

Exploring Cascade Screening for Familial Hypercholesterolemia

by

Mychaela Austin

BS in Biology, University of Central Florida, 2018

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This essay was presented

by

Mychaela Austin

It was defended on

April 30, 2021

and approved by

Andrea Durst, MS, DrPH, LCGC, Human Genetics Department

Bonnie Jin, PhD, MPH, Health Policy and Management

Essay Director: Andrea Durst, MS, DrPH, LCGC, Human Genetics Department

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Abstract

Cardiovascular Disease (CVD) is a leading cause of death in the United States (National Center for Health Statistics, 2020). A genetic factor for CVD is Familial Hypercholesterolemia (FH), a disorder characterized by high levels of low-density lipoprotein cholesterol and premature onset of cardiovascular disease (Bouhairie et al., 2015). One method for diagnosing cases is through cascade screening, which entails contacting relatives of cases and screening them for FH. The Familial Hypercholesterolemia Foundation is a nonprofit organization dedicated to bringing about awareness of FH (*Who Are We?: FH Foundation, 2021*). The FH Foundation is currently exploring the development of an interstate cascade screening program for FH. They have chosen six states to investigate any legal barriers to such a program. This paper categorizes and analyzes select policies of California, New Hampshire, Minnesota, Pennsylvania, Texas, and Vermont that are relevant to the implementation of a cascade screening program. The policies in these states were categorized by whether they applied to communicable diseases, genetic information, privacy, and public health surveillance statutes. The categorization of these policies provides a guide for how a cascade screening program in the afore mentioned states would operate. The Behavioral Risk Factor Surveillance System 2019 survey data was utilized to observe the prevalence of high cholesterol in the US as well as potential disparities in screening and treatment between different demographic groups. Of the initial 418,268 respondents, 143,613 were asked if they had ever been told their blood cholesterol level was high. Of those asked, 63.84% reported ever being told they had high cholesterol. Of the women asked this question, 61% reported ever being told their blood

cholesterol was high, compared to 66% of men asked this question. The difference may be indicative of the disparities described in the literature of statin use between men and women. The data demonstrates that high cholesterol is an issue of public health significance. A public health genetics program such as a cascade screening program targeting Familial Hypercholesterolemia could not only bring about awareness of the disorder but also target those potentially unaware of their need for cholesterol interventions.

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Preface

I would like to thank my advisor, Dr. Andrea Durst for her mentorship and patience throughout this essay writing process. I would also like to thank my essay reader, Dr. Bonnie Jin for her time and input. I am also grateful to Dr. Mary McGowan and the Familial Hypercholesterolemia Foundation for extending me the opportunity to work on their state genetic privacy laws project.

1.0 Background

1.1 Cardiovascular Disease

Cardiovascular Disease (CVD) is a leading cause of death for the United States (U.S.) as a whole and for each of the fifty states individually (National Center for Health Statistics, 2020). According to the Centers for Disease Control and Prevention, cardiovascular disease or heart disease costs the United States about \$219 billion each year, including cost of health services, medicine, and years lost in productivity due to death (Heart Disease, 2020). This particular disease is prevalent in males and females and all racial and ethnic groups in the U.S. and is the leading cause of death among these groups (Heart Disease, 2020). Older age is the most common risk factor for developing CVD, however, more than half of adults with CVD are under the age of 65 (Mensah, 2007). The majority of outpatient and emergency department visits were attributed to the burden of CVD. As with many health issues in the U.S., there are health disparities that exist in cardiovascular mortality rates; the proportion of premature deaths from coronary heart disease was greater among minorities when compared to whites (Mensah, 2007). According to the Behavioral Risk Factor Surveillance System data, the rates of self-reported prevalence of high cholesterol are on the rise in U.S. adults (Mensah, 2007).

The term cardiovascular disease includes vascular diseases as well as diseases of the heart. There are many causes and factors that contribute to disease development and eventually mortality. One cause of CVD is an inherited genetic condition called Familial Hypercholesterolemia. This disorder is characterized by high levels of low-density lipoprotein cholesterol (LDL) and early onset of CVD or even death (Bouhairie et al., 2015). The accumulation of LDL in the blood can

be due to reduced LDL receptor function which can be due to the receptor not being present, not being properly transported for expression on the cell surface, improper binding to LDL, improper clustering for receptor endocytosis, or the receptor not being recycled (Bourhairie et al., 2015). Pathogenic variants in the Apo B-100, LDLR, and PCSK9 genes are known to be involved in the development of Familial Hypercholesterolemia (FH). The pathogenic variant of LDLR affects the LDL receptor, causing it to either be absent from the cell surface entirely or present in a reduced number. Mutations in this particular gene are involved in about 85-90 percent of FH cases (Bourhairie et al., 2015). Pathogenic variants in the ApoB gene leads to diminished ability for LDL particles to bind to LDL receptors. This gene is indicated in five to ten percent of FH cases (Bourhairie et al., 2015). Pathogenic variants in the PCSK9 gene result in a gain of function and leads to increased levels of PCSK9 protein activity which accelerates the degradation of LDL receptors on cell surfaces (Bourhairie et al., 2015).

1.2 Familial Hypercholesterolemia

FH is inherited as an autosomal dominant disorder and is known to have a dosage effect (Bourhairie et al., 2015). The homozygous form of FH (HoFH) is rare but has a large effect on those with this form. Affected individuals are burdened with cholesterol exposure starting in utero and are at an increased risk for early death from CVD (Ito et al., 2015). A true homozygous individual has two copies of the same mutated variant, but compound heterozygotes who have one copy each of different mutations are still considered to have HoFH (Ito et al., 2015). The heterozygous form remains very common in all ethnicities and races. In the U.S., prevalence is estimated at one case in every 250 individuals, which would be about 1,500,000 cases (Bourhairie

