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DNA to Diagnosis to Treatment… A Dependent Paradigm

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> "*The scientific man does not aim at an immediate result. He does not expect that his advanced ideas will be readily taken up. His work is like that of the planter – for the future. His duty is to lay the foundation for those who are to come, and point the way.*"
>
> **Nikola Tesla – physicist, engineer and inventor**

In the hierarchy of health care prevention is the best. Diagnosis leading to intervention before complications is next best. Intervention by surgery, radiology, and medications to treat the problem is last best. From a benefit perspective, medication therapy has become the primary treatment modality in the ambulatory setting, shifting acute care toward a higher severity patient population. Medication therapy has moved towards targeted impacts on patient conditions with a growing emphasis on improved measures and analytics to refine diagnosis and target outcomes.

The technology exists to target and monitor many therapies to defined metrics such as blood metrics, medication blood levels, respiratory parameters, blood pressure, etc. Analytical techniques also exist to refine medication dosages and monitoring parameters to achieve improved outcomes at lower risk. DNA testing adds another dimension to the techniques available. While DNA testing is not applicable for all diseases and therapies it has generated a separate discipline of "precision medicine."

Genomics has allowed for improved diagnostics such that diagnoses can be further refined into subsets of populations that are treatable with new and improved therapies. The therapies, commonly called "Specialty Medications," target these subpopulations with a greater chance of success in cure or stabilization of the disease. Marrying diagnostics with therapy is the next evolutionary opportunity for professionals with extensive training in therapeutics.

This article will discuss the marriage of genetic and genomic testing with medications and its impact on providers. This is a review for providers and is not an exhaustive review of the literature.

The Situation

DNA testing is a relatively new area that is based on scientific principles and will evolve as more and better tests, as well as better medications, are introduced. The field currently has different terms to describe DNA testing. One option that has been published is that genetic testing is a diagnostic mindset that refers to screening large populations to determine who is susceptible to certain illnesses. Alternatively, genomic testing is a treatment mindset that refers to the treatment of a particular illness that will improve the outcome. Clearly, both types of testing require a consideration of the cost-effectiveness of doing any testing to ensure that there is a benefit beyond cost.[1]

DNA Genomics

Deoxyribonucleic acid (DNA) is a molecule that carries most of the genetic instructions used in the growth, development, functioning and reproduction of almost all known organisms. It makes each species unique. DNA is found in the cell nucleus (nuclear DNA) and in the mitochondria (mitochondrial DNA). DNA is composed of four chemical base pairs: adenine (A), guanine (G), cytosine (C), and thymine (T). There are about three billion base pairs in the human body of which 99 percent are the same in all humans. The sequence of these bases determines the information used to provide the genetic instructions for each human. Each base is also attached to a sugar and a phosphate molecule. The base plus the sugar plus the phosphate molecules form a nucleotide. The nucleotides form the spiral double helix, which can be viewed as a ladder with the base pairs forming the rungs and the sugar and phosphate molecules forming the sidepieces. (Figure 1)

Mutations or changes to base pairs, about 1 in every 1300 base pairs, create gene variations that impact pharmacodynamics, drug responses and pharmacokinetics. A mutation is usually signified by an asterisk "*" within the name of the gene. Variations are known as "alleles."

Basic Science Principles: Pharmacogenomics

Pharmacogenomics, also pharmacogenetics, is the study of genetic variations that influence an individual's response to specific medications. Knowing that a patient carries a particular genetic variation (i.e., allele) helps prescribers to individualize medication therapy, decrease the probability of adverse events, and increase the effectiveness of the prescribed medication. Pharmacogenomics is composed of pharmacology (the science of how medications work) with genomics (the science of the human genome).

