TPA Network Research Consortium

Understanding Pharmacogenomics: A Layperson's Guide

Pharmacogenetics is not new. Indeed, its origins date back to an article published by a geneticist in 1957 wherein the author described his patient's adverse reaction to an anti-malarial drug and a muscle relaxant and how he established a link between his patient's unique genetics and the specific enzymes that break down medications, noting that this was an inherited trait. While it was the middle of the twentieth century that the emergence of the concept that inheritance is a major factor responsible for variation in drug response occurred, it has only been during the past decade that the first serious attempts were made to translate this knowledge into clinical practice. The following is an overview of what pharmacogenomics is, how it works and why it is so vitally important.

The Challenge: The Hard Facts About Adverse Drug Effects/Reactions

Pharmacy is the fastest growing cost in commercial healthcare; representing ~ 25% of the total healthcare spend and ~$700 billion in expense. Adverse drug reactions (ADRs), inconsistent prescribing behavior, an upward trend in polypharmacy, poor patient monitoring and an aging population are all contributors to our rising drug spend. In large part, this is because our dated therapeutic selection approach relies on a combination of physician experience and select clinical indicators in what amounts to "trial-and-error" medication management.

Adverse drug reactions represent a major cause of morbidity and mortality. An adverse drug reaction is an unwanted, unintended, noxious response to a medication *that occurs during usual clinical use, at proper doses, following a single dose or prolonged use.* An ADR should be distinguished from an adverse drug effect (or event), an ADE, as the latter is the result of the use of the drug *for any reason* (e.g. misuse, incorrect dosage). Note that there is a causal link between a drug and an ADR. Further, ADEs and ADRs should be distinguished from "side effects" as the latter expression might also imply that the effects can be common and beneficial and a result of drug therapy (e.g., laser treatment for cataracts sometimes improves a person's eyesight). ADRs can cause patients to lose confidence in their doctor, self-medicate and/or reduce their use of a medication, which may consequently cause an ADR. All drugs have the potential for adverse drug reaction.

It is difficult to diminish the impact of ADRs on the quality of treatment and its cost. Consider the following:

- Each year, more than 8.5 million people experience an ADE and more than 2 million of these are severe;
- Annually, ADRs result in 1.3 million emergency room visits; 350,000 hospitalizations; 100,000 deaths;
- ADRs are the 4th leading cause of death in the United States;
- Some 80% of ADRs are a consequence of the medication's primary pharmacological effect;
- ADEs are the 4th leading cause of hospital admissions and the #1 cause of hospital readmissions;
- In the U.S., some 5 - 7% of all hospitalizations are due to an ADR (with an average stay of four days);
- ADEs occur during 10% to 20% of hospitalizations and as many as 20% of these ADEs are severe;
- On average, ADRs extend patient hospitalization up to four days;
- ADRs are responsible for 32,000 hip fractures per year and 28% of all re-hospitalizations;
- Some 20% of discharged patients have an ADE post-discharge, most (72%) of which are caused by drugs;
- Older patients are more than ten times more likely to experience an ADR versus younger patients;
- Several studies have shown that 50 – 60% of all ADRs are preventable and, as a consequence, avoidable.
- It is estimated that as much as $1 of every $2 spent on pharmacy is spent on ADEs (~$150 billion/year).

As startling as these statistics are, experts believe that the actual incidence of ADRs may be much greater as some ADRs mimic natural disease states and, as a result, may go undetected and/or unreported.

The Science Behind How Your Genes Impact Your Health

A gene is the basic unit of heredity. Everyone has two copies of each gene, one inherited from each parent. As it relates to our genes, we are almost entirely alike. While nearly all genes are the same in all people, less than one percent of the total are slightly different between people. Indeed, we are distinguished by literally hundreds of millions of genetic variations which contribute to each person's unique physical features…and how a person responds to certain drugs.

Genes are made up of DNA (deoxyribonucleic acid), a chemical compound that contains the information and instructions needed to develop and direct the activities of your body. DNA is made up of a very long string of more than 6 billion molecules that contain information that is stored as a code that is comprised of four chemical bases: adenine (A), guanine (G), cytosine (C), and thymine (T). Human DNA consists of ~ 3 billion bases, of which more than 99% are the same in all people. DNA molecules are made of two twisting, paired strands, often referred to as a double helix. This distinctive structure keeps DNA tightly compressed and wrapped around spool-like proteins, called histones, without which DNA molecules would not fit inside your cells. In fact, if the DNA molecules of one cell were unwound and placed end-to-end, they would stretch six feet. Humans have ~ 20,000 genes which vary in size from a few hundred DNA bases to more than 2 million bases.

