalized for each individual; diagnostic tests essentially identify characteristics that stratify patients into sub-populations. The payers predominate concerns with personalized medicine are the accuracy of these tests in creating the sub-populations due to limited data used by the manufacturer when seeking regulatory approval and concerns about the efficacy of the relationship between the diagnostic test and the subsequent health outcome (Cohen, 2012). Even when an FDA approved drug or biologic requires use of a biomarker test prior to prescription per the label, such as the drug Warfarin (an anticoagulant used to prevent blood clots), pervasive doubt is observed (Cohen, 2012). In this case, the American Heart Association (AHA) demonstrated little change in their prescribing guidelines due to insufficient randomized data from Warfarin prospective trials and the Medicare system decided not to cover the diagnostics for Warfarin.
patients because of lingering doubts regarding the test’s ability to identify a patient sub-group and the appropriate sub-group dosing (Cohen, 2012).

Personalized medicine coverage is also affected by Medicare’s continued trend of surpassing its targeted expenditures; recently cuts to provider spending were mandated (White, 2012). These cuts are influenced by Medicare Administrative Contractors (MACs) who handle claim payment contracts. Several large MACs instituted new coding for diagnostic tests as of March 1, 2012 that will essentially force government to decide whether it will reimburse laboratories for each genetic test code by charging on the standard lab fee schedule or if they will move the payment to the physician’s fee schedule (White, 2012). The method of Medicare reimbursement for diagnostic tests will clearly impact either the laboratory’s decision to use the test or the physician’s clinical prescription of the test. Due to these kinds of concerns, insurance companies and payers fear that diagnostic coverage will result in use of the tests on many patients in order to identify comparatively few to benefit from modified dosage (Cohen, 2012). It is the predictive quality of the test that must be more thoroughly assessed through rigorous manufacturer testing in order to prove the cost effectiveness from the payer perspective (Cohen, 2012).

Industry Standpoint

Diagnostic and therapeutic test manufacturers face the obstacle of third party reimbursement in order to successfully market their novel products. Insurance company decision criteria for reimbursement are ambiguous despite the fact that payment decisions are made individually for each diagnostic test (Cohen, 2012). Blue Cross and Blue Shield (BCBS) plans provide the most clearly publicized policies in an environment where only 20% of insurers give unrestricted access to coverage policies (Cohen, 2012). Clear BCBS policies state that evidence of a connection between the test and health outcomes as well as FDA approval must be provided; despite regulatory approval, payers frequently determine that diagnostic tests are investigational and do not authorize payment (Cohen, 2012).

In response to policies set forth by insurance companies, manufacturers must strive to provide clinical testing that supports conclusive predicative health outcomes in a defined patient sub-group. Beyond this requirement, manufactures are also faced with daunting barriers in the current structure of reimbursement policy and lack of diagnostic testing incentives for clinicians. In a recent study investigating the barriers to reimbursement for an FDA approved and clinically predictive breast cancer diagnostic test, clinicians stated concern that use of such diagnostic tests might result in less
drug or procedure reimbursement; a decision to decline chemotherapy for example based on a diagnostic test result would reduce the provider’s payment for that treatment (Weldon, 2012). Both clinicians and insurance payers acknowledged that the healthcare provider’s time dedicated to diagnostic test decision-making is not coded for reimbursement in such a way that it creates an incentive similar to preoperative time spent for surgery or other procedures (Weldon, 2012). Interestingly, the study also indicated that patient genetic counseling and supportive psychological care, which are often significant components of diagnostic testing, are also not well reimbursed (Weldon, 2012). If required, genetic counseling created large out-of-pocket sums for patients and resulted in delayed diagnostic testing (Weldon, 2012). These gaps in diagnostic reimbursement for clinician’s decision making time and the patient’s need for counseling need to be addressed in order for diagnostic testing to be accepted throughout the healthcare community.

**New Models of Coverage**

Clearly existing drug and procedure reimbursement does not incentivize the use of diagnostic testing. A significant step towards improved personalized medicine coverage would include a paradigm shift in payment model to a bundled or episode payment where insurance payers provided reimbursement for a collection of services rather than pay-by-service or lump sum coding. The focus of payment must shift from short-term health care procedures to patient health outcomes (Association of Clinical Chemistry, 2007).