et al., 2015). FH can decrease an individual's life expectancy by 20 to 30 years (Allard et al., 2014). Despite the high incidence, this disorder remains underdiagnosed. Barriers to diagnosis include, low physician awareness of FH and its screening guidelines, and lack of patient awareness of family history or perception of risk (Alonso et al., 2020). According to the FH Foundation there are three accepted resources for diagnosis, the Simon Broom criteria, the FH Dutch Lipid Clinic Criteria and the Med Ped Criteria,. The Simon Broom criteria includes having high LDL-C levels while off treatment (≥ 190 mg/dL for those over 20 years and ≥ 160 mg/dL for those younger than 20), tendon xanthomas or cholesterol deposits in the tendons, in the patient or first degree relatives, high total cholesterol (>290 mg/dL), DNA based evidence of a FH associated mutation, family history of myocardial infarctions before 50 years old in a second degree relative or before 60 years old in a first degree relative, and family history of high cholesterol in an adult first or second degree relative or in a child or sibling younger than 16 years old (*FH Diagnosis, Management and Family Screening* 2020). The Dutch Lipid Clinic Criteria includes family history of first degree relatives with premature vascular disease or a high known LDL level, a clinical history of the patient having premature vascular or coronary artery disease, varying classes of high LDL levels and evidence of an FH associated mutation (*FH Diagnosis, Management and Family Screening* 2020). The Med Ped Diagnostic Criteria includes classifying individuals by age range (less than 20 years, 20-29 years, 30-39, and greater than 40) and then by cholesterol level and whether they had a first, second, or third degree relative diagnosed with FH (*FH Diagnosis, Management and Family Screening* 2020). Genetic testing is an important confirmatory part of diagnosing FH. The Centers for Disease Control and Prevention (CDC) has classified this as a Tier 1 genomic application (Alonso et al., 2020). The recommendation includes screening relatives of index cases either with cholesterol and/or genetic testing to confirm diagnosis (*More detailed information on key tier 1*

applications - familial hypercholesterolemia, 2014). However, despite falling costs over the years, it is still expensive to do confirmatory genetic tests. At one time Athena Diagnostics was charging \$620 for a test of the APOB gene and \$1235 for the LDLR gene (Carlson, 2010).

1.3 Treatment

Upon diagnosis with FH, the initial pharmacologic therapy is treatment with statins to lower LDL-C (Bouharie et al., 2015). The sooner treatment is started, the more the lifetime risk of coronary heart disease is reduced. The impact of elevated LDL-C from as young as birth can lead to the development of CVD at a younger age (Raal, Hovingh, & Catapano). According to the 2013 American College of Cardiology and the American Heart Association cholesterol treatment guidelines, statin use is recommended in adult patients with LDL-C levels ≥ 190 mg/dL, as well as lifestyle changes (Bouharie et al., 2015). For patients with the homozygous form of FH, statin treatment is necessary as soon as diagnosis is made. For children with FH, statin treatment can begin as young as eight to ten years old (Bouharie et al., 2015). Statins limit cholesterol synthesis by reducing HMG-CoA reductase, which leads to the increased expression of LDL receptors. For FH patients, moderate to high potency statins are required initially as low potency statins are usually ineffective in this disorder (Bouharie et al., 2015). The typical treatment goal is a 50% or more reduction in baseline LDL-C levels. Although the long-term risks of statin use in children is unknown, the known benefits outweigh the risks in this condition (Bouharie et al., 2020). It is recommended for children aged eight or older with LDL-C levels greater than 160mg/dL to begin statin treatment (McGowan, Hosseini Dehkordi, Moriarty, & Duell, 2019). A more intensive pharmacologic intervention may be needed for higher risk

patients. Heightened risk includes clinical evidence of CVD, diabetes, family history of premature CVD, current smoking, high level of lipoprotein, and two or more risk factors for coronary heart disease (Bouharie et al., 2015). Often FH patients will require multiple medications to get their cholesterol levels to manageable levels. When medication fails to lower lipid levels, LDL apheresis is an intervention done through various methods to remove circulating LDL (Bouhairie et al., 2015). According to the National Lipid Association and ACC/AHA cholesterol guidelines, this intervention is recommended for patients who have not met LDL reduction goals after six months of maximum drug therapy and diet adjustments, functional homozygous FH patients with LDL levels greater than 300 mg/dL, functional heterozygous FH patients with LDL levels greater than 300 mg/dL and risk characteristics, and functional heterozygotes with LDL levels greater than 160 mg/dL and very high risk characteristics (Bouharie et al., 2015). This form of treatment is typically done every one to two weeks for about three hours at a time, with the goal of removing at least 60% of Apo-B lipoproteins in circulation. Although this intervention can lead to increased life expectancy for patients, its high cost and availability limit widespread use (Bouharie et al., 2015). In severe cases when lipid levels do not respond to other interventions, surgery is needed. These options include partial ileal bypass and liver transplantation. After liver transplantation, lipid levels are significantly reduced in these individuals. However, this intervention must be done before cardiovascular complication begin to manifest to be effective against the damage of elevated lipids (Raal, Hovingh, & Catapano).

1.4 Screening

There are several approaches to screen for undiagnosed cases of FH. One approach would be universal screening, meaning that all individuals in a defined population would undergo blood cholesterol screening, and those who meet the criteria for high LDL would then be referred for confirmatory genetic testing (Alonso et al., 2020). It was recommended by the National Lipid Association in the United Kingdom, that children aged 9-11 years old be screened to start medical intervention as early as possible if needed (Alonso et al., 2020). The American Academy of Pediatrics recommends cholesterol screening for children and young adults once between ages 9-11 and once again between the ages of 17-21 (*Periodicity Schedule*). Reverse cascade screening would then be implemented to identify parents among the children who did have FH. Limitations to this approach were noted, such as “cost and resource consumption and ethical issues like insurance compliance” (Alonso et al., 2020). Another approach would be opportunistic screening, which would involve primary care physicians in the screening and care for FH. A multinational survey was conducted to measure where primary care physicians were in their knowledge of FH and diagnosis guidelines. The survey found 34% of these physicians considered themselves familiar with FH. and for this particular approach to work there would need to be country specific guidelines and educational programs implemented (Alonso et al., 2020). Another screening approach is cascade screening. In this approach first degree relatives of newly identified index cases are screened either by cholesterol level, genetic testing or both. Several studies have shown that “the most cost-effective approach for detecting new cases of FH is cascade screening of relatives of a diagnosed index case using lipid levels and genetic testing” (Alonso et al., 2020). A key part of screening is the screening region. In order to be effective and reach the highest number of first-degree relatives a national program would be ideal (Santos et al., 2015).

