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## Pharmacogenomic Management of Familial Hypercholesterolemia: An Integrative Review of the Literature

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HARMACOGENOMIC MANAGEMENT OF FAMILIAL  
HYPERCHOLESTEROLEMIA (FH):  
AN INTEGRATIVE REVIEW OF THE LITERATURE

by

BRIAN SKIBO

A thesis submitted in partial fulfillment of the requirements  
for Honors in the Major Program in Nursing  
in the College of Nursing  
and in the Burnett Honors College  
at the University of Central Florida  
Orlando, FL

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## **Abstract**

The purpose of this thesis is to examine familial hypercholesterolemia (FH) and emerging pharmacogenomics therapies that propose to lower serum low density lipid (LDL) levels. The search of various data bases resulted in nine research articles being selected for review.

Syntheses of the articles suggest emerging pharmacogenomic drug therapy can improve treatment outcomes for individuals with a diagnosis of FH. The Human Genome Project (HGP) has had far reaching applications for genomic technologies and pharmacogenomic interventions, tailored to human conditions associated with select genomic traits. Synthesis of nine research articles demonstrate that little is known on the topic and reveals extensive gaps in the evidence. This thesis concludes with implications for nursing education, practice, policy and research along with limitations are noted.

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## Introduction

The Human Genome Project (HGP), completed in 2003, involved an international cadre of researchers who mapped the sequence of all human genes to develop the *genome of the species Homo sapiens*. Metaphorically, sequencing of the human genome provides a textbook with pages for each gene describing the makeup of the human body. This knowledge has led to the discovery of more than 1,800 disease genes such as Familial hypercholesteremic (FH) (National Institute of Health, 2015). An outcome of the HGP has assisted researchers in identifying a particular gene suspected of causing a specific inherited disease in a matter of days, rather than years. Since the HGP was completed more than 2,000 genetic tests have been developed to identify various human conditions. Another outcome of the HGP resulted in improved genetic testing which allows for specific identification of gene mutations within a strand of deoxyribonucleic acid (DNA) that could determine if a person or family is at genetic risk for developing a particular condition. Likewise, DNA screening can assist the healthcare provider in diagnosing diseases with greater accuracy and then personalizes medical and pharmacological intervention to treat the genetically based condition (National Institute of Health, 2015).

Excessive serum cholesterol (*hypercholesterolemia*) in the body greatly increases an individual's risk of developing cardiac and other vascular related diseases. Familial hypercholesterolemia (FH), a rare genetic condition, is associated with an excessive and persistent accumulation of cholesterol in the blood. It is estimated that one in every 500 individuals has the genetic propensity for developing FH evidenced by high serum cholesterol levels (National Human Genome Research Institute, 2015). There are two types of cholesterol

that people are most familiar with, high density lipoprotein (HDL) and low density lipoprotein (LDL). Sometimes referred to as "good cholesterol" the HDL 'picks up' excess cholesterol in the blood and disperses it to the liver where it is then broken down. A high level of LDL or 'bad cholesterol' over time accumulates in blood vessel wall linings (*plaques*) throughout the body which results in narrowing of vessel. Eventually, plaques can block blood flow which increases the risk of developing coronary artery disease, vascular disease and stroke.

Serum cholesterol level is measured in milligrams (mg) of cholesterol per deciliter (dL) of blood or mill moles (mmol) per liter (L). Regarding the targeted serum level of HDL, the goal should be having a higher number, while for LDL the goal should be for a lower number. One diagnostic measure for FH is having a persistent serum LDL level above >190mg/dL (National Library of Medicine, 2015). A treatment goal for individuals with FH is to maintain a serum LDL level of <190mg/dL (High cholesterol, 2015; Learning about familial hypercholesterolemia, 2015) (See Table 1.). The HGP along with facilitating quicker diagnoses, led to development of new classifications of drugs to treat genetically based FH (*pharmacogenomics*) that tailor treatment approaches for an individual (*precision medicine*). Ultimately, precision medicine can improve treatment outcomes and reduce long term comorbidities, in this case FH which is the focus of this thesis.

## **Problem Statement**

The purpose of this integrative review was to examine the effects of pharmacogenomics in managing or reducing serum cholesterol levels in individuals who have been diagnosed with FH.



## Rational/Purpose

Recently genomics, pharmacogenomics and precision medicine received extensive media attention at the national level. In his 2016 State of the Union Address, President Obama launched a \$215 million *Precision Medicine Initiative* in the 2016 Federal Budget. His initiative focuses on research and data-sharing among researchers and clinicians to advance an agenda of precision medicine and its effects on treatment and outcomes (Williams et al., 2016). In respect to nursing education, the American Nurses Association along with other specialty nursing organizations recommend that curricula include content on genetics to enhance genomic nursing competencies in graduates (Cheek, Bashore, & Brazeau, 2015; Greco, Tinley, & Seibert, 2011; Howington, Riddlesperger, Cheek, 2011). Given these two nationally focused imperatives, this integrative review will focus on pharmacogenomic therapy outcomes in individuals with a diagnosis of FH.