The associated preventative savings in hospital stays, doctor’s appointments, and procedures must be communicated in order to properly allocate reimbursement payments (Association of Clinical Chemistry, 2007). Advocacy groups such as the Personalized Medicine Coalition (PMC) work to represent academic, industrial, patient, provider, and payer communities and collectively communicate the cost benefits of personalized medicine as well as the significantly improved health outcomes; both of these messages are key elements of changing current reimbursement policy (Association of Clinical Chemistry, 2007). For example, Medicare’s coinsurance rate of 20% is fixed regardless of a drug’s effectiveness or the associated clinical outcomes; these drug payment policies must change to account for health outcomes in order to pave a feasible coverage pathway for diagnostic test reimbursement (White, 2012). If Medicare provides coverage for effective diagnostic tests in order to guide prescription of companion drugs, personalized medicine will move rapidly towards a tipping point (White, 2012).

**Ethical Concerns**
**Genetic Discrimination**

Due to the predictive nature of diagnostic testing, there is a pervasive concern regarding genetic privacy for the associated diagnostic test results. The fear is that genetic information such as an individual’s propensity for breast cancer could be used to discriminate against these individuals; employers might look at genetic testing data as a factor in their hiring practices or refer to information collected during employee wellness testing to determine promotions. Insurance coverage could be adjusted based on an individual’s genetic testing results or that of their family.

The increase in diagnostic test availability and the fact that genetic information and family history patterns are part of good standard of care in today’s healthcare environment makes the concern regarding use of this information even more relevant. Employers often ask their workers to participate in wellness programs that assess the occupational exposure of the workplace as well as the employee’s current health (Feldman, 2012). While these practices should continue as demonstrations of good corporate responsibility and protection against employer discrimination and already existed in over 30 states, the advent of personalized medicine created a perceived need for further protection against genetic discrimination possibilities (Bermudez, 2011).

**Genetics Information Nondiscrimination Act**

In order to address the widespread concern for genetic privacy and implement a preventative measure to protect against genetic discrimination, Congress proposed the Genetics Information Nondiscrimination Act (GINA) in 2007. According to polls conducted by the Genetics and Public Policy Center at The Johns Hopkins University in 2007 (prior to the passage of GINA), 93 percent of Americans believed that genetic privacy should prevent employers from using testing data for either hiring or promotion and insurers from increasing premiums or reducing benefits based on genetic testing predictions and seventy six percent of Americans believed that these genetic privacy rights should be protected by congressional action (Association of Clinical Chemistry, 2007). The Act, which ensures these protections against employer and insurance discrimination under Title II are enforceable, was overwhelmingly passed in Congress in April of 2007 and subsequently enacted by Senate vote in May of 2008 and became law (GINA, 2008).

In January 2011, the Equal Employment Opportunity Commission (EEOC) regulations implementing the GINA provisions took effect (Bermudez, 2011). Section 201 of the Act defines the term “genetic information” as information about an individual that is obtained through genetic testing as well as testing information about family members and disease outcomes in family members (Bermudez, 2011). The Act is intended to provide protection in states where there is no existing equal
or greater genetic privacy law (Bermudez, 2011). Since the recent regulations took effect, employers nationwide have taken action to include genetic information in their human resources policies and have trained their leadership on GINA in order to maintain compliance (Bermudez, 2011).

Employers and insurance companies must keep genetic information confidential and separate it from an individual’s personal file while updating all employment forms to remove existing genetic information that is not necessary for other state or federal regulatory purposes (Bermudez, 2011). For insurers, GINA regulation also specifies that group health plans issued after GINA enactment but prior to regulation implementation be nondiscriminatory (Bermudez, 2011). GINA not only provides protection against changes in insurance coverage, it also prevents insurers from requesting, purchasing or using genetic information obtained prior to health plan enrollment in order to determine qualification for enrollment (Bult, 2010).

Conclusion

Diagnostic test payers’ hesitancy to reimburse indicates that they are challenging the drug manufacturers’ blockbuster mentality. Whereas the previous blockbuster drug model targeted huge patient populations and acknowledged that the therapy would be ineffective for many, personalized medicine blockbusters such as the widely known cancer treatment, imatinib, utilizes targeted enzyme inhibitors to produce significant benefits in a narrow patient population (White, 2012). In order for payers to be convinced of the overall benefits of diagnostic testing, personalized medicine manufactures must conclusively demonstrate their tests predictive nature as well as the associated dosage for indicated sub-groups. This level of clinical data should convince insurance payers that diagnostic testing is predicative rather than purely investigational and has substantial quantitative health outcome benefits for the identified patient sub-population.