The cost effectiveness of cascade screening is determined by the cost effectiveness of treatment after diagnosis, the underlying prevalence in the population, and the accuracy of the test (Ademi et al., 2013). A study in the United Kingdom found that over a 30 year period, about 139 cardiovascular events and 23 deaths were avoided per 1,000 relatives tested (Kerr et al., 2017).

From 1994 until 2014, the Netherlands government subsidized a cascade screening program for FH. In that period of time, 28,000 individuals with FH were identified and entered into a national database (Louter, et al., 2017). Since the subsidization ended, cascade screening became part of the national health care system and the national database continued to be maintained (Louter, et al., 2017). In Slovenia, children over the age of 5 years are screened universally. Despite their success in finding cases of FH, the Netherlands did not do the best job of ensuring cases were followed-up for treatment. Almost 80 percent of the children diagnosed with FH were seen by a physician following diagnosis, and only a quarter of them started statin treatment (Louter, et al., 2017). For the adults, half of the identified cases of FH were not already taking statins at the time of diagnosis. Two years following their FH diagnosis, only about 50 percent of the aforementioned adults were on statins. In over half of these cases in the Netherlands, the treating physician advised against of the use of statins. This was indicative of the knowledge deficiency of many providers at the time about FH (Louter, et al., 2017). Their current version of the program places the responsibility of seeking treatment or informing family members on the patient. This led to a significant decrease in the number of cases detected in a year (Louter, et al., 2017). It is evident by the experience of the Dutch that for cascade screening to be successful there must be active efforts to reach out to potential cases, trained personnel, and a central database (Louter, et al., 2017).

In the U.S., a program was implemented in West Virginia that provided screening for children for chronic disease risk. West Virginia was selected because of its high rates of CVD and childhood obesity rate (Elliot et al, 2018). Fifth grade students were screened because children in this age group fall into the recommended lipid screening guidelines. The children were screened for body composition, blood pressure, insulin resistance, and lipid levels (Elliot et al, 2018). Of the screened children, the most common cholesterol abnormality was attributed to obesity and lack of physical activity. However, a small proportion of the children in the study had dyslipidemia unrelated to weight and LDL-C levels indicative of FH. Screening based on a family history of premature CHD alone would have missed one-third of these children (Elliot et al, 2018).

1.5 HIPAA

The Health Insurance Portability and Accountability Act of 1996 established federal standards to protect sensitive patient health information from being disclosed without the patient's knowledge. The covered entities under this law include health care providers, health plans or insurance companies, health care clearinghouses, and business associates (*Health insurance portability and Accountability act of 1996 (HIPAA), 2018*). These entities are permitted to disclose this protected information without patient permission only under certain circumstances. The 12 national priority purposes are, when required by law: public health activities, victims of abuse or neglect or domestic violence, health oversight activities, judicial and administrative proceedings, law enforcement, functions (such as identification) concerning deceased persons, cadaveric organ, eye, or tissue donation, research, under certain conditions, to prevent or lessen a serious threat to health or safety, essential government functions, and workers

compensation (*Health insurance portability and Accountability act of 1996 (HIPAA), 2018*). HIPAA does not allow for the release of medical information to relatives of a patient without the patient's permission. However, the American Society of Human Genetics, prior to HIPAA's compliance date, stated disclosure should be allowed in special circumstances (Clayton, Evans, Hazel, & Rothstein, 2019). Due to the conflicting ideologies and potential harms, clinicians are neither required nor permitted to inform genetically at-risk relatives without the patient's consent (Clayton, Evans, Hazel, & Rothstein, 2019).

1.6 Genetic Information Nondiscrimination Act

In 2008, the Genetic Information Nondiscrimination Act (GINA) was enacted in the U.S. to protect citizens against discrimination based on genetic information in health insurance and employment (National Human Genome Research Institute, 2020) Title I of GINA focuses on health insurance discrimination, prohibiting health insurers from using genetic information to determine eligibility or coverage determination. It also protects against health insurers from requiring an individual or their relatives to submit to genetic testing or offering up genetic test results (National Human Genome Research Institute, 2020) These protections do not apply to disability, life insurance, or long term care insurance.

Title II of GINA addresses employment discrimination. Employers may not use genetic information in employment decisions such as hiring, firing, job assignment and more (National Human Genome Research Institute, 2020). Employers and covered entities related to employment such as labor unions, etc., may not request or require genetic information as a condition of employment (National Human Genome Research Institute, 2020). A notable

exception to this protection is the U.S. military, which is allowed to make employment decisions based on genetic information. Employers with less than 15 employees are also exempted from GINA protections (National Human Genome Research Institute, 2020).

Federal laws such as HIPAA and GINA provide protections to individuals undergoing genetic testing or diagnosis of a genetic health condition. States may also have additional protections in place, which will be the topic of the policy analysis portion of this paper.

1.7 Healthcare Disparities

Particularly in the U.S., health disparities are widespread in the differences of health outcomes between White Americans and most minority groups, as well as between men and women of the same racial or ethnic groups (Graham et al., 2015). African American males in the U.S. have the highest overall cardiovascular death rate, and cardiovascular deaths in African Americans tend to occur earlier in life compared to White Americans (Graham et al., 2015). Native Americans were 1.21 as likely to die of heart disease compared to White Americans according to a 10-year analysis review (Sciences, Engineering & Medicine, 2017). The U.S. is racially segregated in terms of where people live and what resources they have access to (Thorpe et al., 2013). Among men, participation in preventative screening programs vary by race and socio-economic status (SES), and research has shown that increased educational attainment is associated with the use of preventative health screenings (Thorpe et al., 2013). Limited education, health literacy, and access to care are some of the major causes of health disparities in communities of color (Davis et al., 2007).

Regional disparities in health care are another obstacle present in the U.S. One-sixth of the U.S. population lives in rural areas and are faced with higher rates of chronic disease and worse health outcomes (Douthit et al., 2015). According to the Rural Development Act of 1972, rural is defined as an region of less than 10,000 residents (Douthit et al., 2015). These areas tend to be economically fragile and have limited broadband access. Coupled with their geographic isolation, adequate health care in these areas is difficult to achieve. Previous investigations in the literature show that for rural populations, particularly in southern states, patients with driver's licenses were twice as likely to attend their doctor's appointments and patients that lived further from their doctors were less likely to make appointments (Douthit et al., 2015).