**Table 1. Diagnostic Parameters for Serum Cholesterol Levels.**

HDL	LDL	Familial Hypercholesterolemia
Normal: 60 mg/dL or above	Normal: 130 mg/dL or below	LDL: > 190 mg/dL or more
At Risk: 40 mg/dL or below	At Risk: More than 130mg/dL	HDL: < 60 mg/dL

*Note.* Adapted from “*High Cholesterol*,” by Mayo Clinic, 2016, <http://www.mayoclinic.org/diseases-conditions/high-blood-cholesterol/in-depth/hdl-cholesterol/ART-20046388>

## Background

Treatment of choice for managing hypercholesterolemia historically comprised lifestyle behavior modifications and administration of HMG-CoA reductase inhibitors (i.e., *statins*).

However, in individuals diagnosed with FH, lifestyle changes coupled with statin drug therapy generally is ineffective in lowering serum cholesterol, in particular LDL, to recommend target levels (Kolovou, Vasiliadis, Gontoras, Kolovou, & Hatzigeorgiou, 2015). Statin drugs can have a high degree of variability in lowering LDL especially in individuals with FH associated with genetic factors that impact drug responsiveness. For individuals who are resistant to traditional interventions to manage hypercholesterolemia, genetic screening could be the next step in the treatment care plan.

### **Genetic Screening**

Genetic screening may be recommended for individuals who persistently maintain a high serum LDL even with lifestyle modifications (dietary; physical activity) along with statin medication regimen (Thomas, 2014). An individual can have the genetic traits for *heterozygous*, *homozygous* or *polygenic FH*. All three of these genetic mutations are associated with an increased serum LDL that is deposited throughout the body which pose risks for developing coronary heart and other vascular diseases. Other physical manifestations of FH include xanthomas in the eyes, tendons, elbows, hands and knees. Average life expectancy in the US of persons with FH is estimated to be in the early twenties if left untreated compared with a life expectancy of 78.7 years of an individual who does not have the condition (Thomas, 2014).

Individuals having the heterozygous (HeFH) genetic trait have either one mutation in a single gene or multiple mutations in different genes. They are at significant risk for a premature heart attack which is 20 times higher than the general population. Coronary complications are more likely to occur in males with this genetic trait (50%) before 50 years of age and in females (30%) before 60 years of age (Sniderman, Tsimik & Fazio, 2014).

Individuals with the homozygous (HoFH) genetic trait have two mutated copies of the same gene that causes a specific type of FH. Individuals with this genetic trait are at even greater risk of developing CHD and other elevated serum LDL level associated complications. For example, with HoFH acute coronary attacks and cardiac disease can occur in an individual even before the end of the second decade of life (Sniderman, Tsimikas & Fazio, 2014).

The polygenic genetic phenotype of FH, involves a combination of any of 12 different single nucleotide polymorphisms in select genes that are believed to be associated with FH. Precise epidemiological and bio statistical information on this genotype was not available in the literature (Sniderman, Tsimikas & Fazio, 2014).

### **Genomics and Emerging Pharmacogenomic Interventions**

The HGP identified three specific genetic traits that lead to developing FH, specifically the Low Density Lipoprotein Receptor Gene (LDLR), the Proprotein Convertase Subtilin/Kexin 9 gene (PCSK9), and the Apolipoprotein B (APOB) gene. Each of these genetic traits will be discussed in the next few paragraphs (Sniderman, Tsimikas & Fazio, 2014).

The LDLR gene, most commonly associated with FH, is responsible for construction of LDL receptors throughout the body and thereby removing LDL from the blood. This particular gene is integral to controlling serum LDL levels. In turn, an insufficient amount of LDL receptors impairs LDL absorption resulting in high level of LDL circulating in the blood resulting in hypocholesteremia (Sniderman, Tsimikas & Fazio, 2014).

The PCSK9 gene controls the circulating amount of the PCSK9 protein which regulates the number of LDL receptors that adhere to the surfaces of cells. Mutations in the PCSK9 gene can lead to either an increase or decrease in activity of the protein regulators. An increase in activity will lead to an increase in the breakdown of LDL receptors throughout the body; thus,

circulating LDL is not being absorbed by LDL receptors, resulting in hypercholesterolemia. Decreasing the activity of the PCSK9 protein can result in less destruction of LDL receptors; thereby lowering the circulating level of LDL (Sniderman, Tsimikas & Fazio, 2014).

The APOB gene encodes for the APOB protein which transports cholesterol throughout the body and allows the lipoprotein to attach to LDL receptors for absorption. When the gene mutates the APOB protein does not form correctly and impedes the LDL receptor from binding and absorbing LDL, resulting in hypocholesterolemia (Sniderman, Tsimikas & Fazio, 2014).