Pharmacogenomics targets medication activity to DNA variations in the human genome. Variations in the human genome are called "single nucleotide polymorphisms (SNPs)." There are approximately 11 million SNPs in the human population, averaging one every 1300 base pairs. Variant forms of a gene (alleles) usually arise due to mutations. Many genes have different forms which are located at the same position, i.e. genetic locus, on a chromosome. Humans have two alleles at each genetic locus with one allele inherited from each parent. Susceptibility to certain diseases and individual responses to particular drugs are linked to these SNPs. The science of pharmacogenomics, then, targets defective structural proteins that increase susceptibility to disease, and the genes that encode metabolic enzymes that alter a medication's activity.[3]

Diagnoses from Genetic Testing

Each person would need to have the same specific pharmacogenomic test only once because a person's genetic makeup does not change over time. However, one may need other pharmacogenomics tests if one takes another medication. Each medication is associated with a different pharmacogenomics test. The results of all genomic test results are stored with all laboratory tests to be used by health care providers.

There are several general approaches to selecting the patient in need of a biomarker or genetic test –

- Patient: Select a test based on a patient who is not responding to standard therapies
- Medication: Select a test based on a target medication
- Disease/Condition: Select a test based on a well-established relationship between the medication and a variant allele

The treating health care practitioner must decide, but pharmacists and other health care professionals have the responsibility to bring the issue up by counseling that includes the appropriate decision algorithm. Why is a test necessary? What is the published evidence to support a test? What will we do with the results? Can we achieve the same result by other, less costly means?[4]

Treatment Based on Genomic Testing

There are at least one hundred genomic tests paired to specific medications and the number is increasing annually. Warfarin is often cited as the classic medication that is affected by the presence of variant alleles that reduce its rate of clearance from the body. Specifically, warfarin metabolism is encoded by the CYP2C9 gene among others. Variant alleles, e.g., CYP2C9*2 and CYP2C9*3, present in a patient reduce the metabolism of Warfarin, leading to higher concentrations of the medication in the body. As a result, patients with at least one copy of these alleles require a lower dose of Warfarin than do patients who are homozygous for the CYP2C9*1 allele. In addition, Warfarin works by inhibiting vitamin K-dependent clotting factors. The VKORC1 gene codes the vitamin K epoxide reductase enzyme, which is the Warfarin target. If a patient carries the -1639G>A polymorphism in a particular region of the VKORC1 gene, the so-called promotor region, then these patients are more sensitive to Warfarin and require lower doses. Therefore, a patient's CYP2C9 and VKORC1 genotype can be used to determine the optimal starting dose of Warfarin.

Examples of other allele / medication pairings are:

- Patients infected with the HIV virus may receive an antiviral medication abacavir (Ziagen®). This therapy may lead to adverse drug reactions if the patient has a genetic variant. These patients are HLA-B*5701 allele carriers.
- Patients with breast cancer may be given trastuzumab (Herceptin®). This medication only works for patients with an overproduction of a protein known as HER2. As a result, physicians test for ERBB2 overproduction before providing trastuzumab.
- Patients with acute lymphoblastic leukemia may be given mercaptopurine (Purinethol®). Some patients cannot process this medication due to a genetic variation, TPMT, that leads to intermediate or poor metabolizers. The result is severe side effects as well as increased risk of infections. If the standard dose is adjusted, then the risk of these processing problems is significantly reduced.
- Patients with colon cancer may receive combination chemotherapy regimens containing irinotecan (Camptosar®). Some patients have a particular genetic variant that prevents them from clearing the medication resulting in severe diarrhea and increased risk of infections. These patients are UGTIA1*28 allele carriers. They require lower doses of the medication.

There are many more medications that are currently being researched. For example, clopidogrel (Plavix®) is a blood thinner used to reduce blood clots especially after PCI cardiac stents. Certain genetic variants may cause the medication to be ineffective as for example, Omeprazole. Also, gefitinib (Iressa®) and erlotinib (Tarceva®) may be more effective in patients with lung cancer when they have a specific genetic allele. However, cetuximab (Erbitux®) and panitumumab (Vecitibix®) do not work well in about 40% of colon cancer patients with a particular allele. See Table 1 for more examples.