While the passage and implementation of GINA demonstrates that genetic discrimination is proactively treated as a civil rights issue at the federal level, lawmakers and advocacy groups will need to remain vigilant to the rapidly changing personalized medicine environment in order to keep privacy laws on par with current biotechnology practices.
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Regulation is the evaluation of a drug’s safety, efficacy, and toxicity. Preclinical studies are conducted in animal models to demonstrate that drugs are not carcinogenic, mutagenic, teratogenic, or detrimental. Initial dosage amounts as well as potential signs/symptoms from administration can be identified from preclinical data. The pharmacological profile of a drug is established; the capability of
the basic manufacturing processes in drugs with consistent levels of quality, purity, and stability is
determined (Corr & Williams, 2009).

All preclinical data is compiled into an Investigational New Drug (IND) application (an
approved marketing application required by federal law for transporting/distributing a drug across state
lines) (Food and Drug Administration, 2011, June 6) and filed with the FDA with the hope that the
agency provides the go-ahead to begin Phase I Clinical Trials (Corr & Williams, 2009).

Phase I clinical trials are generally performed on healthy subjects or patients of interest with the
aim of evaluating safety and appropriate dosage ranges and identifying side effects. Information on
combinatorial effect, pharmacokinetics, and dosage ranges that minimize side effects can be collected
(Corr & Williams, 2009).

Phase II clinical trials consists of two phases: Phase IIa and Phase IIb. Phase IIa trials allow for
the initial proof of concept (POC) to be attained. Phase IIb are performed to strengthen the POC by
evaluating comparator agents and broader dosage ranges of the drug of interest (Corr & Williams,
2009).

The purpose of Phase III Clinical Trials is to provide proof of drug efficacy and that minimal
side effects arise from administration. The new drug can also be compared to current treatments or a
placebo and is generally administered to several thousand patients. Investment into Phase III is
typically higher due to the number of patients, duration of trials, and various geographies that trials are
held. A New Drug Application (NDA) can be filed with the FDA if Phase III Clinical Trials are
successful. The FDA may take up to one year from the time of submission to review an NDA (Corr &
Williams, 2009).

Phase IV is the marketing and safety monitoring phase and can be conducted once a firm
receives regulatory approval for an NDA. The FDA may request an organization to provide more
long-term safety and efficacy data, driving post approval clinical trials. A firm may also chose to
begin expanding indications or administration routes of a drug and assess a drug’s use in a wider and
more diverse population base. Phase IV must comply with the standards set forth by the agency for
successful completion of Phase III trials (Corr & Williams, 2009).

Medical Devices Regulation

Medical Devices used in the US are regulated by the FDA’s Center for Devices and
Radiological Health (CDRH). Device discovery and development tends to be more variable and quite
different than that of biologics. The primary reason for the increased complexity in the device world is
the range of technologies medical devices include: syringes, catheters, Magnetic Resonance Imaging (MRI) machines, artificial heart valves, surgical sealants, and electric neurostimulators among many more. Many drugs are administered with devices (*combination products*), which raises additional challenges for manufacturers since they must now comply with regulatory requirements for both devices and biologics (Food and Drug Administration, 2011, November 9).

The FDA has established three different categories of devices, each needing different requirements for regulatory approval (Food and Drug Administration, 2011, November 9):

- **Class I Devices** are low risk to patients and generally exempt from the regulatory approval process.
- **Class II Devices** pose a higher risk to users and “require controls for labeling, guidance, tracking, design, performance standards, and post market monitoring (Food and Drug Administration, 2011, November 9).” Class II Devices must undergo Premarket Notification 510(K) submission (discussed subsequently).
- **Class III Devices** pose the highest risk and generally are being used to sustain or support life. Class III Devices must gain approval through the most stringent regulatory process (Post Market Approval or PMA; discussed below).