### **Therapeutic Management of FH**

First line treatment for FH includes the management of cholesterol through lifestyle modification such as limiting animal fat intake to less than 30% of total calories. This can be accomplished by reducing or eliminating animal fats such as pork, beef and dairy products. Another lifestyle modification focuses on increasing physical activity which in some cases also lowers serum LDL cholesterol. If lifestyle modification are not effective pharmacological therapies may be started, the most common being statin drugs. Statins generally are effective for lowering serum LDL levels in most individuals; however, those with FH often demonstrate lower or no less therapeutic response to statins (National Human Genome Research Institute, 2015). Recent genetically based FH pharmacologic interventions can personalize treatment options to manage hypercholesterolemia based on genetic traits such as PCSK9 inhibitors, APOB inhibitors and MTP inhibitors (Sniderman, Tsimikas & Fazio, 2014) (See Table 2).

**Table 2. Genetic Trait, Pharmacogenetics Therapies and Actions.**

<b>Gene Trait</b>	<b>Pharmacogenetics Therapies</b>	<b>Action</b>
Proprotein Convertase Substilan/Kexin 9	alirocumab (Praluent), evolocumab (Repatha)	Monoclonal antibodies that destroys the PCSK9 protein.
Apolipoprotein B	mipomersen sodium(Kynamro)	Inhibits synthesis of APOB protein in the liver
Microsomal Triglyceride Transfer Protein	lomitapide (Juxtapid)	Inhibits MTP which is essential in the formation of very low density lipids

*Note.* Adapted from “The Severe Hypercholesterolemia Phenotype.” by Sniderman, A. D., Tsimikas, S., & Fazio, S, 2014, *Journal of the American College of Cardiology*, 63(19), 1935-1947.

## **Methods**

This thesis presents an integrative review of literature that focused on pharmacologic and lifestyle management of hyperlipidemia in FH. Key terms used in the literature search included: “pharmacogenomics,” “pharmacogenetics,” “genetics,” “familial hypercholesterolemia,” “dyslipidemia,” “genetic screening,” “PCSK9,” “APOB,” “MTP inhibitors,” “statins.” Databases for the search included CINAHL, Medline, PubMed and Cochrane. Inclusion criteria were peer-reviewed research articles published from 2009 to 2015, and written in the English language. Each article was individually evaluated for relevance to the topic and application to FH therapy. A table that summarizes findings from each was developed and is included in the appendices

(see appendix B). Subsequently all of the critiques were synthesized by the researcher and key data were extracted. Consistent and inconsistent findings were noted along with gaps in the literature. Recommendations for future research were identified. Implications for nursing practice, policy and education are included along with limitations of this review.

Eight studies were included in the final analysis and an additional nine articles gave further relevance to this review. Primary searches contained the search terms “pharmacogenomics” or “pharmacogenetics” which yielded  $N=18,312$  studies. Once the topic of FH was chosen subsequent searches contained the search term “familial hypercholesterolemia” and included a specific type of pharmacogenomic therapy (“PCSK9,” “APOB,” “MTP” and “inhibitor”) associated with FH. Each search included the drug class and FH, and an additional limiting factor was the inclusion of statins as a comparison drug, and eight studies met inclusion criteria (see appendix A). Seven of the studies were randomized, double-blind, placebo-controlled experiments; one was a case-study; seven studies used humans as study subjects; and, one used mice. Of these, three studies examined the use of Evolocumab, a PCSK9 inhibitor as potential genetically targeted drug therapy for individuals with FH; another two studies examined Mipomersen an Apolipoprotein B protein inhibitor; and, three other studies examined Lomitapide an MTP inhibitor. In addition to the eight studies, searches that yielded articles that did not include original findings but were useful in giving background information were included ( $n=9$ ) along with other pertinent and relevant sources such as webpages ( $n=4$ ).

## **Results**

This next section highlights each pharmacogenomic therapy in depth using data from drug trials, case-studies and experiments. Results and limitations are noted in each subheading.

Following this is a discussion of the results and the implications of these therapies on individuals with FH.

### **PCSK9 Inhibitors**

The literature indicated that PCSK9 is not involved in the synthesis of cholesterol. For this reason statins tend to be ineffective in individuals with PCSK9 induced FH thus creating the need for another type of intervention. Statins are correlated with a direct increase in PCSK9 levels in individuals with PCSK9 induced FH. Consequently, statin drugs not only are ineffective but not beneficial in reducing the etiological agent of this classification of FH (Faiz, Hooper, & Bockxmeer, 2012).

