

GENETIC INTERVENTION AS A LIFESTYLE APPROACH:  
AN ANALYSIS OF DISEASE AND TREATMENT

by

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## **ABSTRACT**

**Purpose:** The scientific knowledge of how genes affect disease expression and evolution can facilitate more effective environmental and drug therapy interventions delivered by health care professionals. The purpose of this paper is to a) describe the role of genetic science in healthcare; b) explore genotype determinants for environmental and pharmacological interventions; c) and analyze ethical dilemmas, barriers to access, and allocation of resources based on genotype.

**Methods:** A review of literature was conducted from the disciplines of nursing, medicine, psychology, and sociology using the CINAHL, Ebsco Host, Medline, and PsychINFO databases. The search was limited to peer reviewed, full text article in English that dated from 1987 to 2011. Inclusion criteria were articles describing environmental, pharmacologic, and nutritional influence on genetic expression. Forty-five articles on genetic intervention were chosen for further review, in addition to five book publications which met inclusion criteria. Many of the sources retrieved were obtained from the biomedical sciences and published in the last decade, owing to more recent innovations in genetic discovery.

**Results:** Disease and treatment must be approached according to genetic profiles for effectiveness and to increase health outcomes. Several variations were found regarding response to pharmaceuticals, as well as environmental exposures, based on genotype.

**Conclusions:** Health care has been practiced using a “universal protocol” approach;

however, as the literature reveals, each individual genotype must be taken into account to provide optimal care.

## **DEDICATIONS**

For victims of genetic disorders, may you have the strength to overcome,

For my professors, thank you for your encouragement and guidance,

For my family, thank you for your courage,

For my husband, thank you for always believing in me. You are my rock; my accomplishments would be few without your love and support.

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## INTRODUCTION

The emerging science of human genetics is reshaping the way in which diseases are diagnosed, treated, and prevented. Recent advances in the etiology for the genetic composition of disease expression and evolution incorporate various relationships between genetic health, genetic risk, and intervention. In the past, evidence-based practice has focused on the work of Gregor Johann Mendel, which established disease interventions based on the expression of single gene locus disorders with simple, genetically attributed causes (Frazier, Turner, Schwartz, Chapman, & Boerwinkle, 2004). However, diseases are now being studied and treated under the idea of complexity, which involves multi-factorial causes. This is because complex diseases, with extreme individual variation, are a public health concern and consist of more than just standard vulnerability. As the framework implies, there are genetic components with susceptible alleles, that when combined with the right triggers, can initiate or exacerbate disease (Frazier et al., 2004). As concluded by Mendel's work, the genotype of an individual is made up of many forms and specific variants of a gene that can be responsible for hereditary variation. An individual's phenotype is determined by their genotype. However, genetic disease expression and evolution is multi-factorial and can be influenced by the lifestyle an individual pursues, including choice of residence, food preferences, occupation, and personal behaviors the individual chooses to engage in (D'Amato-Kubiet, 2009).



Chronic diseases such as cardiovascular disease, cancer, stroke, and diabetes possess a genetic component. However, environmental factors, including lifestyle and dietary habits have been known to trigger, accelerate, exacerbate, or prolong onset of disease (Greco, Prows, Skirton, Williams, Jones, Middleton, Lewis, Bickford, Daley, Seiler, Carson-Smith, 2007). Response to environmental triggers remains inconsistent from one individual to another. Genetic variation alone cannot account for disease susceptibility in some, without environmental and/or behavioral factors. Although it is well known that disease can be controlled by manipulation of lifestyle and environmental factors, chronic disease rates are still on the rise. This is because current treatments are based on standards of care which establish interventions based on epidemiological studies of large populations, not individuals. As stated by Khoury, Davis, Gwinn, Lindegren, and Yoon (2005), "our current public health approaches to prevention have not been adequate". Therefore, studies that explore the underlying science of the individual gene-environment interactions is expected to unravel more precise interventions to improve quality of life (Andreasen & Andersen, 2009). Recently, the genetic basis for drug therapy has been aimed at uncovering how variations in multiple genes affect the pharmacokinetics and pharmacodynamics of a drug. Genetic variation among individuals has been found to alter the therapeutic response to drugs, and can now be linked to adverse reactions or lack of response to drug therapy. Understanding genetic variation in response to drugs allows medications to be tailored to individual phenotypes and genetic predispositions, rather than the use of a universal (standard) protocol that may be less effective or even

detrimental to select genotypes. The purpose of this study is to examine barriers and access to genetic determinants of disease and their impact on lifestyle based interventions. Two areas of genetic discoveries, ecogenetics and pharmacogenetics, will be examined to determine their implications for lifestyle interventions and research. The knowledge of genetics is rapidly expanding; therefore, there is an increased need to explore the types of interventions available for diagnosing, treating, and preventing disease.

## **IMPACT OF GENETIC SCIENCE IN HEALTH CARE**

### **Human Genome Project**

Several organizations are extensively exploring human genetics in effort to broaden our understanding of the role of genetics in the human species, including The Department of Energy, The National Institutes of Health, and The Center for Disease Control and Prevention. Of these organizations, The Department of Energy established The Human Genome Project (HGP), which began in 1990. The results of this project uncovered many components in the field of genetic variation. The project's primary purpose was to understand the genetic makeup of the human species in an effort to develop medicines and guide decisions in healthcare. The HGP concluded in its results that human beings possess approximately 20,500 genes (HGIP, 2010). Further genetic research is being conducted to explore genetic expression and will provide insight into disease etiology and pathogenesis. Leaders in genetic research propose that disease specific treatments can be developed based on finding the multi-factorial genetic/genomic components of disease. The Human Genome Project (2010) focused on genetic variants of more common, major diseases such as cardiovascular disease, cancer, or diabetes. The results provided the need for greater amounts of genetic testing for the underlying gene components of disease (HGIP, 2010).