After device design and development are complete, a manufacturer must obtain an Investigational Device Exemptions (IDE) for proceeding into clinical trials. Devices that pose unreasonable risk to patients must be approved by the FDA and the Institutional Review Board (IRB). The first 30 days of the IDE application is a probation period, where the FDA carefully oversees the safety profile of the device as well as the strength of the proposed design/management of the clinical trial (Food and Drug Administration, 2011, November 9). After completion of clinical trials, devices can be approved using one of three pathways:

1. **Premarket Notification 510 (K):** Premarket Notification (510(K)) is required when a firm is demonstrating that its new device has substantial equivalence (SE) to a currently licensed device. A device is substantially equivalent if it has the same intended use and characteristics of a *legally marketed device* or predicate. If a firm can prove that a devise is SE to a predicate, it is placed into the same class as the legally marketed device and can proceed with 510(K); if not, the devices is classified as non-SE and considered Class III. 510(K) is a less strenuous process, primarily because clinical data submission is not required (Food and Drug Administration, 2011, November 9).
2 Post Market Approval (PMA): PMA is the process for evaluating safety and effectiveness of Class III devices or devices for which a Class I or II predicate could not be identified. Since Class III devices pose higher risk, the PMA review process is more complex and lengthy. During the PMA process, manufacturers must demonstrate the safety and effectiveness of a device through submission of data clearly showing the benefits of the intended use of the device in the target population. Manufacturers are required to obtain their own safety/effectiveness data rather than leverage data from another device to support the current investigational device (Food and Drug Administration, 2011, November 9).

3 Humanitarian Device Exemption (HDE): HDE submissions are required for devices that are intended to treat patients who have a condition affecting less than 4,000 people in the United States annually. These devices must be demonstrated to pose little to no risk to patients; however, demonstration of effectiveness is not required. HDEs provide manufacturers who seek to treat patients with rare conditions a less risky avenue since returns with such treatments are rarely profitable (Food and Drug Administration, 2011, November 9).

At the time of PMA or HDE approval, the FDA may require post-approval studies as part of the conditions for approval. Guidance is provided by the CRDH Post-Approval Studies Program on performing robust and effective post-approval studies. Similar to Phase IV Clinical Trials with biologics, the purpose of post-approval studies is to evaluate device performance and identify issues with a larger pool of patients and extended periods of time (Food and Drug Administration, 2011, November 9).

The Recent Surge in Personalized Medicine

Issam Zineh, Director of the Center for Drug Evaluation and Research (CDER) Office of Clinical Pharmacology defines personalized medicine as “using genetic or other biomarker information to make treatment decisions about patients (Food and Drug Administration, 2012).” Since 2000, firms have begun to heavily invest in advancing PM treatments. The cost of sequencing the human genome dropped drastically from $300,000,000 in 2001 to $5,000 in 2011, allowing greater advances in this field. In 2006, 13 well-known examples of PM drugs, treatments, and diagnostic products were available; by 2011, the number of prominent treatments increased by more than fivefold to 72 (Personalized Medicine Coalition, 2011).

In 2011, 30% of biopharmaceutical corporations required all drugs currently being developed to have a biomarker. During clinical trials, half of these organizations were collecting genetic
information to advance biomarker development. Between 2006 and 2011, firms increased investments for PM research and development by 75% (Personalized Medicine Coalition, 2011).

The increases in investment clearly highlight the recent rise in the industry’s enthusiasm toward PM discovery and development. In response to the increased fervor, the FDA has had to evolve its regulatory approval process, re-organize its infrastructure, and re-strategize some of its policies.

In 2010, it appeared that the PM diagnostics field was expanding more rapidly than the FDA’s capability to regulate it. The FDA was criticized for providing unclear regulatory guidance and approached by the Personalized Medicine Coalition (PMC) as well as its supporters on areas for improvement. Dr. Margaret Hamburg, FDA Commissioner, claimed that the FDA “must serve as a catalyst for innovation” during an address in front of 150 industry, government, and academe leaders at the PMC’s Sixth Annual State of Personalized Medicine luncheon in Spring 2010 (Personalized Medicine Coalition, 2010). In order for this to occur, she claimed that the FDA needs to do much more than create guidance documents on companion diagnostics; it must increase reach out and collaborate more heavily with industry, academia, and research facilities to identify how drug regulation must evolve (Personalized Medicine Coalition, 2010).

Despite the increased industry-wide investment in PM, a recent survey evaluating the drug pipeline portfolios of about 20 large firms identified a relatively small number of treatments that would be categorized as personalized medicine. When discussing these findings with industry leaders, the majority claimed that the lack of clear PM regulatory pathways or guidelines is the primary reason for this dearth. Firms cannot afford to produce products that are associated with such regulatory uncertainty (Food and Drug Administration, 2012)!

One Step at a Time...