In a study of the PCSK9 inhibitor alirocumab, (i.e. ODYSSEY COMBO I Study) ( $N=316$ ) patients at high cardiovascular risk were administered a PCSK9 inhibitor with a statin medication of which they were at the maximally tolerated dose. In a multicenter study located in 76 sites across the US, data were collected for a phase 3, randomized, double-blind 52 week trial study to observe the effectiveness of alirocumab. Participating subjects over 18 years of age, with an established diagnoses of coronary heart disease, persistent hypercholesterolemia having either as serum LDL $>70$  with coronary artery disease (CAD); or, serum LDL $>100$  and CAD risk equivalents (e.g. diabetes, hypertension, kidney disease, obesity). The study findings indicated that the PCSK9/Statin combo lowered LDL 48% from baseline compared to the serum LDL level in subjects receiving only a statin drug. After 24 weeks of administration of a PCSK9 75mg every 2 weeks lead to a mean LDL of 51 mg/dl vs statin alone (98 mg/dl) in patients with hypercholesterolemia despite maximally tolerated statin therapy (Kereiakes et al., 2015). Combination of alirocumab in adjunct to a statin reduced LDL from baseline by 48.2% where as placebo and statin therapy reduced LDL by 2.3% by week 24. This equated to a mean difference

of 45.9% in baseline LDL ( $P < .0001$ ) between the alirocumab group and the placebo group. Weaknesses of the study include no evidence of subgroup analyses for race or gender. This study did not target the effectiveness of the drug on individuals with FH, yet the findings are still pertinent since individuals with FH often have been on maximally tolerated statin therapy.

In a double blind study by Raal, et al., (2015) PCSK9 inhibitors focused on subjects ( $N=49$ ) with HoFH. Of these,  $n=16$  participants were administered a placebo and  $n=33$  received the drug evolocumab, a PCSK9 inhibitor. All subjects were positive for HoFH and had been on lipid lowering therapy for at least 4 weeks (Raal et al., 2015). After 12 weeks of evolocumab administration a 30.9% reduction in serum LDL and 23% reduction in Apob resulted compared to the placebo group ( $P < 0.0001$ ) (Raal et al., 2015).

Lastly, in another study ( $N= 331$ ) heterozygous subjects received PCSK9 therapy administered evolocumab either on a monthly basis (420 mg) or every 2 weeks (140 mg). Both groups had statistically significant reduction in serum LDL levels. Subjects receiving the monthly dose by the end of 12 weeks had a 61.3% reduction in serum LDL levels compared to the placebo group. This finding equates to a treatment difference of 59.2% ( $P < 0.0001$ ). Bi-weekly doses of 140 mg led to a reduction in serum LDL of 59.2% compared to a placebo ( $P < 0.0001$ ) (Raal et al., 2015).

Limitations of the research include the analysis of responses to therapy based on genotype was completed post-hoc rather than being pre-specified in the study methods or data collection plans. Thus, this approach was used to determine the hypotheses and should not be viewed as findings. Also the study time frame was only 12 weeks, and for that reason durability of serum LDL reductions and safety could not be ascertained.



It is clear that the administration of PCSK9 inhibitors in both patients with or without FH can have significant serum LDL lowering results. In conditions that are of genetic nature, statins alone can be ineffective in lowering LDL concentrations and PCSK9 inhibitors can enhance statins in lipid lowering. This is especially important since statins alone can raise PCSK9 levels in individuals, subsequently FH, this approach exacerbates in individuals with a PCSK9 gene mutation where PCSK9 proteins are already numerous in serum concentration. Also, in patients who do not tolerate statins, this therapy could aid in lowering LDL while titrating the statin dose downward. This strategy could relieve patients of statin induced side effects from poor tolerance to the drug or high doses.

#### **APOB Inhibitors (mipomersen)**

Mipomersen is an antisense agent that inhibits APOB synthesis and reduces the amount of APOB containing lipoproteins in circulation. When used in individuals with mild hypercholesterolemia or even homozygous FH this drug significantly reduced the concentration of circulating LDL and APOB. When combined with other lipid-lowering therapies it is even more effective (Stein et al., 2012). In a double-blind, placebo-controlled trial ( $N=114$ ) subjects were administered mipomersen weekly at 200 mg resulted in a 28% decrease in LDL levels in HeFH individuals with CAD who could not achieve LDL control of  $<100\text{mg/dl}$  on maximum lipid-lowering therapy. Mipomersen is unique as it reduces LDL concentration at almost the same rate for both HeFH and HoFH individuals. Mipomersen lowered LDL by 25% in HoFH subjects and 28% in HeFH subjects (Stein et al., 2012). The LDL lowering ability of mipomersen is similar across all LDL phenotypes and genotypes including HeFH, non-familial hypercholesterolemia and HoFH. Mipomersen was studied in addition to existing lipid-lowering statin therapy.

An adverse effect of APOB inhibitors is the accumulation of hepatic fat which can lead to hepatitis and liver damage. In this study a significant limitation occurred when 30% of subjects in both the placebo and mipomersen groups had unreadable magnetic resonance imaging (MRI) scans. MRI scans were utilized to observe hepatic fat content to determine whether mipomersen therapy should continue or cease. This technical and subject challenge had little effect on the study since there were still an adequate number of readable MRI scans to make a conclusion with and reach statistical significance (Stein et al., 2012).