Much like the way in which letters of the alphabet are used to form comprehensible words and sentences it is the order, or *sequence*, of these bases that determine the information available for building, rebuilding and maintaining your body. It is the determination of the exact sequence of these bases in a strand of DNA that inform researchers of the genetic variations and/or mutations that impact the development or progression of a disease…or the medications that work and don't work for your body. That variation/mutation can be as simple as the substitution, deletion or addition of a single base pair or as large as a deletion of thousands of bases. Researchers access the information contained in genes through genome sequencing, which is simply determining the exact order of the bases in a strand of DNA.

For the body to grow and function correctly, cells must constantly divide to produce new cells and to replace old, worn-out cells. During this division, it is essential that the DNA remain intact and evenly distributed among cells. Chromosomes, comprised of protein and a single molecule of DNA, are a thread-like structure located inside a cell's nucleus that are a key part of this process. We have 23 pairs of chromosomes, for a total of 46 chromosomes as one copy of each chromosome is inherited from each parent (which explains why children inherit some of their traits from their mother and others from their father). These chromosomes ensure that DNA is accurately copied and distributed during the cell division process. While this occurs in the vast majority of cell divisions, on rare occasions mistakes occur as to the number or structure of chromosomes in new cells. While some genetic variations do not produce noticeable negative effects, others are known to cause specific diseases/conditions. By example, some cancers are caused by defective chromosomes made up of joined pieces of broken chromosomes. Similarly, some genetic variations are known to impact an individual's response to certain medications.

A complete set of DNA is called a "genome". Virtually every single cell in the body contains a complete copy of the ~ three billion DNA base pairs that comprise the human genome. Scientists identify, keep track of and manage genes by giving them unique names. As these descriptive gene names can be long, they are often abbreviated with letters and numbers (e.g., a gene on chromosome 7 associated with cystic fibrosis is called the cystic fibrosis transmembrane conductance regulator or CFTR). Genes carry complex instructions for making a specific protein or set of proteins and each of the ~ 20,000 genes in the human genome direct the production of (an average of three) proteins with the assistance of enzymes and messenger molecules. Proteins make up body structures like organs and tissue, control chemical reactions and carry signals between cells. If a cell's DNA is mutated, an abnormal protein may be produced that disrupts the body's usual functioning and leads to the development of a disease.

The Era of Genomic, Personalized (Precision) Medicine

Three decades ago it was inconceivable that it would be possible to "crack" our genetic code and sequence the more than three billion pairs of compounds in our DNA. However, thirteen years later in 2003, it happened when the scientists from around the world who participated in the Human Genome Project *sequenced one gene*. A one-billion-dollar undertaking led by the National Institutes of Health (NIH), the project was successfully completed under budget and more than two years ahead of schedule. Today, gene sequencing is facilitated by technology that can turn around results within a day for less than a thousand dollars.

The implications of genomics for medical science are profound. The Human Genome Project created a global resource to be used for a broad range of biomedical studies, including research into genetic variations that may lead to or increase the risk of disease…and the study of how our DNA impacts our reaction to medications. In the past, doctors could only take genetics into consideration in a limited number of medical circumstances, typically only those involving predictable inheritance patterns from a single gene variation (e.g., birth defects, sickle cell anemia). Today, we know that virtually every human ailment has some basis in our genes. Over the past three decades' researchers, academics, scientists, clinicians and technologists developed powerful tools and technologies with which to define disease, better screening diagnostic tests, more effective therapeutic strategies, evidence-based approaches for demonstrating clinical efficacy, more sophisticated decision-making tools for patients and providers, and better prescribe treatments. One of the inevitable goals of this initiative is to create treatments and medication regimens that are tuned to a person's unique genomic composition.

Today we know that a patient's response to medical treatment is directly dependent upon his or her genetic makeup and molecular profile. Equipped with a much greater understanding of disease biology than ever before, physicians are leveraging this knowledge and using genetic data more extensively to dial-in medication regimens to a patient's unique molecular composition to maximize their therapeutic impact and reduce adverse reactions.

Personalized medicine is generally referred to as the practice of medicine in a manner that considers the totality of a person when assessing and addressing a patient's health. In addition to typical medical factors, a patient's genetics, family history, current medication regimen, diet, exercise and environment are taken into consideration when looking to tailor a treatment plan to the patient's unique DNA, conditions, medications and lifestyle. The aim of precision medicine is to focus on preventing disease, poor health and harmful medication responses by getting the right treatment to the right patient at the right dose the first time with the assistance of genomic diagnostic tests and targeted treatments and medical therapies.

As noted above, in great part, we are all alike in that 99% of our DNA is the same. However, it is that one percent of our DNA that makes us unique and causes two people who are the same age and size, eat similar foods and exercise the same to respond differently to the same medication. It is your unique genetic code that directs your body to create the thousands of molecules called proteins, some of which work better or worse than others as it relates to metabolizing medications and other substances. This process is called pharmacogenomics.