Another barrier to use of preventative screening measures is access to health insurance, an issue that disproportionately affects minority populations in the U.S. (Sankar et al., 2004). This issue is rooted in discriminatory hiring practices that have prevented minority populations from accessing jobs that provide health care coverage. Among American Indian and Native Alaskan tribes, health care funding has been declining since the 1990's, which only increases the disparities in the healthcare they receive (Sankar et al., 2004).

There are noted differences in the medical treatment and interventions regarding cardiovascular care between men and women. A sample of adults in community practice found that women compared to men were less likely to have been offered statin treatment, more likely to decline statin therapy, and more likely to discontinue statin therapy if started. These differences were consistent across education, income, and provider type (Nanna et al., 2019). However, underlying causes for these differences between men and women may be due to the fact that women when compared to the men in the study were less likely to have private insurance, tended to have lower annual household incomes, and were less likely to have been

seen by a cardiologist (Nanna et al., 2019). According to Lowenstern, et al., cardiologists were more likely than primary care clinicians to believe in the benefits of statin use, which may be a reason for underuse of statins in certain populations (Lowenstern et al., 2019).

An outcome of CVD is a Myocardial Infarction (MI), however disparities exist in how this is clinically classified (Hilliard et al., 2020). “The standard definition of MI signifies the presence of an acute myocardial injury detected by abnormal cardiac biomarkers, namely cTn, in the setting of evidence of acute myocardial ischemia (Hilliard et al., 2020).” An accurate diagnosis is important to treatment as well as billing, policy, and resource allocation (Hilliard et al., 2020). MI can be classified as a type 1 or type 2. Type 1 is defined as, “an MI with clinical evidence of ischemia caused by atherosclerotic plaque disruption resulting in coronary thrombosis and detection of a rise and/or fall of cTn values with at least one value above the 99th percentile upper-reference limit (URL)” and at least one symptom of myocardial ischemia (Hilliard et al., 2020). For MI type 2, the same symptoms are included but must be, “due to a supply-demand mismatch of myocardial oxygen in the absence of coronary thrombosis (Hilliard et al., 2020)”. Type 1 MI can be divided again into two types, ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI). STEMI is a persistent ST-segment elevation and electrocardiographic leads. NSTEMI is ischemic symptoms at rest from an acute coronary plaque rupture, longer than 10 minutes, and taking place before hospital admission (Hilliard et al., 2020).

African Americans tended to die more often from MI and a higher prevalence of cardiovascular related health issues that coincide with features of type 2 MI (Hilliard et al., 2020). African American patients were also less likely than white patients to receive evidence based NSTEMI therapies (Hilliard et al. 2020). The same study found that after adjusting for

SES, in-hospital mortality was higher among lower income patients compared to those of higher income (Hilliard et al., 2020). There were also gender disparities noted in the cTn measurements. Since its discovery in 1963, it was considered the gold standard biomarker to detect an MI (Hilliard et al., 2020). However due to the fact that women tend to have lower levels of cTn across different ethnic backgrounds, this may be another source of disparities in women receiving proper cardiac care (Hilliard et al., 2020).

1.8 Disparities in FH

Familial Hypercholesterolemia is very much an underdiagnosed disorder and existing health disparities amplify this issue. In a study of FH patients from lipid specialty clinics in the US, treatment disparities were identified that lead to worse outcomes for women when compared with men and patients from nonwhite compared to white patients (Amrock et al., 2017). Women tended to be diagnosed later in life than men, less likely to receive any statin treatment, and less likely to achieve LDL-C reduction goals. Systemic biases were suggested as a barrier to adequate treatment for women with FH. In one cohort of women with FH, they were found to be less likely to be diagnosed with FH following a hospital discharge after an atherosclerotic CVD event (Amrock et al., 2017). Some women with FH have reported their chest pain symptoms not being taken seriously and have suffered acute myocardial infarctions during pregnancy (Amrock et al., 2017). Statin therapy is a major component of FH treatment and being female is a documented risk factor for statin intolerance (Amrock et al., 2017).

Black patients compared to any other race or ethnicity, tended to be diagnosed with FH at an older age. Black and Asian patients were the least likely to achieve LDL-C reduction goals.

These disparities likely stem from the racial disparities that exist in CVD management overall. Additionally, the lack of minority representation in the study conducted by Amrock et al., suggests unequal access to lipid clinics, socioeconomic status differences, and perceptions regarding LDL-C reduction goals (Amrock et al., 2017). They also note differential metabolism of statins and risk for CVD, which can vary widely between and within racial groups (Amrock et al., 2017).

1.9 Familial Hypercholesterolemia Foundation

The Familial Hypercholesterolemia Foundation (FH Foundation) is a nonprofit organization dedicated to the advocacy and education of Familial Hypercholesterolemia. Their mission is to raise awareness of FH, to increase early diagnosis, and to encourage proactive treatment (*Who Are We?: FH Foundation, 2021*). The FH Foundation has a national patient registry with the goals of increasing knowledge of the disorder, pooling data for research, and observation of therapy effectiveness (*Who Are We?: FH Foundation, 2021*). The FH Foundation is currently exploring any legal barriers to the establishment of an interstate cascade screening program. They are currently looking into six states to start. The states of interest include Texas, California, Vermont, New Hampshire, and Pennsylvania. Their role would be to help individuals with FH contact their relatives to inform them of their risk, testing options, and if needed, resources for treatment options.

2.0 Specific Aims

For this project I will be looking into potential legal barriers and facilitators that may exist in specific states in relation to the implementation of a cascade screening program by the FH Foundation to detect new cases of FH in the United States. I will also use national survey data to explore increased cholesterol prevalence in the U.S. and how this cardiovascular risk factor could be addressed by the current cholesterol screening guidelines for Familial Hypercholesterolemia and the cascade screening program being implemented by the FH Foundation. My final aim is to utilize national data to determine if there are racial or regional disparities in health screenings, which could further support the need for a comprehensive cascade screening program for FH.