Genetic testing involves the analysis of cells for gene products such as proteins, enzymes, metabolites, and/or chromosomes (HGPI, 2010). Genetic testing is the precursor for genomic health care, which is defined as a highly individualized plan of care that utilizes

information related to phenotype responses and gene functions (Shives, 2008). The results of these tests allow early identification of disease susceptibility and treatment with conventional interventions based on individual genetic variation. Early identification of disease involving the application of knowledge about genes is accomplished through the use of reproductive and therapeutic genetic testing interventions. Reproductive genetic testing interventions are suggested for individuals with a known family history of a genetic disorder, to guide reproductive decisions. The testing may be performed on persons who intend to have children, or on the fetus if conception has occurred (Buchanan, Brock, Daniels, and Wikler, 2000). Therapeutic genetic testing interventions involve tailoring environments, nutrition, or medication regimens to optimize health and treatment. In both circumstances, genetic screening for high-risk populations or those with family history will facilitate early prevention and treatment (Ambler & Brown, 1999). Decisions to pursue genetic testing can be determined through the use of genetic counseling. Counseling provides an avenue to assist individuals in understanding, adapting to, and using genetic information. Genetic counseling addresses concerns of cost, by assisting individuals in utilizing resources, becoming active consumers, and determining the benefits of treatment (Greco et al., 2007).

## **ENVIRONMENTAL AND PHARMACOLOGICAL INTERVENTIONS**

### **Ecogenetics**

The recent movement in molecular science has given significant meaning to the principle behind ecogenetics that genes form the basis for disease, but are not expressed unless an environmental trigger is exercised (D'Amato-Kubiet, 2009). Ecogenetics uses knowledge of how genes work in various environments to predict and intervene on the basis of genotype. Exploring ecogenetics provides a basis for understanding how gene-lifestyle interactions enhance our knowledge of disease, design interventions, and eventually facilitate disease prevention (Pomeroy, Soderberg, & Franks, 2009). When considering genetic-environmental interactions, it is important to identify the underlying susceptibility of genes to biologic and physiologic factors. This will give explanation as to why some individuals develop disease when exposed to environmental agents and how genetic predisposition may encourage adaptation to environmental exposures (Frazier et al., 2004). Additionally, understanding how and which environmental stimuli promote manifestation of disease susceptibility genes will lead to individualized disease prevention strategies (Frazier et al., 2004).

Genetic research focused on lifestyle interventions is determining which environmental exposures present disease risk and is using genetic sensitivity to chemical agents to develop individualized drug therapy plans of care. It will require an integrative approach using epidemiologists' future studies of environmental causes of human disease,

as more genes and biologic pathways are researched (Khoury et al., 2005). Furthermore, genetic technology and studies examining large sample groups from defined populations have strengthened causal interpretation of genetic knowledge of disease expression (Frazier et al., 2004). Environment-gene interactions can be difficult to accurately measure or describe because of inconsistent exposure to environmental triggers over time, such as changes in residence or dietary habits. However, technological tools for measuring casual gene-environment relationships with exposure overtime are rapidly being developed. For example, toxicogenomics is being examined to assess the effects of specific chemical exposures using gene and protein expression as markers (Khoury et al., 2005). Additionally, rather than examining only genetic causes, it will prove most beneficial to identify environmental triggers associated with specific genes to better prevent and treat disease.

### **Insulin Resistance in Metabolic Syndrome**

In a recent study by the American Society for Nutrition, gene-nutrient interactions were examined to determine susceptibility to metabolic alterations in metabolic syndrome phenotypes, particularly insulin-resistance. The study's aim was to analyze the degree of influence that genetic as well as environmental factors, specifically dietary fat, have on health outcomes. The interaction between specific alleles of the adiponectin and plasma saturated fatty acids were evaluated to determine responsiveness to dietary intervention. Adiponectin plays a major role in regulating insulin sensitivity, and decreased

concentrations have been found in metabolic syndrome phenotypes (Ferguson, Phillips, Tierney, Perez-Martinez,, Defoort, Helal, Lairon, Planells, Shaw, Lovegrove, Gjelstad, Drevon, Blaak, Saris, Golabek, Wilk, Riserus, Karlstrom, Miranda, & Roche, 2010).) The study included 451 subjects, all having metabolic syndrome phenotypes. Inclusion criteria for metabolic syndrome phenotypes consisted of: body mass index of 20-40kg/m, and required subjects to fulfill  $\geq 3$  of the following 5 criteria: waist circumference  $> 102$ cm (men) or 88cm (women), fasting glucose 5.5-7.0mmol/L, triacylglycerol  $\geq 1.5$ mmol/L, cholesterol  $< 1.0$ mmol/L (men) or 1.3mmol/L (women), and blood pressure  $\geq 130/85$  mm Hg (Ferguson et al., 2010). Genetic analysis tools were then used to identify the presence of single-nucleotide polymorphisms in the adiponcentin gene, which contribute to the development of insulin resistance in metabolic syndrome (Ferguson et al., 2010). As shown in Table 1, the single-nucleotide polymorphisms which showed the greatest interaction between saturated-fatty acids and alterations in insulin sensitivity were rs266729 and rs10920533. Individuals homozygous for the minor allele in both single-nucleotide polymorphisms were found to be more sensitive to an oral fat load and high concentrations of saturated-fatty acids. Exploration of similar studies suggests there is a relationship between genetic expression of insulin resistance and dietary intake that is unique to individuals with diabetes, a component of metabolic syndrome. Personalized nutrition is a modifiable contributor to lifestyle management that can prevent or mitigate disease progression since the genotype of these polymorphisms may play a role in the

responsiveness to dietary fatty acid modification in subjects with metabolic syndrome (Ferguson et al., 2010).