In another study published by the *European Heart Journal*, mipomersen's effects were studied over two years to evaluate the effectiveness and safety of long-term dosing in individuals with FH on maximally tolerated statin therapy. 142 patients were enrolled in the study ( $N=142$ ) with HeFH ( $n=103$ ) and HoFH ( $n=38$ ) respectively who had successfully and recently completed a phase 3 mipomersen trial and did not have any adverse health conditions (clinically significant liver laboratory results, injection site reactions, flu-like symptoms) and did not consume excessive amounts of alcohol (Santos et al., 2013). Mipomersen was administered weekly at 200 mg subcutaneously and a 2 week screening period and 24 week follow up succeeded the test where patients were assessed for drug efficacy and safety. Subject safety was monitored through assessment and laboratory findings every 4-7 weeks and ECGs were conducted to examine QT interval changes, a possible complication of mipomersen of which subjects were effected ( $n=2$ ) (Santos et al., 2013). Laboratory results were monitored for hepatic damage to drug therapy ( $n=2$ ), and other adverse effects ( $n=33$ ). The most common adverse effect was noted to be injection site reactions ( $n=138$ ). Elevated liver enzymes (a reversible condition was found with drug discontinuation) in the form of alanine aminotransferase were monitored and elevated in a small number of subjects ( $n=18$ ) (Santos et al., 2013).

Effectiveness of mipomersen was noted by the 28-31% average reduction in APOB concentrations (Santos et al., 2013). Also noted was the small reduction in triglycerides and slight increase in HDL ( $P<0.01$ ). Mean reduction in APOB by week 104 was 31% ( $P<0.001$ ). Reduction of triglycerides, non HDL cholesterol and LDL was noted throughout the study with a 17% decrease in LDL by week 104 ( $P<0.001$ ) (Santos et al., 2013).

A serious limitation was the association of the authors to outside interests including pharmaceutical companies and research firms exposes a conflict of interest for this study. The authors either worked for or presented for pharmaceutical product developers. Another limitation was the source of funding by Genzyme, a subsidiary of the Sanofi Corporation who paid for the research and open publication of this study (Santos et al., 2013).

### **MTP Inhibitors**

The MTP inhibitor's mechanism lies in its ability to inactivate MTP, a precursor in the construction of LDL and chylomicrons, both of which are lipoproteins. MTP inhibitors lower the amount of apolipoprotein B containing lipoproteins which in turn lowers non-HDL cholesterol (Hewing et al., 2013). This study used rodents (mice) as subjects ( $N=24$ ), to determine the effectiveness of MTP inhibitors in regressing atherosclerotic lesions. The researchers administered MTP inhibitors to the mice through dietary means in mice chow. MTP inhibitors greatly reduced circulating LDL. By the end of one week serum LDL levels were reduced by 84% and by two weeks the level was reduced to by 94%. Atherosclerotic lesion size also were decreased, became less fatty and became more collagenous which is a sign of plaque stabilization in humans. Plaque size when comparing the MTP group against the control group there was a 39.4% decrease in size ( $p<0.001$ ) (Hewing et al., 2013). The only significant limitation is this study was conducted on mice and not in humans: therefore findings may not be

similar in human subjects. Along with a small sample ( $N=24$ ) using mice is not clinically significant for humans.

Another study by researchers in the UK observed correlations between MTP inhibitor use and reduction of serum LDL (Kolovou, Vasiliadis, Gontoras, Kolovou, & Hatzigeorgiou, 2015). The case-study included two subjects ( $N=2$ ) and found the results cannot be either statistically significant or clinically significant but the findings may be useful in developing future studies focusing on FH. Both subjects were homozygous for FH, had severely elevated LDL levels (both  $>300$  mg/dL) and were required to undergo LDL-apheresis (a dialysis-like procedure that removes LDL from the blood). Researchers found that serum LDL cholesterol could be reduced by 40% when MTP inhibitors are combined with statin. LDL-apheresis was also impacted with frequency dramatically reduced. In one subject undergoing apheresis every other week, MTP inhibitors reduced need for the procedure to once every 10 to 12 weeks after 40 weeks of MTP inhibitor use. Another subject had reduced apheresis to once every 16-24 weeks (Kolovou, Vasiliadis, Gontoras, Kolovou, & Hatzigeorgiou, 2015).

Another MTP inhibitor lomitapide (Juxtapid) developed by pharmaceutical company Aegerion in conjunction with the University Of Pennsylvania School Of Medicine is reported to hold promise in HoFH individuals who have not responded to statins. In a phase 2 clinical trial, researchers investigated lomitapide and atorvastatin (statin drug) combination therapy and how it would compare to atorvastatin alone, the study ( $N=50$ ) was conducted over 8 weeks. Researchers found that in combination, lomitapide and atorvastatin significantly lowered serum LDL levels than atorvastatin alone. The findings indicated Juxtapid reduces mean LDL levels 66% from baseline compared to placebo when in combination with atorvastatin; lomitapide alone decreases LDL by 35% from baseline (Aegerion Pharmaceuticals, 2011).