3.0 Methods

The Behavioral Risk Factor Surveillance System 2019 survey data was used to look at the prevalence of high cholesterol across the U.S. “The Behavioral Risk Factor Surveillance System (BRFSS) is a collaborative project between all of the states in the United States (US) and participating US territories and the Centers for Disease Control and Prevention (CDC). The BRFSS is administered and supported by CDC's Population Health Surveillance Branch, under the Division of Population Health at the National Center for Chronic Disease Prevention and Health Promotion. The BRFSS is a system of ongoing health-related telephone surveys designed to collect data on health-related risk behaviors, chronic health conditions, and use of preventive services from the noninstitutionalized adult population (≥ 18 years) residing in the United States” (*CDC - 2019 BRFSS Survey Data and Documentation*, 2020, p.1).

The BRFSS survey data was collected by landline and cellular telephone interviews. Field operations are monitored by state health departments with assistance from the CDC. Many survey questions are the same as those from national surveys like the National Health and Nutrition Examination Survey so that the states have data comparable to national data. One of the objectives of this survey is to have state specific data on chronic disease prevalence and use of preventative health measures. The BRFSS survey has 3 main parts, the core component, the optional modules, and the state added questions. The core component is the standard question set all states use, the questions in this part are focused on health conditions and behaviors, as well as demographic information. The optional modules focus on specific topics and states can choose whether or not to include them. Finally, the state-added questions are chosen by individual states with no oversight by the CDC. The 52 states and territories included in the 2019 survey used Computer-

Assisted Telephone Interview (CATI) systems. The territories included in this dataset were Puerto Rico, Guam, and Washington D.C. New Jersey was not included as they did not submit sufficient data for this year. States have the option to translate the survey if a significant portion of their population speaks another language, however currently the CDC only provides a Spanish translation of the core questionnaire and optional modules. “In the sample design, states begin with a single stratum. To provide adequate sample sizes for smaller geographically defined populations of interest, however, many states sample disproportionately from strata that correspond to sub-state regions (*CDC - 2019 BRFSS Survey Data and Documentation, 2020, p.5*).” For the 2019 survey these states were, Alabama, Alaska, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Hawaii, Idaho, Illinois, Indiana, Iowa, Kansas, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, Nevada, New Hampshire, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Pennsylvania, Puerto Rico, Rhode Island, South Carolina, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, and Wisconsin.

This data provides prevalence information on health behaviors of a nationally representative dataset. This assessment analyzes data related to questions specific to cardiovascular health such as, “Ever had cholesterol checked”, “Ever told blood cholesterol was high”, and “Taking medication for high cholesterol”. These responses were compared by demographic variables such as race/ethnicity and sex. Data analysis was done by tabulating the frequency of the cardiovascular specific responses in StataSE 16. Microsoft Excel was used to create visualizations of the statistical data such as the percent of respondents to specific questions in the BRFSS survey.

Data was collected specifically from the six states of interest identified by the FH Foundation for implementing their cascade screening program. This included the states' statutes that would be relevant in the development of an interstate cascade screening program. The states included were Texas, California, New Hampshire, Vermont, Pennsylvania, and Minnesota. The data for these statutes came mostly from the state government or health department's web pages and a few unrelated legal websites. Population data for each of these states was collected from www.census.gov. Using the BRFSS data, responses to the cardiovascular specific questions were measured by percent for each of the states of interest. The various states' statutes were classified into either "Genetics Statutes", "Communicable Disease/ Reporting Statues", "Privacy Statues", and "Public Health Surveillance/Expansion Statues".

4.0 Results and Policy Analysis

4.1 BRFSS Data Analysis Results

Data from three 2019 BRFSS Survey questions related to cholesterol screening and medication were accessed to assess the number of individuals in the six states of interest to the FH Foundation for a pilot cascade screening program. This data analysis was also used to identify any disparities that might be considered and addressed by a cascade screening program. There were 418,268 total respondents to the 2019 BRFSS survey. The majority of the respondents identified as White, Non-Hispanic (NH) at 74.3%, while 8.94% of respondents identified as Hispanic (Figure 1).

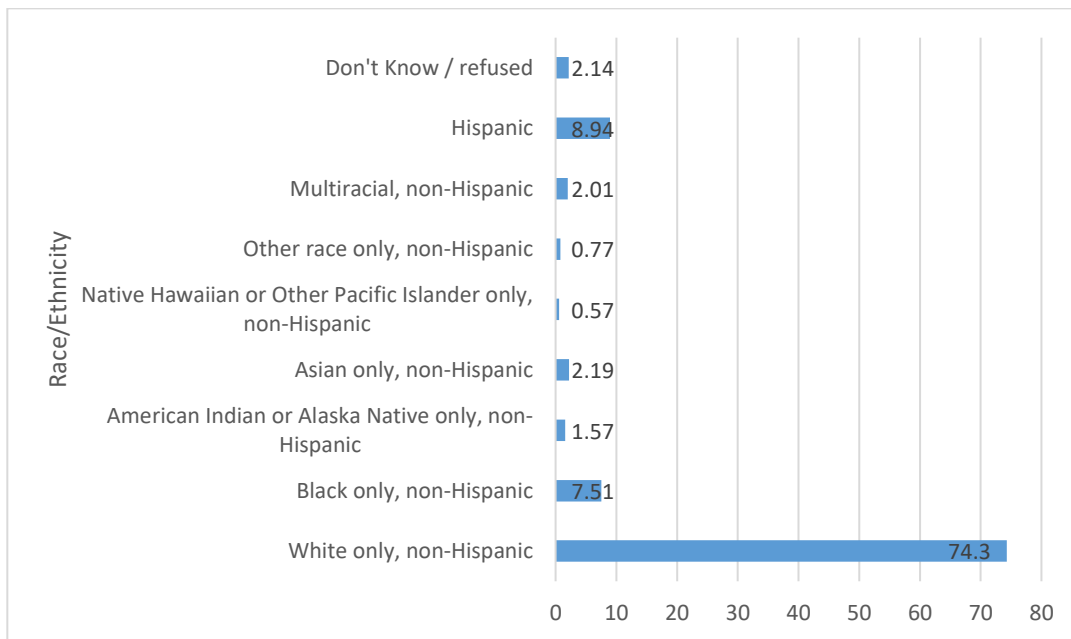


Figure 1. Race/Ethnicity of Respondents, Total: 418,265, BRFSS Survey

However, for the six states of interest the racial make-up of their populations varies with some more or less diverse than the nation at large (United States Census Bureau, 2019). Of the