Precision medicine is the application of science to the risky process of prescribing medications, which is at best a trial-and-error process. Understanding that our genetic variation influences the way drugs are processed and utilized by the body it predicts how this individual genetic variability impacts drug absorption, metabolism and activity and equips physicians with the means by which to develop highly-effective, patient-unique medication treatment regimens (especially for high-risk patients who usually take many expensive, potentially dangerous or ineffective drugs). Here's how it works and why it is such an important advancement in science.

Drug manufacturer dosage guidelines are typically based on the general population's ability to absorb, distribute, metabolize and excrete the medication. The challenge is that many people fall outside the manufacturers' intended therapeutic index for safe and efficacious dosage and these patients are subject to a far greater risk for an ADR when dosage guidelines are followed. Moreover, this is clearly exacerbated when the therapeutic index is narrow. Indeed, the more researchers and scientists discover and learn about the impact of these genetic differences, the cruder the one-pill-fits-all prescribing convention appears. As such, the FDA has identified more than two hundred drugs that may not work as commonly prescribed for those with specific gene variants.

Among the most typical of pharmacogenomics tests are those that look for variations in the specific genes that provide instructions for creating the enzymes in the liver that metabolize (break down and process) medications. Many of these gene variations are very common in the general population and are determinative as to how a patient's dosage should be dialed-in to make the medication optimally effective as the degree and speed by which a person metabolizes medications will directly impact their effects. There are five drug metabolism rates:

- Poor metabolizers who breakdown a certain drug very slowly, thereby causing an unintended accumulation of the drug within the body and potential toxicity;
- Intermediate metabolizers who breakdown a certain drug at a rate between a poor and over-metabolizer, subjecting the patient to a possible accumulation of the drug in the body and possible toxicity;
- Normal metabolizers who breakdown a certain drug at the expected or normal rate;
- Rapid metabolizers who breakdown a certain drug faster than intended such that it will not reach optimal blood levels and lead to a lower than expected drug level and an inadequate response to the medication;
- Ultra-rapid metabolizers who breakdown certain drugs so fast they get no benefit from the standard dose.

As a practical matter, armed with this information, a physician of a patient that carries a gene variant associated with either an elevated drug metabolism, or poor drug metabolism, can adjust the dosage accordingly (up or down) to achieve the desired therapeutic effects and reduce the risk for toxicity and adverse drug effects.

Relatedly, gene mutations and their resultant effects, can have a significant causal influence on drug-to-drug interactions that patients having them may experience. This is because for these people the body's ability to process or properly metabolize one medication may impact the processing and metabolization of *another medication* by what are called inducers or inhibitors which affect gene expression. Here's how. Cytochromes, referred to by scientists as CYPs, are the major enzymes involved in ~ 75% of drug metabolism. CYPs are present in most tissues of the body and many substances are bioactivated by them. They play a role in hormone synthesis and breakdown, cholesterol synthesis, vitamin D metabolism….and function to metabolize potentially toxic compounds, drugs and products. Many medications can increase or decrease this activity by either *inducing* (inducers) or *inhibiting* (inhibiting) the process and, as a result, are a major source of adverse drug interactions as they affect the metabolism and clearance of various medications. In practice, this translates to one drug inhibiting the CYP-mediated metabolism of another drug such that the second drug may accumulate within the body to toxic levels, thus necessitating dosage adjustment or choosing drugs that do not interact with the CYP system. By example, the anti-epileptic medication Phenytoin® induces four CYPs which can critically increase or decrease blood plasma concentration rates.

The following are some examples of how gene variations can impact proper medication usage:

- Sulfation enzymes are an important group of proteins whose genetic code varies greatly within the population. These enzymes perform critical chemical reactions in the body that make molecules more water-soluble, so that they can be quickly excreted in the urine. While these enzymes successfully metabolize many drugs, for certain individuals having a particular genetic code they may also impact other of the body's natural molecules and alter blood levels of many different types of substances metabolized by these enzymes. In fact, scientists have found that people of different ethnic backgrounds have slightly different "spellings" of the genes that make sulfation enzymes and, as a result, they may be putting themselves at risk with certain medications as those spellings cause medications and estrogens to metabolize at different rates.
- Certain medications are converted into their active form in the liver. For patients having a certain genetic variation, these drugs can cause them to need a completely different type of medication. By example, Plavix® (or clopidogrel) is commonly used to prevent blood clots from forming after a heart attack or balloon angioplasty procedure. Unfortunately, for at least 25% of the population having a certain gene variation in a key enzyme, Plavix® is a suboptimal medication choice as it cannot be fully converted by the liver to its

active form and is less effective at preventing heart attacks and strokes. As such, studies have demonstrated that patients having this gene variation who used an alternative to Plavix® had fewer heart attacks, fewer strokes and were less likely to die than those who continued taking Plavix® whereas those who are prescribed the medication are two times more likely to have a repeat attack or die within a year of the first, compared with patients who don't have the gene variant. This starkly highlights the success and better health results of a more personalized approach to providing care. This is a significant issue in that Plavix® was once the second best-selling drug in the world.