Criticism toward the FDA should not be surprising since the FDA framework was not designed for approval of PM (Gibbs, 2011). Issam Zineh has emphasized that guidance documents have or are currently being developed for incorporating PM principles into early drug development. The guidance documents will also aim to help industry use the information to make more informed and better decisions about patient selection or clinical trial design during the latter stages of development (Food and Drug Administration, 2012).

CDER is active in developing and implementing infrastructure programs to remain up to date with leading PM initiatives. As of recently, CDER was collaborating with the other FDA centers to ensure that guidance documents are drafted clearly and practically and can be launched in a timely
fashion. Zineh feels that the development of guidance documents is progressive, but admits that the process is challenging due to the variability in personalized medicine design and development. Since PM generally comprises of a drug or biologic combined with a diagnostic test, policies previously implemented by the Center for Biologics Evaluation and Research (CBER) and CDER that apply to regulatory approval of either biologics or devices are not applicable. In response to the evolution, CDER has modified some of its policies, but the FDA has adopted an agency-wide multi-center initiative to improving policies and guidance on PM. Re-locating the different centers to more proximal locations was an initial step in this process. In 2010, the FDA committed to drafting a guidance document on companion diagnostics by the end of the year. The guidance provided some clarification on the FDA’s requirements by demonstrating the accuracy of a diagnostic test and its use in clinical assessments. A different guidance was drafted on biomarker qualifications (Food and Drug Administration, 2012).

The agency has been relatively flexible in working with diagnostic companies to address some of the difficulties in approving diagnostic treatments. However, such efforts also increased uncertainty in the regulatory world and created additional challenges for incorporating IVDs into the current regulatory approval process (Food and Drug Administration, 2012).

Current FDA device regulations call for submission of new 510(K) or PMA when device modification could impact the safety or effectiveness profile of the treatment. Since new diagnostics used in PM can be readily changed (due to the capability of examining thousands of biomarkers), performance of a diagnostic can improve drastically due to refining of algorithms and identification of new markers. The ability to improve the assay impacts its safety and effectiveness, and therefore, requires a new 510(K) clearance or PMA supplement. Each iteration involves a new set of fees and an agency review period prior to change implementation. While this standard process is appropriate for devices, many feel that these existing device regulations create an undue burden during development of IVDs (Gibbs, 2011). Jeffrey N. Gibbs, a member of the general counsel of the Food and Drug Law Institute, states that “requiring a new clearance to add a new mutation or single nucleotide polymorphism (SNP)—or perhaps an additional 10 or 100 mutations or SNPs—to an assay may not always be appropriate (Gibbs, 2011, p. 14).” The current policy clearly requires improvement if we plan on increasing the use of PM (Gibbs, 2011).

A draft of the guidance for IVDs was published in 2012 and sent to several industry and research leaders for feedback. Currently, the FDA is in the process of revising the guidance based on feedback given from the public. The guidance for approval of companion diagnostics is currently in its final stages and targeted for release soon. Additional guidance documents focused on improving
strategies in the later phase of drug development and co-development are in the early to mid-stages of FDA publication (Konski, 2012).

The current Draft Guidance titled Draft Guidance In Vitro Companion Diagnostic Devices released in July 2011, can be found on the FDA website and serves as a tool for firms planning to develop an IVD or companion diagnostic device intended for use with a biologic therapy. The draft guidance clearly states that approval for use of a drug with use of a device will not be granted unless safety and efficacy data for the device has been reviewed and the device has also been cleared. In the event that device data is not available, the FDA will continue with the approval of the drug’s use with a companion device (Food and Drug Administration, 2011, July 14).

The draft guidance also defines an IVD as a diagnostic device used to make treatment decision in a clinical trial. If the device or test method is used to make critical decisions for treatment, it will have to comply with IDE regulations as it presents significant risk to patient health. The guidance also suggests that both the device and therapeutic product sponsors submit information about the companion device in a pre-IND submission (Food and Drug Administration, 2011, July 14).