### **Environmental Exposure in Children with Fragile X Syndrome**

According to Murphy & Abbeduto (2005) developmental theorists studied the role of genes in behavioral development using transactional analysis as a theoretical framework. This model provides a method for psychosocial analysis, describing patterns of childhood development and external influences (Berne, 2001). The theory implies that an individual's behavior and characteristics are established by an interaction between one's genotype and environmental factors. Within the framework of transactional analysis, a genetic anomaly is labeled as predisposing an individual to a behavioral phenotype; however, the environment determines the extent of expression (Murphy & Abbeduto, 2005). To understand the magnitude of environmental influence, a transactional analysis of behavioral development must be applied to interventions associated with genetic anomalies. In the example of fragile X syndrome, an X-linked genetic disorder, language development with difficulty in communication skills, hyperarousal and hypersensitivity to sensory stimuli are common traits (Murphy & Abbeduto, 2005). Using transactional analysis, developmental theorists concluded that these syndrome-specific behaviors are extremely variable and may be prompted more by environmental factors such as anxiety and arousal than by the severity of the genetic disorder. Therefore, modification of these environmental factors may optimize levels of arousal and enhance learning ability (Murphy



& Abbeduto, 2005). However, it must not be overlooked that environmental modifications used to promote development have the potential to further distinguish the course of the disorder. Behavior and lifestyle factors, including modifications of surroundings enhance development by decreasing arousability (Murphy & Abbeduto, 2005). But, these same modifications may create nonnormative environments, while promoting syndrome-specific behaviors. In an effort to correct or avoid hyperarousal or overstimulation, the child may become dependent on the use self-directed behaviors or avoidance of social interaction (Murphy & Abbeduto, 2005) As a child with fragile X syndrome moves through developmental stages, the behavioral phenotype may be become more apparent. Inadvertently, environmental modifications in which the child interacts with may promote expression, thus decreasing the likelihood of syndrome-specific characteristics diminishing over time (Murphy & Abbeduto, 2005). The environmental intervention of transactional analysis focuses on transactions that occur between the child and interactions within their environment. As shown in Table 1, this approach will assist in identifying counterproductive transactions, in addition to communication distortions (Berne, 2001). Ultimately, growth promotion and development in a child with fragile X syndrome, depend on how the child responds to various environmental input, including responsiveness of caregivers to syndrome-specific behaviors.

## **Traveling Population and Thrombosis Formation**

A major area of concern regarding environmental risk factors in genetically susceptible individuals is the traveling population. When considering the environmental factor of “economy-class syndrome”, there has been concern as to why some individuals experience thrombotic events during long duration travel and others do not, given that all other environmental factors are equal (Sharma & Gohil, 2010). This gap in knowledge led the researchers to examine the influence of genetic factors on the development of venous thrombosis. The results found by Sharma & Gohil (2010) identified mutations in the coagulation Factor V and Factor II [prothrombin G20210A]. A significantly large portion of individuals with single-nucleotide polymorphisms in one of either gene were found to have experienced a venous thrombotic event. The study supported its findings through a meta-analysis review of 173 studies. The results as seen in Table 1, were that a genetic contribution could be attributed to at least 200,000 deaths in one year, associated with a venous thrombotic event (Sharma & Gohil, 2010). The resultant implications are that individuals who are at known genetic risk for developing venous thrombosis, combined with the right environmental stimuli [extended flight], may implement preventative measures such as using anti-embolism stockings or prophylactic use of selective anticoagulants (Sharma & Gohil, 2010).

**Table 1: Ecogenetic Interventions in Metabolic Syndrome, Children with Fragile X Syndrome, and The Traveling Population**

Researcher	Population Studied	Genetic Alteration (SNP)	Environmental Factor	Findings
Ferguson et al., (2010)	451 subjects, all having metabolic syndrome phenotypes	adiponectin gene [rs266729] [rs10920533]	saturated fatty acids	Alterations in either interact with plasma saturated-fatty acids to alter insulin sensitivity. Screening for polymorphisms in the adiponectin gene will help identify those that would likely benefit from modification of dietary fat intake.
Murphy & Abbeduto (2005)  Berne (2001)	children of fragile X syndrome	X -chromosome	sensory stimuli  anxiety  arousal  (transactional analysis)	Interventions that focus on transactions between child & environment, in response to sensory stimulation & socially-adaptive behaviors will decrease the extent of expression.
Sharma & Gohil (2010)	traveling population	coagulation factor V  factor II (prothrombin G20210A)	extended flights	Individuals with either SNP are at increased risk for experiencing a venous thrombosis event and would benefit from prophylactic anticoagulant therapy &/or preventative measures (anti-embolic stockings).