## Discussion

The serum LDL lowering effect of new classifications of Pharmacogenomic drugs is evident with treatment of FH. More specifically, PCSK9 inhibitors, ApoB inhibitors and MTP inhibitors all were found to have better outcomes for individuals with FH either as an adjunct or replacement for traditional statin therapy. The variability of statins and the genetic factors that predispose an individual to statin intolerance resulted in a gap for successfully treating individuals with FH. Pharmacogenomics in some cases can be used as an adjunct to statin drugs to achieve lower target LDL levels in FH individuals who are on maximum tolerated statin therapy, or who do not tolerate statins. Pharmacogenomic therapies also have potential for tailoring treatments for individuals with non-familial dyslipidemias as the aforementioned pharmacotherapies have a substantial effect on serum LDL levels, ApoB, triglycerides and chylomicrons and, in some cases, weight reduction.

Based on this review of only eight studies, the evidence suggests that genomic research advances with genetically based pharmacotherapies can lower serum LDL levels in individuals with a diagnosis of FH. However, additional studies are needed with larger sample sizes and more diverse subjects. More information is being discovered about genetic traits and FH and the role of precision medicine may have in managing symptoms and disease processes in individuals with this genetic trait. As the HGP continues to uncover genetic markers for other disease, more diagnostic and treatment options may become a reality for these conditions. While much remains unknown, the research evidence in this review suggests that the new pharmacogenomic medicine are effective in regulating the disease process of FH and hypercholesterolemia; thus, reducing long term health risks and other associated comorbidities specifically, PCSK9 Inhibitors, ApoB inhibitors and MTP inhibitors.

## **Implications for Nursing**

The next section highlights implications for nursing in respect to education, practice, policy and research followed by limitations of this integrated review of the literature focusing on the management of FH using pharmacogenomics.

### **Education**

Given the mandate of the American Nurses Association and other professional nursing specialty organizations (Cheek, Bashore, & Brazeau, 2015; Greco, Tinley, & Seibert, 2011; Howington, Riddlesperger, Cheek, 2011), there is a need for nurse educators to integrate genomics into content curricula. This nursing mandate, coupled with President Obama's Initiative on Precision Medicine reinforces an urgent need for a more robust understanding of human genomes, pharmacogenomics and precision medicine (Williams et al., 2016). More specifically, students must be informed about concepts related to human genetic traits in disease formation which is vital in developing, treating and evaluating nursing care plans in particular individuals who are at risk for or have been diagnosed with FH. As genetically based therapies become more specific to the genome of an individual it is ever more important that nurses understand precision therapies' physiological processes (Cheek, Bashore, & Brazeau, 2015). Informed health professionals, specifically nurses, can be more effective at patient education and informing about genetic treatment principles. Not only is genetic related content important for students in pre-licensure nursing education programs, but continue education offerings must be mandatory for nurses who have been in the workforce for an extended period of time (Williams et al., 2016).

Electronic resources are a source of current information that can augment nurses' knowledge on genomics. For instance, the National Institute of Health Pharmacogenomics

Research Network's Clinical Pharmacogenetics Implementation Consortium (CPIC) (Caudle et al., 2014) provides information on current research relating to genetics and precision medication. This consortium, on a regular bases, releases peer-reviewed guidelines involving genetics and pharmacogenomics data is useful to improve treatment outcomes (Cheek, Bashore, & Brazeau, 2015). The National Institute of Health's Pharmacogenomics and Pharmacogenetics Knowledge Base (PharmGKB) (Thorn, Klein, & Altman, 2013), is another site that provides current evidence on pharmacogenomics that nurses in advanced practice, research and education can readily access (Cheek, Bashore, & Brazeau, 2015).

### **Practice**

Clinicians must understand genetics concepts as these relate to disease processes and precision medicine for nursing assessments, care planning and outcomes evaluation. Core competencies related to genetics and pharmacogenomics have been identified and are important to enhance clinical reasoning and decision making (Williams et al., 2016). In the roles of advocate, educator and counselor, nurses are expected to inform, assess, monitor and obtain signed consent from individuals who are considering genomic screening and pharmacogenomic treatment options. Nurses often educate individuals and family members about genetic tests; sometimes interpret results along with the physiology of genome traits and mutations that can lead to disease processes. The influence of genetic traits and the associated pharmacodynamics and pharmacokinetics that inform about drug transport and metabolization are even more important for advanced practice nurses to understand who are involved in prescribing and titrating medications that are genome dependent (Cheek, Bashore, & Brazeau, 2015). Another responsibility of nurse clinicians is administering and monitoring responses to pharmacogenomic interventions (Cheek, Bashore, & Brazeau, 2015). In the case of an individual diagnosed with

FH, the nurse would monitor serum LDL levels and interpret pertinent laboratory values as well as monitor for side effects of the drug such as liver impairment.