Mental health, especially depression, is also a current target. Treatment requires weeks of therapy to determine if the medication will be effective, and if not, then another medication must be used. Selective serotonin receptor inhibitors (SSRIs) are a standard of therapy. Clinical trials are underway to identify genetic alleles that predict SSRI responsiveness. One example is that current studies indicate that patients on citalopram (Celexa®) are influenced by specific genetic variations. If these studies are validated, then there will be genetic variations for testing before administering SSRI antidepressants.

Ordering Genetic Tests

The volume of genetic tests (biomarkers) is increasing annually. As a result, medical specialists must focus on medications applicable to their specialty. To assist, the FDA has provided physicians, pharmacists and other generalists with some guidance. The Food and Drug Administration (FDA) requires/recommends information on genotyping drugs with their complementary biomarkers. FDA recommendations are listed in Table 2.

In addition to the FDA table, the Stanford University School of Medicine PharmGKB group provides tables to summarize good and bad news for drug interactions, side effects and dosing from genetic testing. These tables offer a level of information that clinicians may use to order genetic testing for prospective management of drug interactions and for confirmatory purposes. (Tables 3, 4)

Pharmacogenomics and New Drug Development

Pharmacogenomics offers an opportunity to improve the targeting of existing medications to the patient population that can benefit the most. The goal is to produce new drugs that are highly effective and do not cause serious side effects.

Different from traditional drug development that involves screening for medications with broad action against a disease, researchers are now using genomic information to design drugs aimed at patients with specific genetic profiles. Researchers are also using pharmacogenomic tools to find drugs targeting specific molecular and cellular pathways involved in diseases.

For example, bucindolol (Gencaro), a beta-blocker to treat heart failure, was never marketed. However, after tests showed that the drug worked well in patients with two genetic variants that regulate heart function, there is renewed interest.

Cost-Benefit Issues

Marrying drugs to genetic biomarkers adds cost to health care. It is necessary to be sensitive to the value of a test versus the benefit derived from its use. As with all laboratory testing, genetic biomarkers have been studied to a greater or lesser degree and have established benefits limited by their specificity (true negatives) and sensitivity (true positives). Many references, including Lexicomp, reflect the evidence supporting testing with scoring criteria.[7]

The American Medical Association (AMA) has made the case that testing leads to cost savings for the overall healthcare system, by cost avoidance although not necessarily for each patient. The AMA cites:[8]

- Decreasing the number of adverse drug reactions
- Decreasing the number of failed drug trials
- Decreasing the time it takes to achieve drug approvals
- Decreasing the duration of therapy for specific medications
- Decreasing the number of medications to achieve an effective result
- Decreasing the effects of disease through early detection

Ultimately, the cost-benefit must be decided for each patient. The value equation is a result of the sum total of all interventions. As the science is new, it is incumbent on the entire health care team, including the patient, to identify, discuss and participate in the decision to utilize a pharmacogenomic test.

Conclusion

Tesla was right. Science takes time to integrate into clinical practice. Furthermore, the complexity of DNA knowledge integrated into clinical practice will require extensive training for current and future practitioners. As practitioners are trained in the benefits of pharmacogenomic testing, the practice will expand. It will be incumbent on all practitioners to understand the benefits of these tests on particular patients. Since the application of this knowledge requires experts in multi-specialties, the application of this knowledge fits well into a team approach. The science requires objectivity, and patients need this type of objective information in order to make more informed decisions. Pharmacists are in a unique position to

select appropriate patients, offer guidance, education and monitoring for applicable medications. Pharmacogenomics and precision medication offers a new area for pharmacy practice that is both exciting and challenging.