Note: <sup>a</sup> Results from Ferguson et al., (2010). Gene-nutrient interactions in the metabolic syndrome: single nucleotide polymorphisms in ADIPOQ and ADIPOR1 interact with plasma saturated fatty acids to modulate insulin resistance. *American Journal of Clinical Nutrition*, 91, 794-801. <sup>b</sup> Results from Murphy, M. Abbeduto, L. (2005). Indirect genetic effects and the early language development of children with genetic mental retardation syndromes, the role of joint attention. *Journal of Special Care Practices*, 18(1), 47-59. &Berne, E. (2001). *Transactional analysis in psychotherapy*. London: Souvenir. <sup>c</sup> Results from Sharma, P., & Gohil, R. (2010). Genetic risk factors for venous thrombosis: the end of the beginning?. *Expert Review of Cardiovascular Therapy*, 8(1), 11-13. doi:10.1586/erc.09.159

## **Pharmacogenetics**

Pharmacogenomics is the study of how genes affect individual drug responses. An individual's genetic makeup can result in alterations in genes that code for metabolizing enzymes and drug targets. Through an analysis of an individual's complete DNA structure, the body's response to medicines can be studied to predict therapeutic and adverse effects (HGPI, 2010). Pharmaceutical interventions can be tailored to an individual to produce more effective and safe medications when the genetic susceptibility of a drug's pharmacokinetics are determined. The benefits of individualized drug therapy are exceptionally profound for the treatment and management of disease conditions. Through the analysis of human DNA/RNA molecules, proteins, and enzymes and the genes associated with specific diseases, a stronger therapeutic response can be created, with drug targets that are disease specific (HGPI, 2010). When beginning an individualized drug regimen, genetic results can be analyzed to determine the most effective drug response that can be elicited for a specific individual. Tailoring drugs to an individual's genetic composition can optimize therapeutic response to a drug while minimizing the risks of adverse reactions to the agent. Pharmacogenetics focuses on identifying genotypes that drive favorable or unfavorable drug responses (O'Malley, 2011). This can also lead to a reduction in the cost of a therapeutic agent by lessening the risk associated with prescribing ineffective drugs to certain genotypes. Currently, pharmacodynamics and pharmacokinetics are based on anthropometric measurements and age (HGPI, 2010). Using one's genotype provides a more accurate measurement of how the body metabolizes

a drug and determines dosage requirements. In fact, the Federal Drug Administration (FDA) has issued a warning that states, “drug outcomes are the function of genetic makeup and response variance, and side effects and adverse outcomes can be significantly controlled by prescribing based on a genetic profile” (O’Malley, 2011). Perhaps the most important indication for receiving the correct medication the first dose would be to eliminate the 100,000 deaths that occur annually as a result of pharmaceutical-genetic-mismatch (HGPI, 2010). These deaths resulted from either drug accumulation of toxic levels in the blood or the body’s inability to use the drug based on genetic factors. Other topics to consider while examining the benefits of pharmacogenetics are the use of new medications in clinical trials for drug discovery and development, vaccinations, and the reduction of overall health care costs (HGPI, 2010). Genetic profiling allows researchers to categorize individuals for clinical trials based on genotype, resulting in shorter clinical trials and reduced number of subjects needed (O’Malley, 2011). Furthermore, with the use of genetic profiling to identify individual variation in drug response, the time for drug development has the potential to reduce from 10 to 12 years to 3 to 5 years (O’Malley, 2011).

### **Ethnopharmacology in Psychotropic Drugs**

According to The Human Genome Project (2010), there are over 30 classes of drugs identified which are metabolized by the liver. The rate and amount of metabolism is influenced by DNA variations of cytochrome P450 genes. In the example of

ethnopharmacology (Shives, 2008), variations in the metabolism of psychotropic drugs are found, based on ethnicity. When prescribing psychotropic medications in the treatment of psychiatric disorders, differences in ethnic hepatic-biotransformation must be taken into consideration. Individuals who possess high enzymatic activity metabolize these medications at a very high rate, whereas individuals with less or inactive enzymatic activity metabolize the medications much slower (Shives, 2008). Adverse drug events can be a direct result of the rate and ability to metabolize medication. Literature reviewed by Shives (2008) identified that a large percent of the Eastern Asian population are considered “poor metabolizers”. Additionally, the same percentages of African Americans have been found to metabolize these drugs at a slower rate, in comparison to Caucasians. The resulting effect, shown in Table 2, can lead to an increased incidence of adverse effects (Shives, 2008). In consideration of a specific drug, lithium, it has been found that these particular ethnic groups also require reduced doses. Variations in plasma protein that binds lithium result in accumulation of the drug in the blood. Therefore, a dosage reduction is required to reduce the risk of lithium toxicity in the central nervous system (Shives, 2008).

### **Hepatic Metabolism of Anticoagulants**

Hepatic pathways that metabolize anticoagulants are the latest trend in genetic testing that combines an individual’s cellular environment with genetic vulnerability to drug therapy. The FDA recommends that patients undergo genetic testing for alterations in

enzymatic activity prior to prescribing the treatment of the anticoagulant agent, warfarin [Coumadin] (Lehne, 2010). When daily antithrombotic therapy is necessary, dosage adjustments should be considered in individuals with alterations in the cytochrome P450-2C9 [CYP2C9] and Vitamin K epoxide reductase [VKORC1] (refer to Table 2). Warfarin is used in the treatment for long-term prophylaxis of thrombosis formation, including prevention of venous thrombosis, prevention of thrombosis during atrial fibrillation, and to reduce the risk of recurrent transient ischemia attacks (Lehne, 2010). The enzyme CYP2C9 is responsible for warfarin metabolism; hence, individuals with alterations in this enzyme metabolize the drug at a slower rate. Additionally, VKORC1 is the target enzyme that warfarin inhibits, thus genetic alterations increase the enzyme's sensitivity to warfarin. Because warfarin has a narrow therapeutic index, these individuals are at greater risk for warfarin-induced bleeding, which concludes that these individuals require a dosage reduction (Limdi, Wiener, Goldstein, Acton, & Beasley, 2009).