- For codeine to be effective it must undergo a chemical reaction in the liver to be converted into morphine by the body's cytochrome P450 enzymes, CYP2D6. Codeine is another example of how a person's genetic code influences a medication's metabolism as an estimated 10% of the population has a genetic mutation in the CYP2D6 gene that closes down this enzyme process, thereby making codeine of little to no value to them. A physician equipped with the knowledge of the patient's CYP2D6 mutation would prescribe a different pain control regimen, rather than having to take a trial-and-error approach.

As evidenced above, the use of pharmacogenomic testing could be used in any of these situations to both maximize therapeutic benefit and avoid or reduce the incidence of ADRs

Black Box Warnings and Genomic Medicine Guidance

First implemented in 1979, *black box warnings* (BBW) represent the strictest labeling requirements that the FDA can mandate for prescription drugs when there is reasonable evidence of an association of a serious hazard with the drug. They highlight serious and sometimes life-threatening adverse drug reactions within the labeling of prescription drug products and are designed to call attention to serious or life-threatening risks. Most BBWs contain vital clinical information, such as information about possibility of death, specific populations at risk, and monitoring that can mitigate these risks. BBWs can be mandated by the FDA immediately upon approval of a medication however many prescription medications that patients rely on subsequently receive new black box warnings or are withdrawn from the market because of safety concerns years after they are approved.

Here are just a few facts on medications that are required to carry a black box warning:

- Remarkably, since its inception in 1979, more than one in five medications has been required to have a black box warning. What's worse, that percentage has increased to more than one in four meds today.
- There could be a reason for this. In 1992, Congress passed the *Prescription Drug User Fee* Act to accelerate the drug approval process at the FDA. Since PDUFA was enacted, median drug approval times for new medications has decreased by more than half from ~ 34 months to approval to ~ 16 months. Concerns have been raised as to whether or not this expedited drug approval process has occurred at the expense of the public's safety and resulted in an increased percentage of medications earning the BBW. As it turns out, since the passage of the PDUFA, drugs approved were ~ 26% more likely to receive a new black-box warning or be withdrawn than drugs approved before its passage.
- In recent years, almost three quarters of BBWs were issued at the time of FDA approval.
- Some 60% of these BBW drugs were expected to be used chronically for a period of two years or more.
- Well over half of BBW medications have available (safer) alternatives without a BBW.

Understanding the above, it is reasonable to assume that the use of medication having a BBW is somewhat limited; unfortunately, that's not the case. In one study, it was found that within a 30-month period ~ 40% of the patients in an ambulatory care setting were prescribed at least one medication having a BBW for a serious adverse drug reaction that could potentially affect them. In another study, for the ten-year period ending 2009, there were more than 270 million scripts written for just nine medications that were subsequently either withdrawn from the market for safety reasons or that received BBWs for potentially *lethal* side effects.

Lastly, you might expect that if a physician prescribes a medication requiring a BBW that he or she would have a conversation about the warning; unfortunately, that is not necessarily be the case. In a study conducted on the use of rosiglitazone and pioglitazone (two diabetes drugs having BBWs re: their raising the risk for congestive heart failure) it was determined that the FDA-mandated BBW reduced rosiglitazone use by 70% but not nearly as much for pioglitazone (which had a similar warning). The reason: rosiglitazone use slowed as a result of the combined effect of media exposure, advisory and scientific publications that pioglitazone did not get. Even then, with a 70% usage reduction, nearly four million patients were prescribed rosiglitazone.

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

The effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 *[see Warnings and Precautions (5.1)]*. Plavix at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Plavix at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy *[see Clinical Pharmacology (12.5)]*. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers *[see Dosage and Administration (2.3)]*.

Plavix® (clopidogrel), a product of Bristol-Myers Squibb, was approved by the FDA in 1997. It is a blood thinner to reduce the risk of blood clots and is prescribed to patients having a higher risk of cardiovascular problems as it has been touted as being more effective than aspirin in preventing clots and reducing the risk of heart attacks.

Plavix® was enormously popular (and profitable) for more than a decade, reaching sales of $7 billion in the U.S. in 2011. It was the top-selling drug in the U.S. and the second best-selling drug in the world with 50 million U.S. users and twice as many worldwide. Plavix® cost ~ $4 per pill versus pennies for the safer alternative, aspirin.