A common theme among reviewers of the draft guidance documents is praise for the FDA’s flexibility during this change process. Industry leaders also appreciate the FDA’s efforts in creating an approval process for co-development of companion products. Not all comments were positive and many gaps in the guidance were identified. For example, the guidance does not clearly spell out which tests are intended to be regulated as an IVD companion diagnostic. Questions regarding the oversight and approval of Laboratory Developed Tools (LDTs) were also posed after release of the draft guidance (Konski, 2012). In Regulation of Personalized Medicine: A Status Report, Antoinette F. Konski reported that industry reviewers criticized the Draft Guidance as lacking “a real world appreciation of the typical development pathway” for IVDs (Konski, 2012). Biotechnology Industry Organization (BIO), the world’s largest biotech trade firm (Biotechnology Industry Organization, n.d.), argued that the FDA expectation for simultaneous submission of therapeutics and diagnostics was unrealistic in the current industry, where co-development was very rare. BIO explained that diagnostics test often may not be developed until after the safety and efficacy profile of a drug is established (Konski, 2012).

The FDA is also attempting to establish internal policies and procedures to improve the simultaneous review of drugs and diagnostics. Unfortunately, milestones for finalization of all guidance documents and policies are not available (Food and Drug Administration, 2012). The agency is clearly making PM and combinatorial medicines a priority; however, much improvement is needed to ensure that approval of PM is a smoother and more efficient process in the future. The agency
recognizes that the current applied regulatory program for evaluating personalized medicine is still underdeveloped.

Final Thoughts

Many industry, government, and research leaders believe that the flexibility of the FDA and the creation of an initial Draft Guidance for IVDs are strong steps toward improving regulation. The FDA has placed heavy emphasis on co-development, suggesting that therapeutic and diagnostic manufacturers should collaborate at the early stages of development to minimize the impact of regulatory obstacles (Konski, 2012). The lack of clarity in the existing approval process for PM is unacceptable but feedback from the scientific community and industry has encouraged the FDA to actively resolve regulatory gaps.

Nonetheless, industry and research leaders, particularly the key drivers and supporters of PM, need to understand that novel products will always generate confusion and new questions in the regulatory world. Expecting the FDA to be able to address all questions with clarity in the initial stage of the transformation process is unrealistic. As corporations learn about the products and co-development process, knowledge will increase, and initial feedback by the agency may no longer be applicable. Publications or papers by professional societies closely tied to the topic may drive re-assessments of regulatory policies on an on-going basis (Gibbs, 2011). Both the FDA and IVD manufacturers should expect the process to be challenging.

Jeffrey N. Gibbs acknowledges that the regulatory evolution process hasn’t been optimal; however, he feels that organizations can take action to minimize the impact of the challenges. Gibbs proposes that IVD companies need to improve communication channels with the agency so that the advancement in the field is not hampered. He recommends that firms are more attentive during pre-IDE meetings, when the FDA provides suggestions and tips for making the approval process smoother. Issues identified by the agency cannot go unaddressed by PM developers. Manufacturers must also be careful when designing clinical trial protocols to ensure that data generated is specific to the intended use of the IVD. Most importantly, Gibbs emphasizes that quality should never be sacrificed to meet aggressive deadlines (Gibbs, 2011).

The development and submission of more IVDs will make risk assessment during the approval process even more complex and ultimately determine the overall time and cost needed to bring an IVD to the market. Evolution of the industry, on a global scale, is inevitable as PM begins to surpass the current standard of trial-and-error medicine. Harmonized evolution of regulatory science (with the
goal of providing clear and reasonable requirements for IVD development) is also required as the PM industry advances to ensure that the benefits of PM are maximized for patients and the science community.
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Personalized medicine represents a major disruption in many healthcare fields. Despite the movements’ infancy, it is beneficial to extrapolate ahead: examining scenarios in the future allows us to plan today. The focus of this chapter will be on how organizations will continue growth in a new world of genomic and personalized medicine. Since extrapolation utilizes data from the past and present, previous disruptions will be analyzed; for instance, the dropping price of genetic sequencing and the biotechnological disruption caused by recombinant DNA in the late 1970’s. These observations will then be used to illustrate the massive changes ahead for two major business models: pharmaceuticals and hospital systems.

**Driving force: falling price of genomic sequencing**

Of the many factors affecting the growth and implementation of personalized medicine, the most important will be the plummeting cost of full genomic sequencing. Recognition of genetic variants responsible for disease requires large-scale genomic sequencing at low cost, and ultimately, commercial use of individualized therapies will require the sequencing of millions of patient genomes. The timeline of genomic sequencing cost is illustrated here:
The results of this price decline will most likely mirror the advances in computing power as driven by Moore’s Law through the 1970’s. Although it began as an observation (defined as the doubling of processing power in computers every two years), Moore’s Law became a self-fulfilling prophecy as microchip designers felt the pressure to stay competitive and maintain production of more powerful processors. Observation or prophecy, this exponential rise in power drove many of the innovations in computing from the 1970’s and beyond. The prohibitive cost of genome sequencing is a rate-limiting factor in genomic medicine. The National Human Genome Research Institute hopes to achieve a sub-$1,000 genome sequence by 2014, thus imitating the transition to a self-fulfilling prophecy seen in Moore’s Law. Affordable whole-genome sequencing will allow researchers to perform studies which link variations in sequence to human diseases, a step which is absolutely essential to the implementation of personalized medicine.