In regards to genetic influence on drug responses, several European phenotypes, shown in Table 3, demonstrate genetic tendencies to be slow metabolizers of succinylcholine, resulting in a need for dosage adjustments (Lehne, 2010). As shown in Table 4, approximately 52% of Caucasians are slow metabolizers of the drug isoniazid, used in the treatment of tuberculosis (Lehne, 2010). In the treatment of cancer, Table 3 demonstrates that a small percentage of the United States population have genetic alterations in alleles that slow the metabolism of the drug fluorouracil, a chemotherapeutic agent used in the treatment of cancer for over 40 years (Lehne, 2010). In some cases, this

reduction in metabolism has resulted in death (Lehne, 2010). Lastly, Asians have been found to have alterations in human leukocyte antigens [HLA-B 1502], which increases the risk for developing life-threatening skin reactions when using the drug carbamazepine [Tegretol] (refer to Table 4). The FDA states that tests are available to identify genetic alterations in metabolism and recommends genetic screening prior to initiation of treatment (Lehne, 2010).

### **Ethnic Variation in Biotransformation of Chemotherapeutic Agents**

Ethnic variations in response to chemotherapeutic drugs in the treatment of leukemia have been a focus of genetic susceptibility research. Displayed in Table 3, some Caucasians possess genetic variations of the enzyme thiopurine methyltransferase (HGPI, 2010). This enzyme is responsible for breaking down chemotherapeutic agents for use in the body. Genetic variations result in the inactivation of enzymatic activity that promotes the breakdown and excretion of the drug. The inability to metabolize the drug results in toxic blood levels of highly chemotoxic agents to remain in the body longer (HGPI, 2010). Therefore, screening for the deficiency prior to administering this class of medications is essential (HGPI, 2010).



**Table 2: Pharmacogenetic Interventions in Warfarin Users, and Eastern Asian and African American Populations**

Researcher	Population Studied	Genetic Alteration	Pharmaceutical Factor	Findings
Shives (2008)	Eastern Asian	cytochrome P450	psychotropic drugs, especially lithium (used in the treatment of psychotic disorders)	possess lower enzymatic activity in the metabolism of psychotropic drugs and require a dosage reduction
Shives (2008)	African American	cytochrome P450	psychotropic drugs, especially lithium (used in the treatment of psychotic disorders)	possess lower enzymatic activity in the metabolism of psychotropic drugs and require a dosage reduction
Lehne (2010)	Warfarin Users	cytochrome P450-2C9 [CYP2C9]  Vitamin K epoxide reductase	warfarin [Coumadin]  (used in the prevention of thrombosis)	metabolize this drug at slower rates than current prescribing guidelines follow, and require dosage adjustments to decrease the risk of warfarin induced bleeding

*Note:* <sup>ab</sup> Results from Shives, L.R. (2008). *Basic concepts of psychiatric-mental health nursing*. Lippincott Williams & Wilkins: Philadelphia, PA <sup>c</sup> Results from Lehne, R. A. (2010). *Pharmacology for nursing care* (7th ed.). St. Louis: Saunders Elsevier.

**Table 3: Pharmacogenetic Interventions in Europeans, U.S. Populations, and Caucasians**

Researcher	Population Studied	Genetic Alteration	Pharmaceutical Factor	Findings
Lehne (2010)	European (1 in 3500)	butyrylcholinesterase (enzyme)	Succinylcholine  (used in neuromuscular blockade)	reduced rates of the enzyme responsible for the metabolism of this drug, requiring a dosage reduction to prevent permanent paralysis.
Lehne (2010)	1 % of the U.S. population	dihydropyrimidine dehydrogenase (enzyme)	Fluorouracil  (used in the treatment of cancer)	produce a poor form of this enzyme, which is responsible for metabolism of the drug
HGPI (2010)	Caucasian	thiopurine methyltransferase (enzyme)	chemotherapeutic agents  (used in the treatment of cancer)	results in inactivation of enzymatic activity that promotes the breakdown and excretion of this drug, increasing the risk for toxic blood levels

*Note:* <sup>ab</sup> Results from Lehne, R. A. (2010). *Pharmacology for nursing care* (7th ed.). St. Louis: Saunders Elsevier. <sup>c</sup> Results from HGPI, Human genome project information. (2010). U.S. Department of Energy Genome Program's Biological and Environmental Research Information System (BERIS). <http://genomics.energy.gov>.

**Table 4: Pharmacogenetic Interventions in Asian and Caucasian Populations**

<b>Researcher</b>	<b>Population Studied</b>	<b>Genetic Alteration</b>	<b>Pharmaceutical Factor</b>	<b>Findings</b>
Lehne (2010)	Asian	human leukocyte antigens [HLA-B 1502]	carbamazepine [Tegretol]  (used in the treatment of seizures)	produce this unusual antigen which increases the risk for developing life-threatening skin reactions when using the drug
Lehne (2010)	Caucasian (1 in 14)	cytochrome P450	Morphine  (used in the treatment of pain)	are unable to convert codeine into morphine (its active form), resulting in no pain relief
Lehne (2010)	U.S. Caucasian	<i>N</i> -acetyltransferase-2 (enzyme)	Isoniazid  (used in the treatment of tuberculosis)	2 different forms of the enzyme: 52% were found to be slow metabolizers, putting them at risk for toxicity; 48% were found to be rapid metabolizers, putting them at risk for treatment failure

*Note:* <sup>abc</sup> Results from Lehne, R. A. (2010). *Pharmacology for nursing care* (7th ed.). St. Louis: Saunders Elsevier.