As noted above, Plavix® is metabolized by the drug-processing enzyme CYP2C19 and certain genetic variations can affect the activity of this enzyme placing the patient at a higher risk of treatment failure or ADR at normal dosages. Studies have shown that Plavix® users develop twelve times as many recurrent and bleeding ulcers than those who take aspirin with the heartburn pill Nexium® suggesting that Plavix® users consider switching to a potential safer alternative such as aspirin (which is also greatly less expensive at only a few cents per pill). In 2010, the FDA required Plavix® to have a BBW, which warned about diminished efficacy in poor metabolizers.

In 2014 the State of Hawaii filed suit against the manufacturers of Plavix® claiming that it knew and did not disclose that the medication would be ineffective, or only partially effective, in certain patient populations due to genetic variations. The state had a solid foundation for its interest as it was determined that Hawaiians would be especially vulnerable to treatment failures with Plavix® due to the state's ethnic makeup of Pacific Islanders and East Asians which have a 40% to 80% chance of having the genetic variation. Since then, several other states lodged suits against the drug's makers (Bristol-Myers Squibb and Sanofi-Aventis) alleging they knew about the medication's risk due to genetic variations as early as 1998 and failed to inform the public. Today, through pharmacogenomics, we know that nearly one in three of the more than 110 million patients that took Plavix® had a genetic predisposition for an adverse reaction to the drug (and paid $4 per pill for a drug that not only didn't benefit them but put them in significant risk)

Appreciating the importance of genetic biomarkers to prescribing physicians, pharmacists and patients alike, the FDA has been rightfully very involved in influencing the development and control of pharmacogenomics tests. As of this writing (March, 2019) there are 212 medications that have labels that contain pharmacogenomic information (see Table of Pharmacogenomic Biomarkers in Drug Labeling with Labeling Text). This list includes some of the most prescribed medications and about 10% of all drugs approved by the FDA. As helpful as this is, it is hardly enough however as this is still a very small percentage, especially when you consider that some 99% of people have biomarkers that would benefit from such indications. In addition to the relatively small percentage of medications having pharmacogenomic information, that which is provided is fairly limited…and not of great value. Typically, it includes the classification of the subject drug into three categories: test required, test recommended, and information only – whatever that latter classification is supposed to mean. Clearly, this is hardly enough information to assist a physician or pharmacist with guiding them in the use of PGx testing in practice. This list is important however as it evidences the FDA's appreciation of the relevance and need to get this information out to the provider and patient public.

How Pharmacogenomics Works

Our medication selection and prescribing process is very broken…or at least able to be greatly improved upon. Armed with the knowledge gleaned from the discussion above, it should be obvious to most that the present one-pill-fits-all, doctor-knows-best prescribing convention is rather crude given the scientific discoveries that form the foundation of pharmacogenomics. This is especially evident when one considers the current process.

Because most drugs are metabolized by the body by various enzymes, and some drugs are made more active, less active or even inactive through the patient's unique metabolism, the challenge in establishing an optimal medication regimen is to make sure that the active form of a drug stays in the system long enough to perform as intended. Today, when a physician designs a medication plan to treat a particular condition, they prescribe one of several appropriate medications following dosage and timing guidelines that are based upon the anticipated rate of metabolism and clearance from the body in the "average" person (whoever that is). That "standard" dose is based on factors such as weight, sex, and age…despite the fact that each patient responds differently to the medication dosage based on their uniquely genetic composition. In most cases, a physician will monitor the effects of the medication with blood tests and adjustments to the medication dosage are made accordingly, increasing or decreasing the drug level within the therapeutic range established by the drug's manufacturer. This particularly unscientific follow-up and adjustment process is referred to as "therapeutic drug monitoring". As the medication's effects are monitored, if increasing or decreasing the dosage does not yield the intended effect in treating or controlling the patient's condition (or the patient suffers an adverse reaction), the physician will most often prescribe another alternative medication…and continue to do so until one works. Outside of the practice of medicine, this process is commonly referred to as the *trial-and-error* method… repeated attempts to accomplish something by trying various means until the correct one is found. Generally speaking, most people would not tolerate the use of this technique by their auto mechanic: why then, do they tolerate it when it is employed by their healthcare providers…especially when alternative, science-based alternative processes exist?

Just as there are known drug-drug interactions, there are also known drug-gene interactions that affect how a person responds to specific medications. It is a form of precision medicine and the application of science to the inefficient and risky process of prescribing medications. It is the study of how genetic differences influence the metabolic pathways of drugs and how individual patients respond to specific pharmaceutical interventions based on their unique genetic makeup. This science forms the basis of precision medicine and value-based healthcare.