About the Author

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Figure 1. DNA Molecule

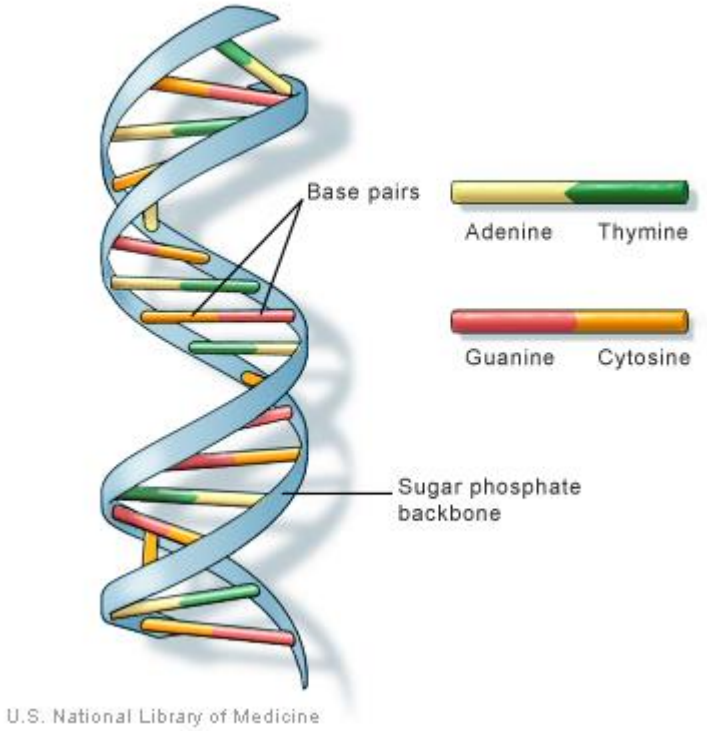

Table 1. Mature Medication Genetic Testing Examples

Drug Name	Gene	Reference Subgroup	Action	CPT Codes
Anastrozole	ESR1, PGR	Hormone receptor positive	Positive	88360
Azathioprine	TPMT	TPMT intermediate or poor metabolizers	Negative	81401
Carbamazepine	HLA-B	HLA-B*1502 allele carriers	Negative	81380
Carbamazepine	HLA-A	HLA-A*3101 allele carriers	Negative	81380
Peginterferon alfa-2b	IFNL3	IL28B rs12979860 T allele carriers	Positive	81400
Phenytoin	HLA-B	HLA-B*1502 allele carriers	Negative	81380
Rifampin, Isoniazid, and Pyrazinamide	NAT1-2	slow inactivators	Negative	81479
Tretinoin	PML/RARA	PML/RAR_alpha (t(15;17)) gene expression positive	Positive	81315
Valproic Acid	POLG	POLG mutation positive	Negative	81406
Valproic Acid	NAGS, CPS1, ASS1, OTC, ASL, ABL2	Urea cycle enzyme deficient	Negative	81405
Warfarin	VKORC1	VKORC1 rs9923231 A allele carriers	Negative	81355
Warfarin	PROC	Protein C deficient	Negative	85302

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Table 2. FDA Recommended List of Biomarkers

MEDICATION	BIOMARKER
Azathioprine (Imuran®)	TPMT deficiency
Carbamazepine (Tegretol®)	HLA-B*5101
Celecoxib (Celebrex®)	CYP2C9
Cetuximab (Erbitux®)	EGF receptor
Gefitinib (Iressa®)	EGF receptor mutations
Imatinib mesylate (Gleevec®)	C-kit mutations, BCR/ABL translocation
Irinotecan (Camptosar®)	UGT1A1, homozygous for the *28 allele
Maraviroc (Selzentry®)	HIV-CCR5 receptor site
Mercaptopurine (Purinethol)	TPMT deficiency
Trastuzumab (Herceptin®)	HER2-neu
Warfarin (Coumadin®)	CYP2C9; VKOR

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Table 3. Summary of Genetic Good News – Stanford University