## **ECO-PHARMACO-GENETIC INTERVENTIONS**

### **Hypertension in the African American Population**

Currently, a gap in knowledge exists in the development and treatment of hypertension associated with African Americans. The prevalence of hypertension in African Americans is nearly twice as much compared to other races (Ambler & Brown, 1999). The increasing incidence of hypertension in this population has influenced researchers to investigate genetic variations and physiological differences among African Americans. Ambler & Brown (1999) concluded that this population possesses unique genetic allele expressions that may interact with environmental-behavioral conditions to increase blood pressure. These characteristics include an elevated sensitivity of blood pressure to sodium transport, with alterations in renal sodium handling (Ambler & Brown, 1999). Exposure to environmental risk factors (Table 5), such as sedentary lifestyle, increased sodium and caloric intake, and stress further influence these characteristics and associated complications. In the treatment hypertension, Ambler & Brown (1999) examined the response of antihypertensive therapy and gene variations in the rennin-angiotensin-aldosterone system (RAAS). African Americans were found to be better responders to diuretic and calcium channel blocker therapies, and less to ACE inhibitors. The authors attributed these findings to the mechanism of action the therapies had on the RAAS. This study demonstrated a correlation between polymorphisms in the rennin and atrial natriuretic peptide genes and hypertension in African Americans (Ambler & Brown, 1999).

Further clarifying these findings, an additional study conducted by Frazier et al. (2004) examined therapeutic response to antihypertensive therapy in African American women. The results concluded that variations in genes in the RAAS of this population were responsible for the blood pressure response to diuretic therapy.

### **Percutaneous Interventions in Cardiovascular Disease**

Knowledge of environmental stimuli that trigger disease susceptible genes can be used in healthcare education to promote disease prevention and maintenance. Genetic susceptibility in individuals with cardiovascular disease and comorbidities related to complications from cardiac conditions are being explored for their potential to prevent disease. More than 2 million people annually undergo cardiac procedures in the United States (O'Malley, 2010). Genetic determinants of disease suggest that certain polymorphisms of alleles can predetermine poor physiologic outcomes which increase the likelihood of complications and the need for further therapeutic interventions (Frazier et al., 2004). Genetic susceptibility for adverse events such as: thromboembolism, restenosis, or death, exists in individuals who possess polymorphisms in prothrombin [G20210A] and antithrombin III, as seen in Table 5. Prothrombin plays a significant role in hemostasis, while antithrombin III keeps the hematologic system under control by inactivating clotting factors (Frazier et al., 2004). A genetic disruption in either hematologic cascade can potentially increase the risk of complications in individuals with cardiovascular disease undergoing treatment. Therefore, the environmental components, or individual treatment

options, can be determined based on genetic profiling for susceptibility to drug therapy effectiveness.

Clopidogrel [Plavix] has been the antiplatelet drug of choice in the prevention of stenosis of coronary stents (Lehne, 2010). A study conducted by O'Malley (2011) determined that patients with alterations in the gene that is responsible for the metabolism of Plavix, CYP2C19, are less likely to benefit from this drug therapy and are at increased risk thrombotic events. Additionally, the study found that individuals with polymorphisms in the enzyme PON1, required in the transformation of Plavix into an active metabolite, experienced higher risk of thrombosis formation post-stent placement and use of the drug (O'Malley, 2011). Genetic screening for these polymorphisms will lead to more individualized planning, resulting in better patient outcomes regarding cardiac procedures (Frazier et al., 2004). The monetary cost for invasive cardiac procedures is steep and the associated emotional stress of undergoing a cardiac procedure can sometimes worsen the condition (Caldwell, Arthur, Natarajan, & Anand, 2007). Identifying individuals susceptible to targeted therapies, such as a new drug regimen or diet and lifestyle modifications, can help decrease the emotional stress and healthcare cost of invasive procedures and expensive drug therapies (Caldwell et al., 2007).

**Table 5: Eco-Pharmaco-Genetic Interventions in African American populations and Individuals Undergoing Invasive Cardiac Procedures**

Research er	Population Studied	Genetic Alteration	Pharmaceutical Factor	Environment al Factor	Findings
Ambler & Brown (1999)  Frazier et al., (2004)	African American	renal sodium handling  rennin-angiotensin-aldosterone system (RAAS)	anti-hypertensive drugs  [diuretics, calcium channel blockers, ACE inhibitors]	sedentary lifestyle  increased sodium intake  increased caloric intake  stress	increased sensitivity to elevated blood pressure, especially in response to favorable environmental triggers; respond better to diuretic or calcium channel blocker therapies & less to ACE inhibitors
Frazier et al., (2004)  O'Malley (2010)	Individuals Undergoing Cardiac Procedures	prothrombin (G20210A)  antithrombin III  CYP2C19 (enzyme)  PON1 (activator enzyme)	clopidogrel [Plavix]  (used in the prevention of stenosis post stent placement)	cardiac procedures  percutaneous intervention [PCI, stent]  Coronary Artery Bypass Graft [CABG]	both cause increased risk for adverse events: thromboembolism, restenosis, or death; determine if patient is better candidate for PCI or CABG  inability to metabolism drug or convert to its active form for use

Note: <sup>a</sup> Results from Ambler, S., & Brown, R. (1999). Genetic determinants of blood pressure regulation. *Journal of Cardiovascular Nursing*, 13(4), 59. Retrieved from EBSCOhost. & Frazier, L., Turner S. T., Schwartz, G. L., Chapman, A. B., & Boerwinkle, E. (2004). Multilocus effects of the renin angiotensin aldosterone system genes on blood pressure response to a diuretic. *Pharmacogenomics Nature*, 4, 17-23. <sup>b</sup> Results from Frazier et al. (2004) Multilocus effects of the renin angiotensin aldosterone system genes on blood pressure response to a diuretic. *Pharmacogenomics Nature*, 4, 17-23. & O'Malley, P. (2011). Pharmacogenomics for the clinical nurse specialist---genetics, prescribing, and outcomes. *Clinical Nurse Specialist: The Journal for Advanced Nursing Practice*, 25(3), 110-112. doi:10.1097/NUR.0b013e3182170fc2.