In practice, the process of employing pharmacogenomics is a fairly simple, straightforward and uncomplicated. As we see it, employing a pro-active PGx testing approach, the process is best designed to follow this format:

- A risk stratification analysis is done to identify who would benefit most from a PGx test;
- PGx candidates are invited to participate in a PGx testing program and enrolled in it;
- Patients wishing to speak to a genetic scientist or physician re: the test are invited to do so;
- Each patient's prescribing physician is contacted to get them engaged and onboard with the testing;
- A test-kit is provided to the patient and a saliva sample is collected and submitted to the lab;
- The lab performs the test, interprets the results and produces an actionable go-forward Rx game plan;
- Test results are presented to the patient by a genomic expert, and to the physician by a Pharm D; and
- The actionable Rx game plan is executed by making the necessary medication adjustments.;

One test is good for a lifetime. Once enormously expensive, comprehensive saliva-based PGx tests are now much more affordable…ranging in price from $350 to $500 inclusive of patient/provider genetic guidance.

Pharmacogenomics is an emerging area of science that is not only here to stay, it will soon become the first clinical tool used by most physicians. By applying science to the risky process of prescribing medications we equip physicians with the means by which to develop highly-effective, patient-specific medication treatment regimens that are based on one's unique DNA and the way their body reacts to certain drugs. The difference between a typical trial-and-error approach to a complex medical situation, and the use of pharmacogenomics, is the degree

of reliance on genomic data to make decisions about specific treatment paths that may be less risky and more effective for the patient. As pharmacogenomics becomes more commonplace, options for PGx interventions will expand greatly across all therapeutic areas and quickly change the way medicine is practiced.

As described above, pharmacogenomics looks to predict how individual genetic variability impacts medication absorption, metabolism and activity. It looks for changes or variants in a person's genes to determine how the patient will react to various medications. It recognizes that while one treatment approach may work well for one patient, the same approach may not be effective for another patient or cause an adverse drug reaction. This analysis predicts a patient's response to select drugs and helps physicians be certain that the patient gets the *Right Drug, the Right Dose at the Right Time for the Right Indication*. Ample evidence exists that PGx testing improves the efficacy, accuracy and safety of personalized drug treatment plans and reduces waste. Clinically actionable tests can predict a drug's effectiveness, guide dosage and improve patient safety by determining if it will or will not be an effective treatment for a patient or cause a side effect. It creates a solid foundation upon which a medication treatment plan may be structured to avoid prescribing medications to patients that could result in an adverse reaction, and ensure that the medication plan created is optimal for the patient's unique genetic make-up. In fact, the effectiveness and efficacy of a drug is entirely dependent on a patient's DNA.

The FDA on Pharmacogenomics

As the FDA states: "Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose. Drug labeling may contain information on genomic biomarkers and can describe: drug exposure and clinical response variability, risk for adverse events, genotype-specific dosing, mechanisms of drug action…"

A Practical Example: Pharmacogenomics and Antidepressants

A good example of how PGx testing can be employed to reduce risk and optimize medication use can be found in its application to antidepressants. Regularly prescribed by PCPs and specialists alike, antidepressants are the third most common prescription drug type in the U.S. and taken by more than 10% of the population.

As helpful as they can be, the fact is that many people have difficulty with antidepressants in the form of side effects having to do with their unique genetic composition; as a result, it is not at all uncommon for physicians to have to prescribe one antidepressant after another to get to the right medication and the right dosage. As a result, it is not uncommon for patients to discontinue the use of their antidepressant prescription (without their physician's knowledge or approval) due to side effects or drug intolerance. In fact, more than 40% of patients using antidepressants discontinue taking the medication within the first thirty days of treatment…creating a potentially very dangerous situation. Moreover, more than 65% percent of patients taking antidepressants also take other medications that may increase the risk of ADEs, often due to genetic-related causes.

Several comprehensive PGx tests assay the several genes that inform a patient's response to antidepressants. These tests provide prescribing physicians with the information they need about their patient's unique DNA that can enable them to select the best medication the first time with the confidence of knowing that it is safe and will be effective; thereby avoiding the trial-and-error scenario that is synonymous with antidepressant prescribing, reducing the number pf potential adverse drug reactions; restoring the patient's confidence in his/her physician; and facilitating greater medication treatment adherence.

The Employment of PGx Testing by Plan Sponsors

In that healthplan resources are finite – and highly regulated under ERISA – PGx testing must be carefully managed to be fair, equitable, safe and cost-effective. There are three ways that payors and plan sponsors can make PGx testing available to their plan participants:

- Global – offered to everyone on either a voluntary, employer-sponsored or shared-cost basis,
- Random – available to those few patients in active treatment and having a physician who is familiar with PGx testing, when submitted as a medical claim to be reimbursed (if deemed medically necessary),
- Targeted – offered to individuals who are identified as high-risk based on specific medical indicators, claims history and Rx profiles; covered under the plan as a medical service / cost management measure; must be designed and implemented in an ERISA- and GINA-compliant way.

