

Genetic Counselling, Pharmacogenetics and Gene Therapy: The Paving-Stones Leading to Brighter Futures

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Abstract

In today's day and age, technology is constantly evolving, rendering other forms of technology once considered state-of-the-art to become obsolete. These technological innovations which are occurring affect nearly every, and all fields of medicine. These trending innovations can be seen in the field of genetics as well where Geneticists are able to identify an individual's risks of transmitting a genetic disorder on to the next generation, through their offspring. This non-directive branch of genetics, known as genetic counselling goes hand-in-hand with two other branches of genetics to allow the counsellor to identify certain genetic abnormalities and also provide hope to the patient that there is the possibility of having a normal child. One such branch is known as pharmacogenetics, a field of genetics that is advancing rapidly, and still has much allure and mystique to it. Its main aim is to make a significant impact, clinically, on the lives of patients it is employed to treat. It is a field that has quite a bit of potential to affect a large number of different groups within the healthcare field that ranges from pharmacists and physicians to pharmaceutical and insurance companies. Gene therapy is the other branch involved, and it has to do with the insertion of genes into the cells and tissues of an individual in order to treat a specific pathosis present. At the current time, both are new fields but with the commonplace innovations in technology occurring around us, it is not long before these two techniques will fulfil the hopes and aspirations of many people.

Keywords: Paving-Stones; Pharmacogenetics; Phenotyping

Introduction

In today's day and age, technology is constantly evolving, rendering other forms of technology once considered state-of-the-art to become obsolete. These technological innovations which are occurring affect nearly every, and all fields of medicine, and does not discriminate to certain fields of medicine or a specific diagnostic or therapeutic modality, such as MRI or ERCP technology. These trending innovations can be seen in the field of genetics as well where Geneticists are able to identify an individual's risks of transmitting a genetic disorder on to the next generation, through their offspring. The consequences are outlined with the potential parents and possible solutions are outlined in order for the parents and the patient to have peace of mind. This non-directive branch of genetics, known as genetic counselling goes hand-in-hand with two other branches of genetics to allow the counsellor to identify certain genetic abnormalities and also provide hope to the patient that there is the possibility of having a normal child [1]. One such branch is known as pharmacogenetics, a field of genetics that is advancing rapidly, and still has much allure and mystique to it. Its main aim is to make a significant impact, clinically, on the lives of patients it is employed to treat. It is a field that has quite a bit of potential to affect a large number of different groups within the healthcare field that ranges from pharmacists and physicians to pharmaceutical and insurance companies. Gene therapy is the other branch involved, and it has to do with the insertion of genes into the cells and tissues of an individual in order to treat a specific pathosis present [2].

Genetic counselling refers to where individuals, who present with a specific inherited disorder, or its risk factors, are advised of the

consequences and nature of the disorder in question [1]. The probabilities of developing or transmitting the disorder are further explained coupled with the different management options currently available to prevent, avoid or ameliorate it, through something known as family planning. This complex process must be objectified from two different perspectives, the diagnostic aspect, where the actual estimation of risk is determined for an individual, and the supportive aspect, which comes in the form of family planning [2].

Patients seeking genetic counselling could be parents that were newly diagnosed with a child with a genetic disorder, new couples who are planning a pregnancy, or even an individual who feels that they may have inherited a condition from their biological parents [2]. For instance, a woman may undergo genetic counselling during her pregnancy along with her regular prenatal tests. If there are any abnormal results, the genetic counsellor will be able to evaluate the risk that the woman has of having an abnormal pregnancy and what some of her options may be post-delivery, if she chooses to continue with the pregnancy [2]. However, a person is not barred to only seek genetic counselling prenatally, as many an individual has sought out genetic counselling postnatally, usually after the birth of a child who presents with a genetic condition.

Generally speaking, Genetic Counsellors work as an entity of a larger health care team, acting as an advocate for patients and a genetic resource for physicians. The traditional route of referral, through a general practitioner or a hospital consultant usually occur post-diagnosis of a genetic syndrome of disease [1]. Their aim is to bridge the gap between the everyday world of the patient and the complex and often fast moving field of medical genomics [1]. Genetic counsellors allow the patient to understand the nature of the disease in question, and what having this disease would mean in practical terms.

They also provide options that may be available for prevention or testing the patient or the risk of recurrence of the syndrome in future children, along with possible implications affecting other family members is also addressed [1]. It is important to note that genetic counsellors are non-directive, which means that they do not tell the couple what to do, but rather, they provide support and the necessary resources for the people to make their own decisions about whether they wish to have children or not [1]. Counsellors are trained to help patients persevere through the psycho-social fluctuations that ever-present and go hand-in-hand with negative diagnoses.