Drug	Summary	Level of Evidence	PMID	Gene	rsID
HMG COA Reductase	No increased risk of myopathy	High	18650507	SLCO1B1	rs4149056
Inhibitors (statins)					
Statins	No increased risk of myopathy	High	12811365	SLCO1B1	rs4149056
Desipramine; Fluoxetine	Depression may improve more than average	Medium	19414708	BDNF	rs61888800
Fluvastatin	Good response	Medium	18781850	SLCO1B1	rs11045819
Metoprolol and other CYP2D6 substrates	Normal CYP2D6 metabolizer.	Medium	19037197	CYP2D6	rs3892097/rs18007 1 6
Pravastatin	May have good response	Medium	15199031	HMGCR	rs17238540
Pravastatin, Simvastatin	No reduced efficacy	Medium	15199031	HMGCR	rs17244841
Caffeine	No increased risk of heart problems with caffeine	Low	16522833	CYP1A2	rs762551
Calcium channel blockers	No increased risk of Torsades de Pointe	Low	15522280	KCNH2	rs36210421
Carbamazepine	SNP is part of protective haplotype for hypersensitivity to carbamazepine	Low	16538175	HSPA1A	rs1043620
Nevirapine	Reduced risk of hepatoxicity	Low	16912957	ABCB1	rs1045642
Efavirenz; Nevirapine	Reduced risk of hepatoxicity	Low	16912956	ABCB1	rs1045642
Epoetin Alfa	Lower dose of iron and epo required	Low	18025780	HFE	rs1799945
Fexofenadine	Average blood levels expected	Low	11503014	ABCB1	rs1045642
Irbesartan	Irbesartan may work better than beta-blocker	Low	15453913	APOB	rs1367117
Lithium	Increased likelihood of response	Low	18408563	CACNG2	rs5750285
Paroxetine	May have improved response	Low	17913323	ABCB1	rs2032582
Pramipexole	More likely to respond	Low	19396436	DRD3	rs6280
Pravastatin	No reduced efficacy	Low	15226675	SLCO1B1	rs4149015
Rosiglitazone	May have good response	Low	18693052	LPIN1	rs10192566
Succinylcholine	No increased risk of apnea	Low	1415224	BCHE	rs28933389

PharmGKB, http://www.pharmgkb.org/

Table 4. Summary of Pharmacogenetic Bad News – Stanford University

Drug	Summary	Level of Evidence	PMID	Gene	rsID
Clopidogrel & CYP2C19	CYP2C19 poor metabolizer, many drugs may need adjustment.	High	19106084	CYP2C19	rs4244285
Warfarin	Requires lower dose	High	15888487	VKORC1	rs9923231
Warfarin	Requires lower dose	High	19270263	CYP4F2	rs2108622
Metformin	Less likely to respond	Medium	18544707	CDKN2A/B	rs10811661
Troglitazone	Less likely to respond	Medium	18544707	CDKN2A/B	rs10811661
Cisplatin	Increased risk of nephrotoxicity	Low	19625999	SLC22A2	rs316019
Citalopram	May increase risk of suicidal ideation during therapy	Low	17898344	GRIA3	rs4825476
Escitalopram; Nortriptyline	Depression may not respond as well	Low	19365399	NR3C1	rs10482633
Morphine	May require higher dose for pain relief	Low	17156920	COMT	rs4680
Paclitaxel	Cancer may respond less well	Low	18836089	ABCB1	rs1045642
Pravastatin	May require higher dose	Low	15116054	SLCO1B1	rs2306283
Talinolol	May require higher dose	Low	18334920	ABCC2	rs2273697

PharmGKB, http://www.pharmgkb.org/

Notes: PMID is a unique number used to identify articles in PubMed. rsID stands for Reference SNP cluster ID. SNP, or single-nucleotide polymorphism, is the variation in a single nucleotide that occurs at a specific position in the genome. rsID is the accession number used by researchers and databases to refer to specific SNPs. When genome-wide association studies linking SNPs or traits to conditions are reported, they use the rsID for reference.