While PGx testing can greatly reduce adverse drug reactions, emergency room visits, hospital admissions and re-admissions and their attendant costs and suffering, it is *wasteful* and *not cost effective* if performed on an entire covered population. Moreover, offering PGx testing on a voluntary basis as a part of wellness program is neither a fair nor an equitable use of plan assets as those who select to avail themselves of the test may not be the plan participants who would benefit most from such testing. An argument could be made that in such a case limited plan assets were being used to benefit a "curious" plan participant looking to be tested for "recreational" reasons at the expense of high-risk, high-cost patients who would benefit more from having the test done. Some legal experts have even asserted that such a practice may be a violation of ERISA and/or GINA.

Likewise, reimbursing PGx testing solely as a random claims expense, is a *policy or practice*: not a *program* or *solution*. Payors cover "medically necessary" genomic testing for those high-cost patients fortunate enough to have one of the few physicians who are familiar with PGx testing; willing to argue medical necessity with a UR firm; and confident enough to follow or support the test's actionable results. It is an illogical, subjective and unscientific process by which to select patients for testing. It leaves the determination of "medical necessity" up to a UR or case management nurse, claim processor or PBM employee rather than experts following a scientific, evidence-based process and protocol. It results in a universe of patients that consists only of plan participants actively in treatment whose physicians have knowledge of PGx testing and when it should be requested. It is a potentially discriminating practice, and may constitute the use of plan assets inefficiently by failing to identify the population with the most emergent genomic risks to best use the plan's finite financial resources. This approach is unsophisticated, inefficient and results in sub-optimal financial and population management results. In practice, this process is the equivalent of restricting access to mammograms to only those women who evidence signs of cancer: it is reactive rather than pro-active and simply makes no sense. Unfortunately, most physicians are not familiar with PGx testing and fewer possess the patient genetic data, and ability to interpret it, without assistance. As such, few of the many opportunities to benefit from PGx testing are acted upon. Ergo, most agree; encumbering access to this game-changing science is unfair, unethical, nonsensical, wasteful and a possible violation of ERISA.

Risk stratification (as it relates to PGx testing) is the analytical process used to identify plan participants (or patients of a medical practice or health system) who would benefit most from a pharmacogenomics test versus trying to identify or predict high-risk patients. The precise processes used by various organizations to identify high-risk candidates who would benefit from PGx testing are typically proprietary, so none will be detailed herein. That being said, the process combines various statistical analysis and modeling techniques with clinical segmentation analytics based on as much data as can be collected including medical claims data, prescription drug data, EMR records (if available) and patient demographic data (if available). Employing a best-fit test / goodness-of-fit measure, and the application of various regression models and clinical algorithms, a risk-based scoring system is used to rank patients re: their propensity to benefit from a pharmacogenomics test.

PGx Test Rationale: Who Should Be Tested for PGx?

The following is a list of the types of people who would benefit from a PGx test (from Admera Laboratories)

- Patients prescribed medications with FDA's black box warnings that require/recommend PGx testing;
- Patients experiencing unexpected or exaggerated responses to medications;
- Patients who had a severe adverse drug reaction or complications due to one or more ADRs;
- Patients who have experienced pharmacotherapy failure (multiple unsuccessful drug trials);
- Patients who have demonstrated sensitivity or lack of symptom relief with recommended drug dosages;
- To identify patients who require a higher-than- standard dosage to achieve the desired therapeutic result;
- Polypharmacy patients who have chronic conditions and are on multiple (>5) drugs prescribed to minimize drug-drug interactions, risk of ADRs, and potentially reduce the number of drugs prescribed;
- Patients diagnosed with new conditions with no previous pharmacological treatment to compare/evaluate;
- To provide effective treatment and avoid the prolonged trial-and-error heuristic approach of medication prescribing (e.g., an example being the strategy of selecting an antidepressant to manage depression);
- To select treatment strategy, drug selection and dosing in patients with grave/life-threatening conditions;
- Patients with a family history of a serious adverse drug reaction or known pharmacogenomic variant;
- Patients who have a history of poor medication compliance/adherence;
- MDs who need guidance to select the right drug the first time based on the patient's genetic makeup;
- Healthy patients on no medications, who desires to take the PGx test preemptively so that results are readily available to be immediately factored into the decision-making process prior to drug exposure;

The Potential Impact of PGx Testing

The number of individuals who could benefit from PGx is huge when you consider that 99% of the population has a high-risk variant for a gene associated with a medication….and the number of people on medications.