six states, California had the largest total population of 39,512,223. California also had the lowest percent of individuals identifying as White alone, at 71.9%. This state also had the highest percent of individuals identifying as American Indian and Alaska native alone/Non Hispanic at 1.6% and Asian alone/Non Hispanic at 15.5% (Table 1). Texas had the second largest population at 28,995,881, and was similarly diverse in its population to California. For individuals identifying as Black alone/Non Hispanic, Texas had the highest percentage, at 12.9%. Texas also had slightly more individuals than California who identified as Hispanic or Latino at 39.7% compared with California's 39.4% (Table 1). Although Pennsylvania was fifth in terms of population, the commonwealth had the second highest percentage of individuals identifying as Black alone/Non Hispanic, at 12% and had the third highest percent of individuals identifying as Hispanic or Latino, at 7.8% (Table 1). New Hampshire, Minnesota, and Vermont, each had almost 80% or more of their population identify as White alone/Non Hispanic and had relatively low percentages of individuals identifying as non-White or Hispanic (Table 1).

Table 1. Population Demographics by State (United States Census Bureau: Quick Facts, 2019)

	TOTAL POPULATION	White alone, %	Black alone, non-Hispanic %	American Indian and Alaska Native alone, non-Hispanic %	Asian alone, non-Hispanic %	Native Hawaiian and Other PI, non-Hispanic %	Two or More Races, non-Hispanic %	Hispanic or Latino %	White alone, Non-Hispanic %
CA	39,512,223	71.9	6.5	1.6	15.5	0.5	4	39.4	36.5
TX	28,995,881	78.7	12.9	1	5.2	0.1	2.1	39.7	41.2
NH	1,359,711	93.1	1.8	0.3	3	2	1.8	4	89.8
MN	5,639,632	83.8	7	1.4	5.2	0.1	2.6	5.6	79.1
PA	12,801,989	81.6	12	0.4	3.8	0.1	2.1	7.8	75.7
VT	623,989	94.2	1.4	0.4	1.9	2	2	2	92.6
U.S.	328,239,523	76.3	13.4	1.3	5.9	0.2	2.8	18.5	60.1

There was almost an equal number of men and women participating in the survey (Table 2), and within the racial/ethnic groups there were almost an equal number of men and women from each group, except for the “Black only, NH” group, that was 39% male to 61% female (Table 2).

Table 2. Race/Ethnicity and Sex Frequency, Percent

	White only, non-Hispanic	Black only, non-Hispanic	American Indian or Alaska Native only, Non-Hispanic	Asian only, non-Hispanic	Native Hawaiian or other Pacific Islander only, Non-Hispanic	Other race only, non-Hispanic	Multiracial, non-Hispanic	Hispanic	Don't know/Not sure/Refused	Overall
Male	45	39	46	53	47	54	47	46	51	45.39
Female	55	61	54	47	53	46	53	54	49	54.61

In regard to previous experience with checking cholesterol levels, only 5.74% of the 418,249 respondents reported never having their cholesterol checked (Figure 2). The majority at 70.77% reported having their cholesterol checked in the past year (Figure 2). Of note, 5.76% of respondents did not know whether/when they had had their cholesterol checked (Figure 2).