## **Policy**

Stated objectives of the *Whitehouse Initiative on Precision Medicine* include accelerating biomedical research, providing health professionals with tools to treat genetic disease and incorporating researcher and evidence based medical interventions (Williams et al., 2016). This initiative at a societal level reinforces an urgent need for research on pharmacogenomics and appropriately treating genetic induced conditions. In turn, the evidence should be disseminated for use by clinicians to develop and implement precision interventions to treat and manage a particular genetic based condition such as FH (Cheek, Bashore, & Brazeau, 2015). Nurses are in a position to influence policy at national, state and local levels first by being informed; then, contacting and informing policy makers about genetic related initiatives. Another policy implication relates to reimbursement levels by third party payers for genetic screening and precision medicine. While pharmacogenomics may initially be deemed to be more costly by 3<sup>rd</sup> party payers, long term outcomes may be far more cost effective when applying pharmacogenomics and precision medicine. As advocates, nurses must have a greater presence on local, state and national advisory boards and other regulatory agencies in order to present the nursing perspective as well as advocating for consumers, specifically, in the area of genomics and FH.

## **Research**

Based on a review of only eight articles for this thesis reinforces that limited research that has been published in the area of FH and precision medicine to treat this genetically based condition. There are multiple gaps in the literature. Studies are needed focusing on nursing



topics, such as effective counseling approaches with individuals who are considering genetic screening. Evidence is needed on appropriate educational strategies focusing on pharmacogenomic interventions, managing associated side effects and supporting individuals that are recipients of precision medicine. Additional research is needed that isolates FH phenotypes and measuring short and long term drug efficacy with these genetic traits; as well as developing primary, secondary and tertiary prevention strategies. Since genomics and pharmacogenomics are a new medical frontier, studies are needed that focus on demographic diversity including gender, ethnic, racial and age factors to establish both statistical and clinical significance.

### **Limitations**

Several limitations are noted with this integrative review of the literature focusing on pharmacogenomics in FH. Associated with the inclusion criteria limiting publication time frame of five years 5 (2010-2015) that were written in the English language only eight articles were reviewed; seven of which had a very small sample size; and, one of which used rodents as subjects. The studies that were reviewed focused on select drugs and their effectiveness in treating individuals with persistent hypercholesterolemia, with minimal information on the drug effects on subgroups and side effects. There also was evidence of conflict of interests among the researchers and their financial sponsor (pharmaceutical companies) for the studies.

### **Summary**

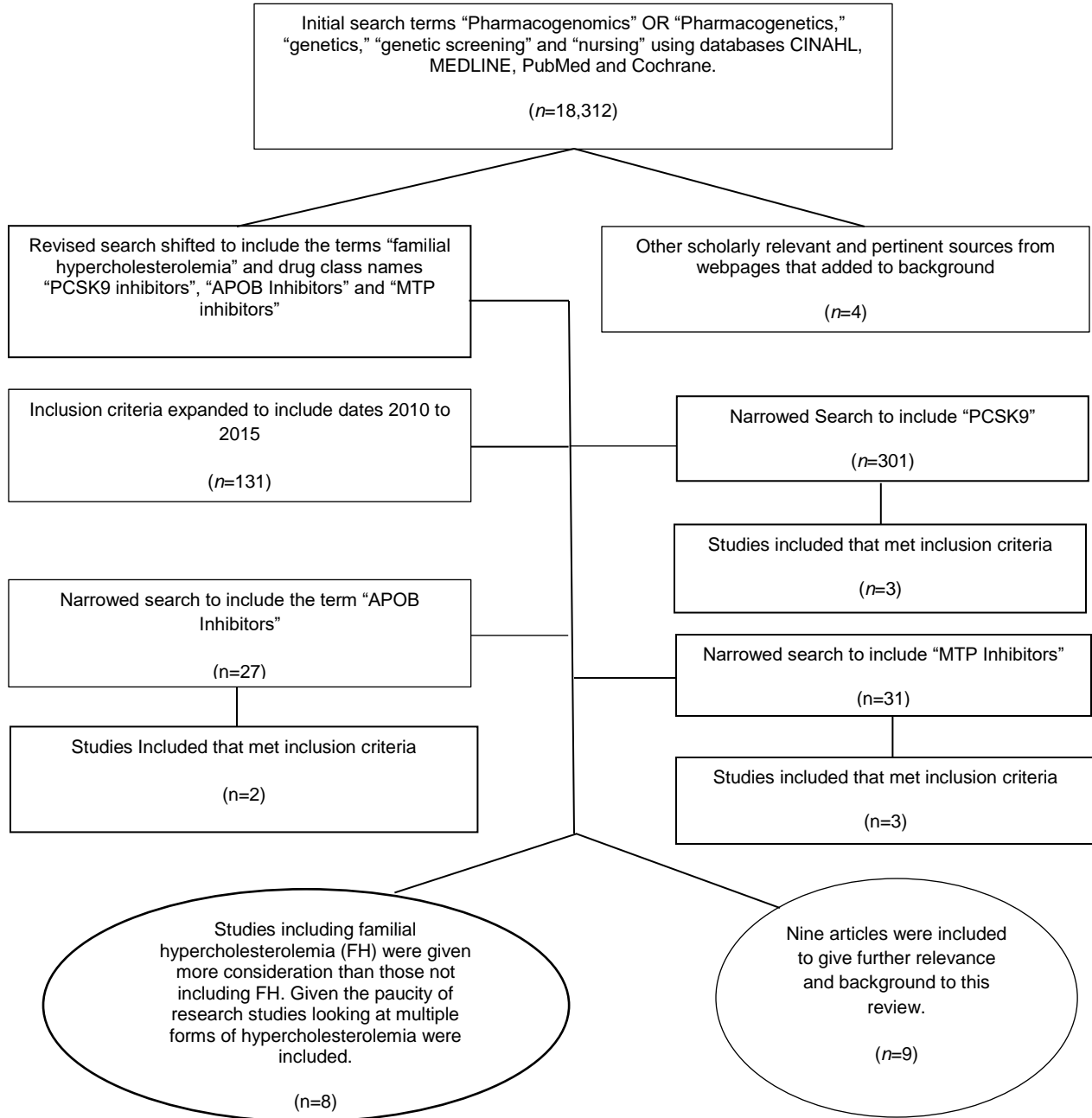
The Human Genome Project has had far reaching applications for genomic technologies and pharmacogenomic interventions that are tailored to human conditions that are associated with genomic traits. Based on the integrative research literature review focusing on familial hypercholesterolemia, there is a paucity of articles on the topic. The research predominately is on