- Some 750 million scripts were written in the US alone for pharmacogenetically high-risk drugs.
- Overall, 29% of Americans take more than 5 medications regularly. In the patient population aged 65 years and older this percentage increases to > 50%. Some 12% of all patient take ten or more drugs daily.
- It is estimated that the cost of mismanaged polypharmacy patients is $1.5+ billion in the U.S. alone.

Here are some widely-used statistics that evidence the potential for, and impact of, proactive PGx testing:

- Only about half of patients respond positively to the medications that they are prescribed;
- About one of every five prescriptions given to elderly patients are inappropriate;
- One of six individuals will have an actionable finding from a PGx test that will change their care;
- Experts believe that emergency room visits could be reduced by 40% through proactive PGx testing;
- Hospital readmissions are a key contributor to rising healthcare costs and some 20% of Medicare patients discharged from hospitals are readmitted within 30 days of discharge, and more than half of all hospital readmissions are potentially avoidable, a waste estimated to be more than $10 billion;
- 17,000 strokes annually could be prevented if dosing guidelines were followed based on genetic tests; and
- Hospitalization rates for patients on warfarin could be reduced by ~30% with proactive PGx testing.

Once considered non-preventable, many ADRs may now be preventable with pharmacogenomic testing. Utilized properly, the ROI on PGx testing can be considerable by greatly reducing the incidence of adverse drug reactions, emergency room visits, hospital admissions / re-admissions…and their attendant costs and suffering.

Not All PGx Tests Are Alike

The scope, quality, accuracy and security of DNA-based tests, labs and processes vary considerably. Dozens of DNA testing companies have emerged; most are direct-to-consumer companies focused on offering insight into a person's ancestry or a propensity to develop a disease. These tests bear no semblance to the sophisticated (exome sequencing) tests required to base a medical diagnosis or therapeutic treatment; it's the difference between an x-ray and a CT scan. We consider these consumer-based tests to be "recreational" genomics.

There are presently 75,000+ different "medical grade" genetic tests (panels) on the market. Because they aren't equal, navigating genetic testing without genetic expertise is a lot like driving without a GPS. These tests provide information and recommendations for an extensive range of common drugs used widely in anesthesiology, autism, cardiology, dentistry, endocrinology, gastroenterology, gynecology, hematology, immunology, infectious disease, neurology, oncology, ophthalmology, pain management, psychology, respiratory, smoking cessation, supplements, toxicology, urology, weight management, and multiple other clinical specialties.

These pharmacogenomic panels inform physicians' treatment decisions based on a patient's unique genetic profile by analyzing as many as 50 or more critical genes, and more than 200 genetic variants, against as many as 300 or more commonly prescribed medications. Once interpreted, these tests provide providers with medically actionable, clinically relevant data and information across a broad spectrum of therapeutic areas.

Genetic Benefit Management

Genetic Benefit Management is a recently coined term to describe the systematic, comprehensive, cost-effective and value-focused process for optimizing the use of genetic data, information and testing to help control healthplan costs and improve plan participants' health. A genetic benefit management program can be designed to help manage the cost associated with testing and, at the same time, the resulting clinical interventions may help ensure genetic information is used to inform or influence treatment protocols, e.g., medication therapy.

Genetic benefit management programs provide plan sponsors with expertise in clinical criteria and evidence- based methodology that support the identification of genetic testing opportunities and the translation of these opportunities into tangible results, from a cost and health perspective. Such programs feature the vetting and contracting of genetics laboratories selected for their advanced scientific methods to assure high quality and accurate testing with reliable turnaround times, at a good value. They also bring to the table experienced genetic counselors, clinicians and specialty pharmacists able to educate and inform physicians and plan participants about PGx testing opportunities and assist with the interpretation of test results.

Last Word: Pharmacogenomics vs. Predictive Genetics vs. Recreational Genetics

Genetic testing takes many forms. Pharmacogenomic testing is focused on applying science to determine which medications work best for patients. It should not be confused with predictive genetic testing which is designed to indicate a person's propensity to have or contract a disease…or "recreational" tests to determine ancestry. At the present time, it appears that pharmacogenomics is best able to demonstrate value and a return on investment.

About the Author

A seasoned industry veteran having four decades of C-suite experience in the self-funded, managed care and outsourcing sectors, Richard Nicholas has owned and held executive positions with national TPAs, BPOs and MCOs; represented 200+ TPAs before the U.S. Congress; and been trusted to facilitate more TPA mergers and acquisitions than anyone. An innovator, author and newly - minted "social entrepreneur", he created the *Research Consortium* to conduct payor-focused translational research on new and emerging health innovations and medical technologies and to facilitate more, smarter, and less costly medical research. Richard earned a BA with distinction from Boston College and an MBA from Duke University's Graduate School of Business.