The study of pharmacogenetics serves to explain variability in pharmacological response resulting from genetic differences. Pharmacogenetics is based on the observation of phenotypes and investigates variations in genes as they relate to drug metabolism. It allows for better comprehension of pharmacodynamics and pharmacokinetics, in order to reduce potentially harmful side effects [3-5]. Pharmacogenetics is not just used in the context to describe an individual's response to a particular drug, now it is used more broadly to describe the commercial application of genomic technology in drug development and therapy. Scientists will identify or design therapeutic agents that interact with these targets in a way that achieves positive clinical outcome and minimal toxicity [6]. In context with the original definition of pharmacogenetics, genetic variations, also known as

polymorphisms that alter drug concentrations and responses are identified [6]. This variation exists because the DNA sequences in individual humans varies from one individual to another, and the genetic and protein differences are able to induce a different systemic drug concentration in each individual's body [6,7]. Some drugs act on drug receptors that have certain polymorphisms, resulting in varying structures. The systemic drug concentration is the end result of ingestion, absorption, metabolism, clearance, and excretion [7]. These differences in systemic drug concentration and polymorphism in drug receptors are just some of the explanations why certain patients respond differently to a certain drug than others. Some drugs act on cell receptors that have different structures throughout the population (polymorphisms). Variations in systemic drug concentrations and receptor polymorphisms help explain why some patients respond well to drugs, while others do not [7]. A drug might be toxic to one individual and not another. Physicians and pharmacists have been aware of these different responses, but there has been no accurate way to predict them. Pharmacogenetics is leading the way and providing a beacon of light to assist in predicting these specific responses [6,8]. Tables 1 and 2 illustrate some of the drugs for which pharmacogenetic testing is currently available, along with other pertinent information with regards to the specific biomarkers tested, and whether pharmacogenetics testing is recommended for that particular drug.

Medication	Biomarker	Label Section(s)	Evidence Rating
Abacavir	HLA-B*5701	Boxed Warning, Contraindications, Warnings and Precautions, Patient Counselling Information	A
Carvedilol	CYP2D6	Drug Interactions, Clinical Pharmacology	A
Citalopram	CYP2C19/CYP2D6	Drug Interactions, Warnings	C
Clopidogrel	CYP2C19	Boxed Warning, Dosage and Administration, Warnings and Precautions, Drug Interactions, Clinical Pharmacology	A
Metoprolol	CYP2D6	Precautions, Clinical Pharmacology	C
Pravastatin	APOE2	Clinical Studies, Use in Specific Populations	C
Tamoxifen	ER, Factor V Leiden, PT	Indications and Usage, Precautions, Medication Guide, Warnings	B
Tramadol	CYP2D6	Clinical Pharmacology	B
Warfarin	CYP2C9, VKORC1	Dosage and Administration, Precautions, Clinical Pharmacology	A

Abbreviations: HLA: Human Leukocyte Antigen; CYP: Cytochrome P450; APOE: Apolipoprotein E; ER: Estrogen Receptor; PT: Prothrombin Time; VKORC1: Vitamin K Epoxide Reductase Complex subunit 1

^aDataFrom:<http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm>

Table 1: Pharmacogenetic biomarker and label section^a

It was in the 1950s that the field of pharmacogenetics evolved as an attempt to understand what genetic differences induced diverse metabolic responses to different drugs in different individuals [7]. Pharmacogenetics, before the introduction of technology to isolate individual genetic variation or genotypic variation, was based on ethnic differences. According to this model, there was three major ethnic groups: The Negroid, the Mongoloid and the Caucasoid [6]. It was further narrowed down by ill-defined categories of geography,

anthropology, language, and race. Interestingly enough, it was the inability of patients to taste Phenylthiourea (PTU), an organosulfur thiourea containing a phenyl ring which first demonstrated the merits of pharmacogenetics testing for particular traits in response to different chemical compounds. Individuals with PTU insensitivity could not taste the chemical. It was the first chemical insensitivity shown to be heritable, and incidence varied within population groups [6].

CYP2D6, CYP2C9	Metoprolol, tramadol, paroxetine, venlafaxine	Testing: N Therapeutic: Y
CYP2D6, CYP2C9, CYP2C19	Tamoxifen	Testing: N Therapeutic: N
CYP2D6, CYP2C19	SSRIs	Testing: N Therapeutic: N
CYP2C9, VKORC1	Warfarin	Testing: N Therapeutic: N
HLA-B*5701	Abacavir	Testing: Y Therapeutic: Y
CYP2C19	Clopidogrel	Testing: N Therapeutic: Y
CYP3A4	Statins	Testing: N Therapeutic: N
Recommendations given in the guideline regarding the utility of general pre-treatment testing (Testing) or regarding genotype-specific treatment (Therapeutic); N: guideline does not recommend testing or does not give recommendations; Y: guideline recommends testing or gives genotype-specific treatment recommendations [9].		

Table 2: Existing clinical practice guidelines for pharmacogenetic biomarkers.