**Ethical trends**

The arrival of advanced technology in the biological fields has always brought with it dissent. The elemental nature of DNA evokes fear from those who think that continued research will strip humans from their individuality and privacy. The specific arguments have changed, but the basic fears are very similar to those brought up during the rise of recombinant technology in the 1970s, i.e., just prior to the biotechnology revolution. Some were concerned that toying with DNA would alter the fundamental process by which organisms produce offspring or evolve. Many others considered recombinant DNA a method for harmless organisms to be transformed into pathogens. The 1975
Asilomar Conference was called to address these concerns, with the outcome being a set of originally restrictive guidelines on research, which were subsequently relaxed as knowledge of recombinant techniques grew. The same respect for ethical considerations should be expected in the era of personalized medicine.

Future ethical concerns will be more complex, centering on the proper use of the sequenced genome. Politicians have already shown that they support non-discrimination in genetics (NHGRI, 2012); more specific legislation will be necessary to prohibit discrimination by insurance providers in the future. Considering the fast pace of research, we can expect some of this legislation to come from President Obama in his second term. His science-based policies and focus on civil liberties will certainly push nondiscriminatory laws into effect as these fears arise.

The Asilomar conference also served to bring these new technologies into the public knowledge. It is a common theme to be afraid of that which is not understood, but research is no longer completed in secret labs. A public becoming increasingly scientifically aware will demand to know the latest advancements, and as such, will develop a more mature ethical position in personalized medicine.

**Major theme: downfall of the traditional ‘Big Pharma’ model**

The current model of pharmaceutical value creation is already eroding. In the past, companies thrived on the ‘blockbuster’ model: one highly successful drug whose profits more than match the losses incurred from the many failures along the drug discovery path. These companies are no longer thriving but barely surviving, as R&D pipelines dry up and generic competition invades drug sales. The value of individualized treatments in personalized medicine will render one-size-fits-all blockbuster drugs all but obsolete, leading these large firms to seek out smaller markets.

One method of value creation at these firms is the acquisition of smaller firms who present with a breakthrough technology. Since 1980, ‘small’ pharmaceutical firms have almost tripled their development and approvals of new drugs; since 2004 small firms beat out all 15 top pharmaceutical companies in drugs developed (Munos, 2009). Small biotech firms have the agility to explore in uncharted markets; while their failure rate is higher their successes often lead them to get picked up by larger firms. This acquisition-based model is much of how larger firms currently stay agile. To survive in the future, these larger organizations will need to adopt a more flexible partnering strategy with small firms and academic research institutions.

One obvious choice of partnership is diagnostics companies, a trend known as *companion diagnostics*. 60% of projects in Roche’s current pipeline are coupled with a pharmacogenomic test to
identify the patients for which the drug will be most effective (Copley, 2012). It is likely that regulatory bodies will issue guidance soon requiring all drugs to be developed in conjunction with a diagnostic test, and partnerships with these companies will expedite the development process.

The more stagnant companies may cling to the blockbuster model, augmented with a strong customer focus. After the launch of generic Lipitor, Pfizer released a mobile application for patients on the drug which includes healthy eating tips and recipes (Dolan, 2012). Although blockbuster drugs themselves will not continue to be supported, a customer-driven approach may lead to innovative products that still create value for the organization.

Large firms will also branch off smaller organizations with the resources and passion to explore emerging, not-yet profitable products and markets of size (Christenson, 2000). Those markets that become successful are nurtured by the networks and resources of the larger organization, and those that do not are cut free with a minimum of losses. This new model is clearly favored by the advent of personalized medicine, and not just in the pharmaceutical arena; there is tremendous potential for ‘early growth’ in the markets of genetic sequencing technologies (Thompson, 2012), companion diagnostics (Westenberg, 2012), and even genetic counseling (Hazell, 2009). Abbott Labs is one of the first in this trend, set to spin off independent company AbbVie as a pharmaceuticals ‘division’ in early 2013, while Abbott Labs retains medical products research (Japsen, 2012).