## **BARRIERS AND ETHICAL DILEMMAS TO GENETIC INTERVENTION**

### **Barriers, Allocation and Access**

Barriers to genetic determinants of lifestyle management regarding ecogenetic and pharmacogenetic interventions include disparities in the availability of appropriate nutritional or medication resources among different income levels, geographical locations, and ethnic differences. Likewise, barriers in identifying and determining which gene variations affect drug response can impact pharmaceutical efficacy. Genetic coding that determines individualized drug therapy can potentially reduce the marketable populations for pharmaceutical stakeholders and places limitations on drug therapy alternatives available to consumers (HGPI, 2010).

Although genetic research is currently revealing lifestyle modifications and selective drug therapy based on genetic variation, increasing concern exists about the accessibility of resources. Molecular profiling technology, genetic sequencing and mapping, are currently being used to expand genetic profiling and interventions; however, a financial foundation for funding has not yet been established. So the questions are: do individuals wait for technology to become cheaper? And when and where do we start screening (Sharma & Gohil, 2010)? Therefore, as research progresses, there is an increased need for program development focused on how and which individuals will obtain genotype-based resources. One program in favor of resource accessibility, the Genetic Diseases Act in 1976, brought



funding of state and federal programs to genetic services, and continues to represent the importance of integrating genetics into health care services (Greco et al., 2007).

Exploration of future genetic studies that will alter lifestyles and interventions to prevent or maintain disease will focus on mitigating questions pertaining to access of genetic testing and outcomes. The new wave of genetics comes with risks of discrimination in finances, employment and insurance (O'Malley, 2011). To begin with, the genetic community lacks consistency in determining if intervention and testing is made available only to individuals who have the financial means. There is also no clear definition for how health insurance programs will be impacted based on genetic profiling, which poses major ethical and financial implications to genetic use. Other barriers to enacting genetic lifestyle management principles include cultural beliefs, individual access to health care services, and genetic screening, as well as employment opportunities and education of health care providers in regards to genetic interventions. The moral and ethical duty of individuals to the community is also a concern where environmental health issues can influence interventions, regardless of personal beliefs. Health care institutions and professionals must be prepared to put concepts related to genetic disease management to use for consumer health to be initiated (Frazier et al., 2004).

### **Cambridge Genetics Knowledge Park**

Currently, The Cambridge Genetics Knowledge Park of the United Kingdom (CGKP) is investing substantial time and money to develop programs that will lead to the

involvement of the general public with ethical, legal, and societal issues associated with advances in human genetics (Dutta, Brice, & Wallace, 2005). The ethical and social issues that are brought forth are not necessarily new to the health care industry. Ethical issues associated with human genetics may include individual obligation for genetic susceptibility testing and to community/family awareness. Societal issues arise from individuals having equal access to care and appropriate allocation of resources (Frazier et al., 2004). In an effort to minimize such dilemmas, this organization has included experts in the fields of philosophy, law, health economics and social science, epidemiology, molecular biology, and clinical and public health medicine in genetic decision making (Dutta et al., 2005). Ultimately, collaboration across the domains of ethicists, scientists, philosophers, individuals, insurers, and employers will guide genetic use in health care. The CGKP is also working with the insurance industry to determine the basis for insurance premiums based on genetic screening profiles. GINA, the act passed disabling insurance companies from discriminating or raising premiums based on genetic profiles, will protect individuals from discrimination based on genetic findings. Additionally, the CGKP is training specialists to further genetics education to the next generation (Dutta et al., 2005). The organization researched the current knowledge level of a wide variety of healthcare providers, as well as patients, to assess the needs of different groups for education in genetics, and to implement effective ways of providing the necessary knowledge and skills based on those findings (Dutta et al., 2005).

## **Ethical Principles of Autonomy and Justice**

When considering the principle of autonomy, or self-determination, genetic interventions are described as services offered to individuals as goods for private consumption, to be accepted or refused as individuals see it (Buchanan et al., 2000). Buchanan et al. (2000) argues that this personal service model honors only those who are in a position to chose or afford genetic interventions, and not necessarily those affected who may be in need. However, with proper allocation of resources and the incorporation of laws and insurance policies, all of society may benefit. With new discoveries, a public health model will guide genetic interventions. The interventions will become the norm of health care services, which will affect the overall genetic health of society.

Equal opportunity must be examined when considering the principle of justice in the use of genetic intervention. To ensure justice, no individual must be discriminated upon by characteristics such as ethnicity, religion, race, or gender. Rather than being excluded for these characteristics as with discrimination, individual characteristics will guide/individualize interventions. Another valid point stated by Buchanan et al. (2000) is Norman Daniels's theory of just health care. This theory proposes that a "just health care system should strive to remove barriers to opportunity that are due to disease" (Buchanan et al., 2000). Genetic interventions will be an important means of eliminating barriers to opportunity posed by disease.