Since the 1950s, there has been much innovation going on in the field of science and a considerable amount of technology has allowed pharmacogenetics to become markedly advanced in the present day, versus its humble beginnings [4]. The technology that was so essential in the development of this field was gene and protein sequence machines, which allowed geneticists to determine nucleotide and amino acid sequences of different proteins and genes, allowing genetic variations to be noted [4]. Genotyping and Phenotyping are the two main strategies that have been used in polymorphism screening. Phenotyping encompasses an observable biochemical measure. It determines both the presence and activity of a metabolic enzyme in a tissue biopsy, which is often referred to as functional phenotyping [6]. Level of metabolites in different individuals after drug administration is conducted in metabolic phenotyping. This approach is usually more invasive and detrimental to the patient, as it has many adverse side effects. Along with phenotyping, there is genotyping which goes about determining the specific genetic code of an individual. This technique is safer than phenotyping as it is less invasive when obtaining a tissue sample. However, these results are usually harder to interpret and give the root cause of the different responses versus phenotyping which provides the pharmacogenetic variations present between individuals. These modalities, along with biotechnological analyses, are the cutting edge technology which has allowed the advancement of the discovery of new genetic variation which could help improve the administration and employment of older drugs [4].

Gene therapy has to do with the insertion of genes into the cells and tissues of an individual in order to treat a disease present. Such diseases include hereditary diseases where there is a non-functioning mutant allele that is replaced by a functional allele. Even though this technology is still in its early stages, there has been some success and there is so much hope in this field of genetics, where individuals who have genetic disorders may be able to live a normal life [3].

It was on September 14, 1990 that the first approved procedure of gene therapy was performed by W. French Anderson, M.D., R. Michael

Blaese, M.D., C. Bouzaid, M.D., and Kenneth Culver, M.D., at the US National Institutes of Health [3]. The procedure was performed on a four year old girl, who was born with a rare genetic disease, known as severe combined immunodeficiency (SCID). This meant that the patient lacked the active components necessary for the body to have a competent and healthy immune system, thus being susceptible to a number of different infections [3]. In this particular gene therapy procedure, white blood cells were removed from the patient's body and allowed to grow within the laboratory. The missing gene was then inserted into the cells and the infused back into the patient's body [3]. Many believe that this study was very ground-breaking in the field, with very promising results [3].

As gene therapy is still in its infantile stages, the road to attaining the first approved gene therapy procedure was not smooth and there was also some controversy involved. Gene therapy is a very complex field of study and there are still some techniques that need to be developed and certain diseases need to be understood more fully before the appropriate utilization of gene therapy can be done. At the current time, scientists are looking at ways of introducing genes straight into the human cells, placing their focus on diseases that are caused by single-gene defects, such as, haemophilia, cystic fibrosis sickle cell anaemia, and muscular dystrophy [4].

There are two main types of gene therapy. The first type is known as germ-line gene therapy, where there is a modification of sperm or eggs through the introduction of functional genes, integrated normally into their genomes. This change would then be a heritable one and passed on to the next generation, and should be effective in counteracting genetic disorders [7]. Somatic gene therapy is the other form of gene therapy where therapeutic genes are transferred directly into the somatic cells of a patient. Any changes that occur will be individual, and have no chance of being passed to the next generation [7].

A number of different methods exist to replace and repair different target genes. First, a normal gene could be inserted into a location that

is nonspecific within the genome in order to replace a non-functional gene. This approach is the most common one used. Homologous recombination could allow an abnormal gene to be replaced by a normal gene. Second, abnormal genes could be repaired by a process known as selective reverse mutation, where a gene or other nucleotide sequence that has undergone mutation returns its normal function [6].

Genetic counselling is a very useful tool in assisting future parents, at risk of a genetic disorder, the consequences of having a child, and what they can do if they do, in fact decide to have children. Along with genetic counselling, pharmacogenetics and gene therapy can be two very useful tools that can be offered as a solution for these families, who are usually so emotionally distraught after discovering that they are at high risk of having a child with a genetic defect. This can be very difficult for certain families when a negative diagnosis is given by a physician. Certain people want the opportunity to have a normal child or do something that can allow them to have the opportunity. This is where pharmacogenetics and gene therapy come into play. This is the reason that there are many hopes linked to these areas of genetics [9]. There is a great desire to allow families to be able to lead happy lives, to see the light at the end of the tunnel. Both fields focus on going to root genetic cause and trying to alleviate the problem from that level. At the current time, both are new fields but with the commonplace innovations in technology occurring around us, it is not long before these two techniques will fulfil the hopes and aspirations of many people. However, one has to weigh both aspects of the spectrum, as there should be no compromise of ethical considerations, which, as of

recent, have been gaining increasing attention in the scientific community, with regards to patient privacy, and possible patient discrimination based upon results of pharmacogenetic testing, which reflect that a patient may present with a certain condition, or be more prone to certain environmental factors.

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