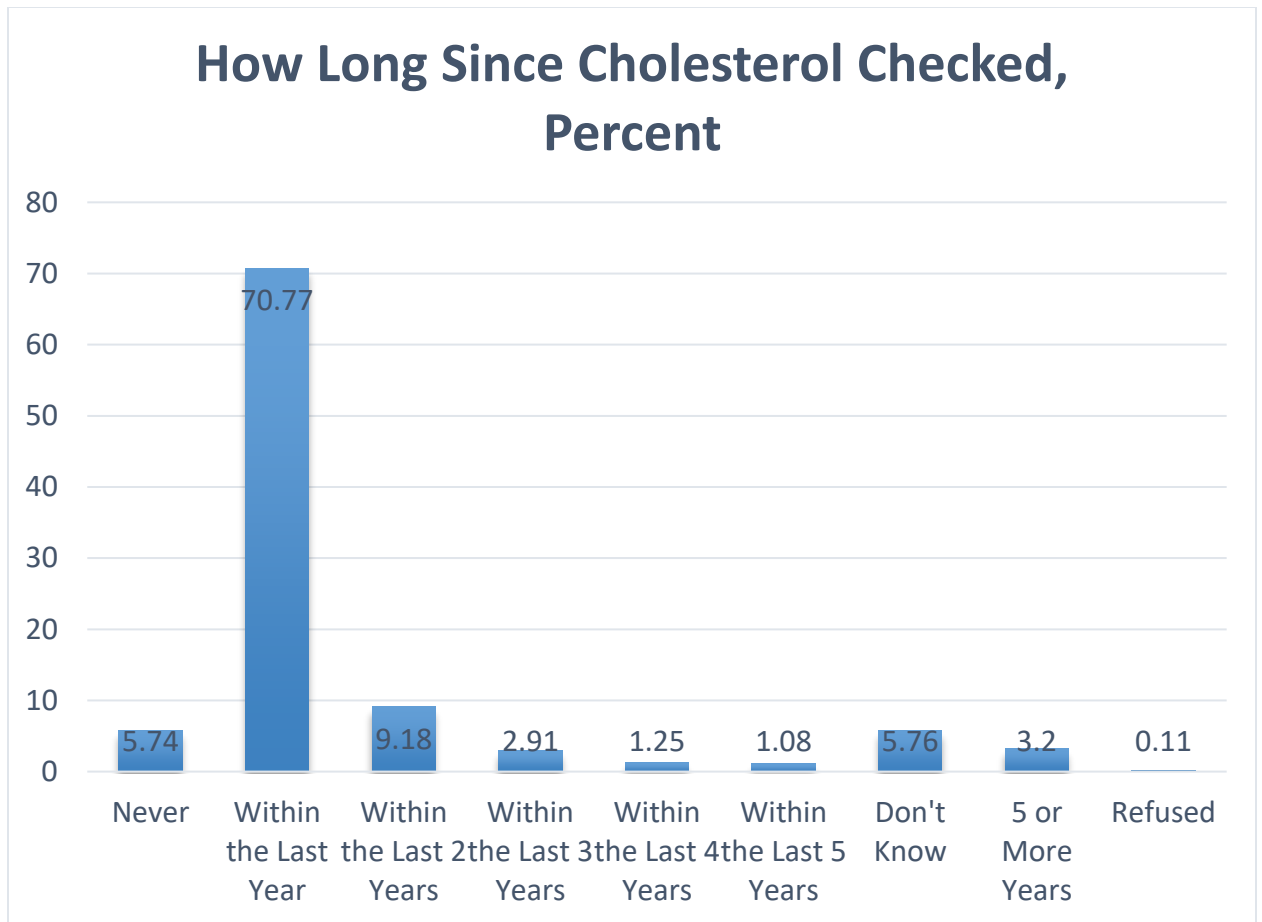


Figure 2. Percent of Respondants to "How Long Since Checked", Respondents 418,249

Of the 23,987 who responded “Never” to the question “How Long Since Cholesterol Checked”, more men (7%) responded to never having their cholesterol checked than women (5%) (Figure 3).

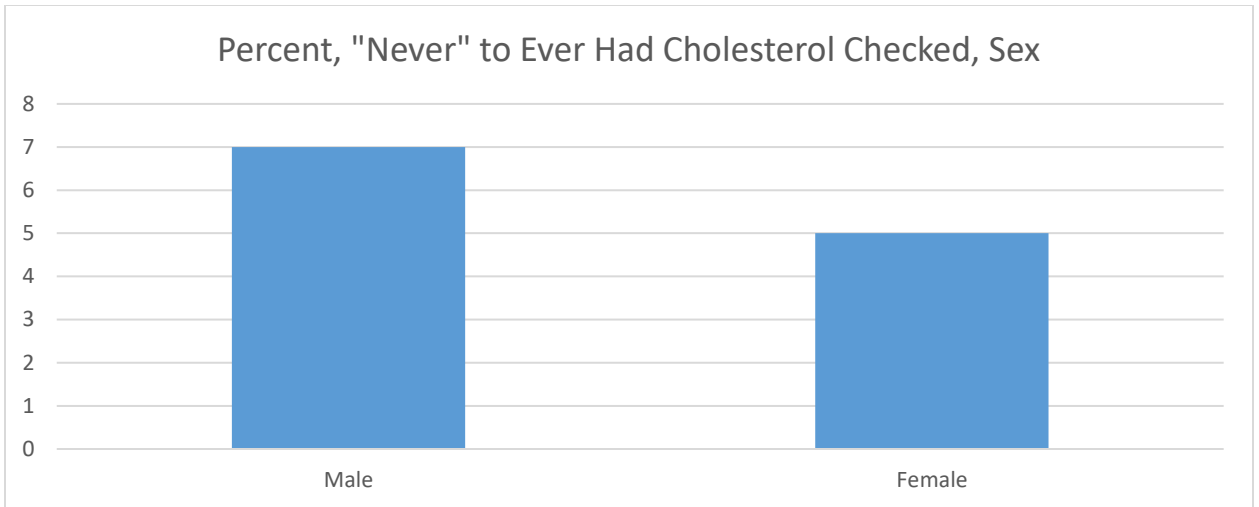


Figure 3. Percent who responded "Never" by Sex, Respondents, 23,987

Among the racial/ethnic groups the percent that responded “Never” to the question “How Long Since Cholesterol Checked”, were relatively low but showed variation among them. The highest percentage was in “Native Hawaiian or Other Pacific Islander only, NH” (11%) and the lowest was in “Black only, NH” (4%) (Figure 4).

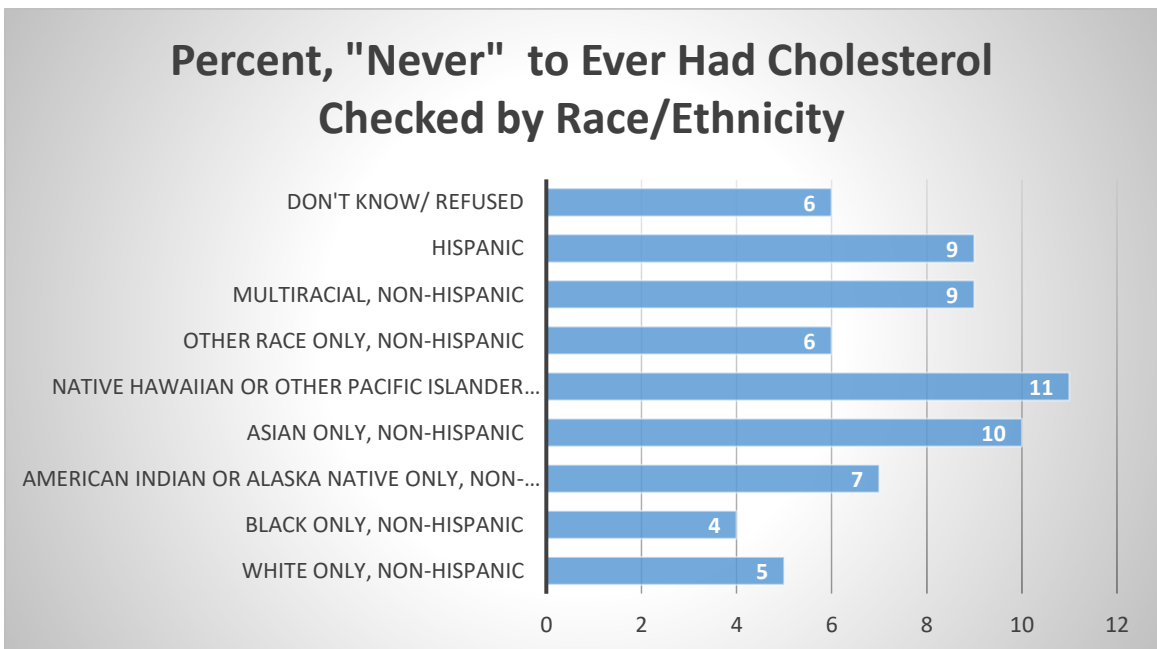


Figure 4. Percent who responded "Never" by Race/Ethnicity, Respondents, 23,987

The state with the lowest response of “Never” to “How Long Since Cholesterol Checked” was New Hampshire (4%). Four states tied for the highest percentage (6%), Texas, Pennsylvania, Minnesota, and California (Figure 5). The four highest percentage states were also the states with the most racially diverse populations (Table 1).