## **IMPLICATIONS FOR GENETICS IN NURSING PRACTICE**

Genetics in nursing practice will focus on health issues, genetic conditions, and diseases or susceptibilities to diseases caused or influenced by genes in interaction with other risk factors that may require nursing care (Greco et al., 2007). The International Society for Nurses in Genetics (ISONG) of the American Nurses Association, established in 1988, is responsible for defining and developing the scope of professional nursing practice in genetics for nurses globally (Greco et al., 2007). ISONG's vision of "caring for people's genetic health" has been the foundation for defining knowledge and the scope of genetics nursing practice. Credentialing for the practice of genetics in nursing care is available through the Genetic Nursing Credentialing Commission. Although genetic nursing may occur in any health care setting, credentialing is currently reserved for nurses who spend at least 50% of their time providing genetic-related nursing care (Greco et al., 2007). The delivery of care will be based on the nursing care model, with the incorporation of genetics into assessment, diagnosis, planning, implementation, and evaluation. As with other practices in the discipline, genetic nursing practice will consist of basic and advanced level care degrees. The future of basic genetic knowledge in nursing will provide a role in the delivery of genetic services to all licensed registered nurses, as society becomes more aware of the influence of genetics regarding health and disease (Greco et al., 2007).

Responsibilities in nursing practice will use genetic information in health promotion and teaching, coordination of care, resource referral, consultation, advocating,

and counseling. Nurses will assist individuals in becoming informed consumers of the established plan care, as well as identifying and evaluating cost-to-benefit factors, safety, and availability of interventions (Greco et al., 2007). The challenge for nursing in personalized health care lies in the increasing complexity of healthcare associated with the expansion of genetic knowledge (Greco et al., 2007). Nurses must be prepared to incorporate individual genotype into the delivery of care. Strategies to overcome this challenge focus on an interdisciplinary approach, which is reliant on the overlapping skills and knowledge of other disciplines in the implementation of care (Greco et al., 2007). The National Coalition for Health Professionals in Genetics has defined core competencies that provide a framework for educational programs in nursing. These competencies address the biological, ethical, and psychosocial impact of genetics in nursing practice (Greco et al., 2007). To be prepared for the challenges of genetics, nurses must participate in addressing ethical issues and applying genetic research to practice, in collaboration with other team members. Nurses will need to stay current with information to provide families and patients education about disease process and treatment, while incorporating knowledge of the interaction of genetic and environmental factors in disease progression (Frazier et al., 2004). Lastly, as advances in human genetics expand rapidly, practicing nurses must continue to increase technological and educational competencies in the delivery of nursing care (Greco et al., 2007).

## CONCLUSIONS

Results from this literature review have revealed individualized interventions based on genetic profiles. The Human Genome Project (2010) has been the most recent foundation for discovery of genetic components, and has provided a basis for current and future research in the molecular science field. Genetic testing poses many challenges to society, and therefore should rely on genetic counseling to determine its appropriateness. Therapeutic interventions have been discussed, based on ecogenetics and pharmacogenetics. Understanding the etiology of disease from a multifactorial standpoint will open the door to the next generation of therapeutic interventions (Ambler & Brown, 1999). In example, when considering genetic vulnerability and environmental factors in metabolic syndrome phenotypes, screening individuals for polymorphisms in the adiponectin gene will help identify those that would likely benefit from modification of dietary fat intake. Understanding metabolic related polymorphism and its interaction with dietary fatty acids assists in identifying causes of insulin-resistance in individuals with this genotype. For children with fragile X syndrome, environmental factors that decrease sensory stimulation while still promoting socially-adaptive behaviors will decrease the extent of expression. Identifying children at early stages in the disease to intervene with appropriate environments will halt the progression. Genetic vulnerability in cardiovascular disease must be considered when implementing treatment options and establishing plan of care. Individuals must be screened for polymorphisms in the prothrombin and

antithrombin III nucleotides prior to percutaneous interventions or coronary artery bypass to determine the safest treatment option. These polymorphisms are not only specific to cardiovascular disease treatment procedures. Individuals, such as the traveling population, with these genetic alterations may encounter favorable environmental triggers, extended flights, which also increase their risk for experiencing a thromboembolic event.

With the use of pharmacogenetics, health care models will be developed to create more effective drug therapy regimens, while decreasing the risk of adverse events. Uncovering genetic variance has demonstrated the differences in ethnic variations, as well as single nucleotide polymorphisms that can affect human response to drug therapy. Identification of single nucleotide polymorphisms provides a framework to understand genetic variation in drug response to create targeted individualized drug therapy (Ambler & Brown, 1999). Variations in the hepatic metabolism and the renal system illustrate that African Americans are less likely to respond to specific treatments based on genetic influence, and would benefit through selective classes of drug therapy. Ethnic variations in hepatic metabolism were also analyzed in the East Asian populations and concluded that these individuals would benefit from dosage reductions in psychotropic drugs. With the number of adverse events and decreased response to drug therapy occurring from improper identification to genetic profiling, pharmacogenetics must be implemented to improve health outcomes.

Future studies will need to establish guidelines, roles, and career opportunities for health care professionals that incorporate the new evidence pertaining to genetic

discoveries and health outcomes into practice. There is also a need to continue research in environmental triggers associated with expression of susceptibility genes, as well as how genes interact with other genes to promote disease. Genes encode instructions on how to make proteins; therefore, proteomics, or studies that explore protein structure and activity will need to be focused on in future research. Millions of alterations in single nucleotides, single nucleotide polymorphisms, must be identified to determine their involvement in drug response (HGPI, 2010). Universal [standardized] protocols will be replaced with treatment options based on genetic profiles. Lastly, an in-depth analysis of ethical-decision making must be researched pertaining to the use of genetic interventions for treatment versus enhancement. With further research, it can be predicted that genetics will assist in closing the therapeutic gap between disease and treatment.



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