This fragmentation trend spotlights the coming timeline for Big Pharma. As the blockbuster model is exhausted, so too will the ‘fully-integrated’ business model go. The idea of being ‘everything to everyone’ will be replaced by diverse partnerships as described above. Secondly, the smaller patient markets will eliminate much of the massive scaling strategies utilized with blockbuster drugs. When companies need to produce multiple $300 million drugs to replace the loss of $1 billion blockbusters, selectivity of markets will become much more important than the scale reached within them. Finally, these changes will not be possible without companies recognizing and developing their independent capabilities. It is the direction-oriented organization, vitally aware of its own strengths and pursuing innovations in a given specialty area, which will most quickly adapt to this new model.

**Major theme: transition of medicine to an IT field**

With fragmentation in ‘Big Pharma’ comes the rise of ‘Big Data’ and an overall transition of medicine to an IT (information technology) field. Stored and condensed into byte format, the human genome amounts to roughly 3 gigabytes. This raw information volume does not include downstream biological elements which account more directly for cell and system physiology (active/inactive genes,
proteins, and small molecules). As the traditional medical model evolves into individualized treatments, healthcare providers will need not only storage for this “fundamental substrate”, but algorithms for its complex analysis in patients (Fassett, 2012).

The only infrastructure capable of supporting this immense data volume is the scalable cloud. Secured data sharing in the cloud has already greatly decreased the timeline for clinical review of data between disparate users; speedy access to this data, however, will not be a rate-limiting factor in the future. Lack of integration of this data across systems will quickly stall how effectively it can be transformed into action for the patient. Hospitals will need a way to track medical histories through other hospital systems and data from differing medical devices, drugs, and treatment protocols. The established trend is the storage of medical data in electronic medical record (EMR) databases, which can include genomic data. Already more than half of hospitals plan to develop integration for Electronic Medical Records (EMR) systems with medical devices (Ziegler, 2012).

Developing ways for these systems to talk, both internally and to other EMRs will become a necessity, as will a universal language to speak in. The new Enterprise Data Trust (EDT) in development at Mayo Clinic is an example of an advanced system that may emerge further from healthcare organizations (Chute et al., 2010). Unlike simple EMR databases, the EDT not only collects clinical information but presents it analytically, determining relationships between patient outcomes and other business events (for instance, the implementation of a new pain management drug would be automatically linked to values for patient-reported pain). Importantly, the EDT also utilizes a universal vocabulary which allows it to communicate internally and externally via common, regulated medical terminology.

The higher the volume of data, the more important that its analysis be delegated to automated algorithms such as the one used in Mayo Clinic’s EDT. Just one challenge to these algorithms is the interpretation of ‘unstructured’ data: medical histories or notes that do not fit into established vocabularies – perhaps dictated in physician ‘shorthand’. Rather than rely on a change in the data entry methods, the algorithms that will emerge for use in the personalized medicine markets will handle unstructured data via natural language processing (NLP). NLP utilizes statistical learning to automatically translate unstructured language and ‘bad data’ (i.e., entry errors) into recognizable database entries (Chute et al., 2010).

Solutions to these challenges in the future of clinical medicine, much like pharmaceuticals, will be driven by strategic partnerships with software firms. These will be ubiquitous, but due to the variety of data input with individualized therapies, the most successful databases and algorithms will be those that were built and validated across many patient subtypes. In this way, as small patient subtypes are
further characterized via genotype, the database grows and analysis learns, producing a ‘win-win’ for both partners.

**What will health sciences innovation look like?**

Innovative partnerships across both the pharmaceutical and medical fields are the coming business model, and these partnerships will be built out of a need not only for strategic focus, but recognition of a highly dynamic industry. As the distance between the underlying science and the customer shortens, those employees well-versed in science (proteomics, genomics, biochemistry) and technology (database design, dynamic programming) will become the innovators of the personalized medicine frontier. Management teams will recognize these innovative players inside their own organization rather than outsourcing the expense. Just as it was done in companion diagnostics, they will develop new ways to combine distant ideas through technology brokering.

Although changes in technology will be the most visible, the first required change is that of the management mindset. The coming revolution is inevitable: bigger will not always be better, and specialization is no longer a vision just for startups. In the future of personalized medicine, the individual patient is king.
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