emerging pharmacogenomic drugs and their effects on managing FH. This synthesis of eight research articles by this researcher summarizes that little is known on the topic along with extensive gaps in the evidence. Finally, implications for nursing education, practice, policy and research along with limitations are noted.



## APPENDIX A

**Figure 1: Selection Method of Literature**



Limiters: English-language, peer reviewed, published between 2010-2015, included HMG-CoA reductase inhibitors (statins) as a comparison drug.



## APPENDIX B

**Table 3: Research Literature Reviewed**

Author (last/First name)	Date of study	Study design	Sample size	Data collection method	Key Findings	Gaps/conflicting information
Aegerion Pharmaceuticals	2011	Randomized Controlled Trial	<i>N</i> =50	Laboratory/ Imaging	Lomitapide effective at lowering LDL in subjects with HoFH up to 66%	Research supported by pharmaceutical company. Could be conflict of interest for researchers at University of Pennsylvania
Stein, E. A., Dufour, R., Gagne, C., Gaudet, D., East, C., Donovan, J. M., . . . Mcgowan, M.	2012	Randomized Controlled Trial	<i>N</i> =124	Laboratory/ Imaging	ApoB inhibitors reduce LDL in heterozygous FH subjects by 28% from baseline when compared to a placebo ( <i>p</i> <0.001)	About 30% of MRIs not readable to determine hepatic fat content; medication side effect. Significance of hepatic fat and ALT level increases are uncertain.
Hewing, B., Parathath, S., Mai, C. K., Fiel, M. I., Guo, L., & Fisher, E. A.	2013	Animal experimental	<i>N</i> =24	Laboratory/ Physiological	MTP inhibitors reduce LDL & size of atherosclerotic lesions	Study conducted on mice instead of humans.
Santos, R. D., Duell, P. B., East, C., Guyton, J. R., Moriarty, P. M., Chin, W., &	2013	Randomized Controlled Trial	<i>N</i> =142	Laboratory	Safety and efficacy of mipomersen in subjects with FH. APOb reduction was 31% at 104 weeks( <i>P</i> <0.001).	Authors had associations with pharmaceutical companies. Funding came from a pharmaceutical company for research and publishing.

Mittleman, R. S.					HDL increased (P<0.01).	
Kereiakes, D. J., Robinson, J. G., Cannon, C. P., Lorenzato, C., Porfy, R., Chaudhari, U., & Colhoun, H. M.	2015	Randomized Controlled Trial	N=316	Laboratory	PCSK9 inhibitors reduce LDL by 48% from baseline in subjects at high CV risk who were on maximally tolerated statins.	Relatively small for analysis of subgroups.
Kolovou, G., Vasiliadis, I., Gontoras, N., Kolovou, V., & Hatzigeorgiou, G.	2015	Case study	N=2	Laboratory	MTP inhibitors reduce LDL by 40% in homozygous FH subjects on statin therapy.	Very small sample size that isn't statistically significant.
Raal, F. J., Honarpour, N., Blom, D. J., Hovingh, G. K., Xu, F., Scott, R., . . . Stein, E. A.	2015	Randomized Controlled Trial	N=50	Laboratory	PCSK9 inhibitors reduce LDL by 30.9% compared to placebo (p<0.0001) in homozygous FH subjects	Short, 12 week study. Did not control for some subgroups.
Raal, F. J., Stein, E. A., Dufour, R., Turner, T., Civeira, F., Burgess, L., . . . Gaudet, D.	2015	Randomized Controlled Trial	N=331	Laboratory	PCSK9 inhibitors in heterozygous subjects reduce LDL by 60% when compared with placebo.	Analysis of response to treatment based on genotype was not pre-specified. Short duration of study, only 12 weeks.

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