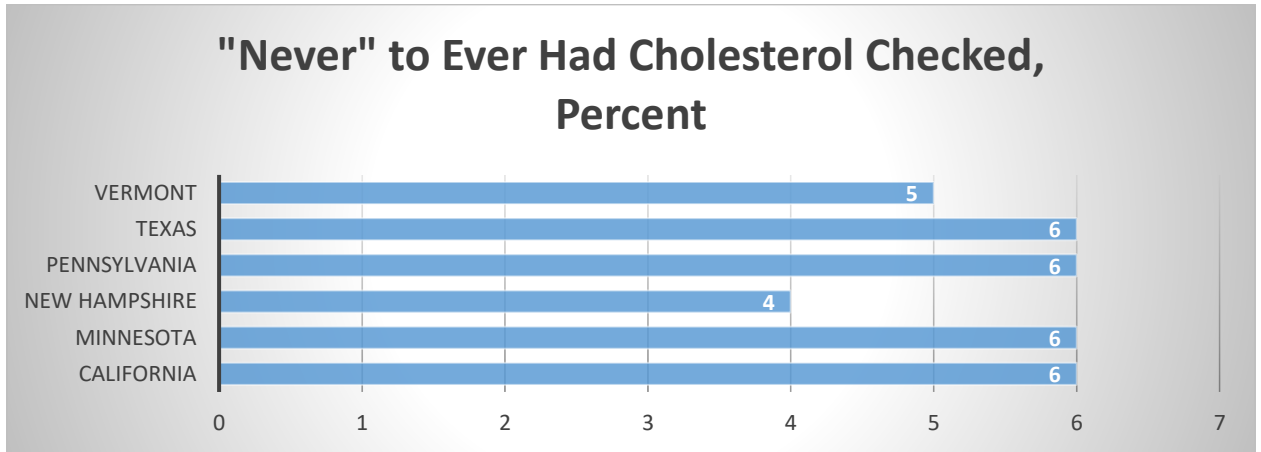


Figure 5. Responded "Never" to Ever Had Cholesterol Checked, Respondents, 23,987

Of the 418, 268 participants who responded to “Ever Have Been Told Blood Cholesterol was High”, 36.61% or 144,170 responded “Yes” (Figure 6). The majority at 62.23% or 245,065 responded “No” (Figure 6).

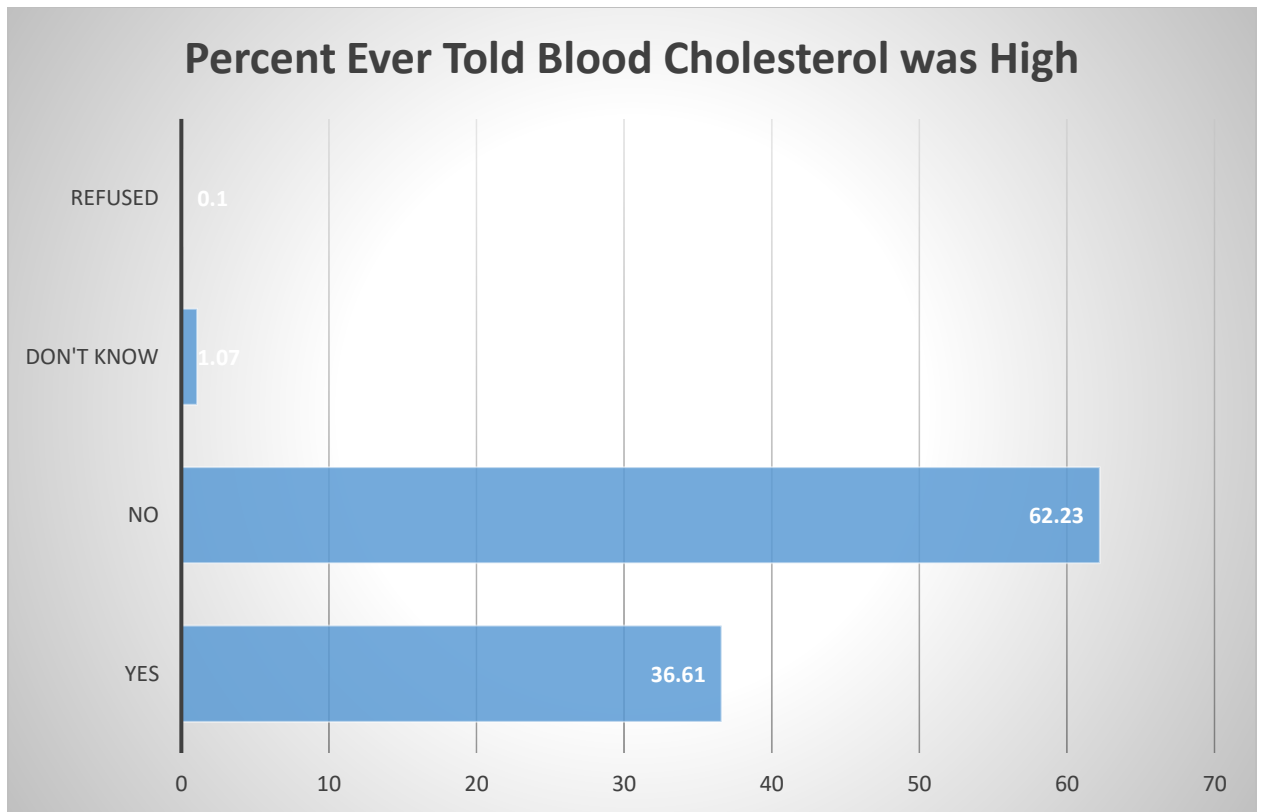


Figure 6. Percent who responded, 418, 268 Total Respondents

Of those 245,065 respondents to “Ever told blood cholesterol was high”, was 55% or 134,786 were female and 45% or 110,279 were male (Figure 7).

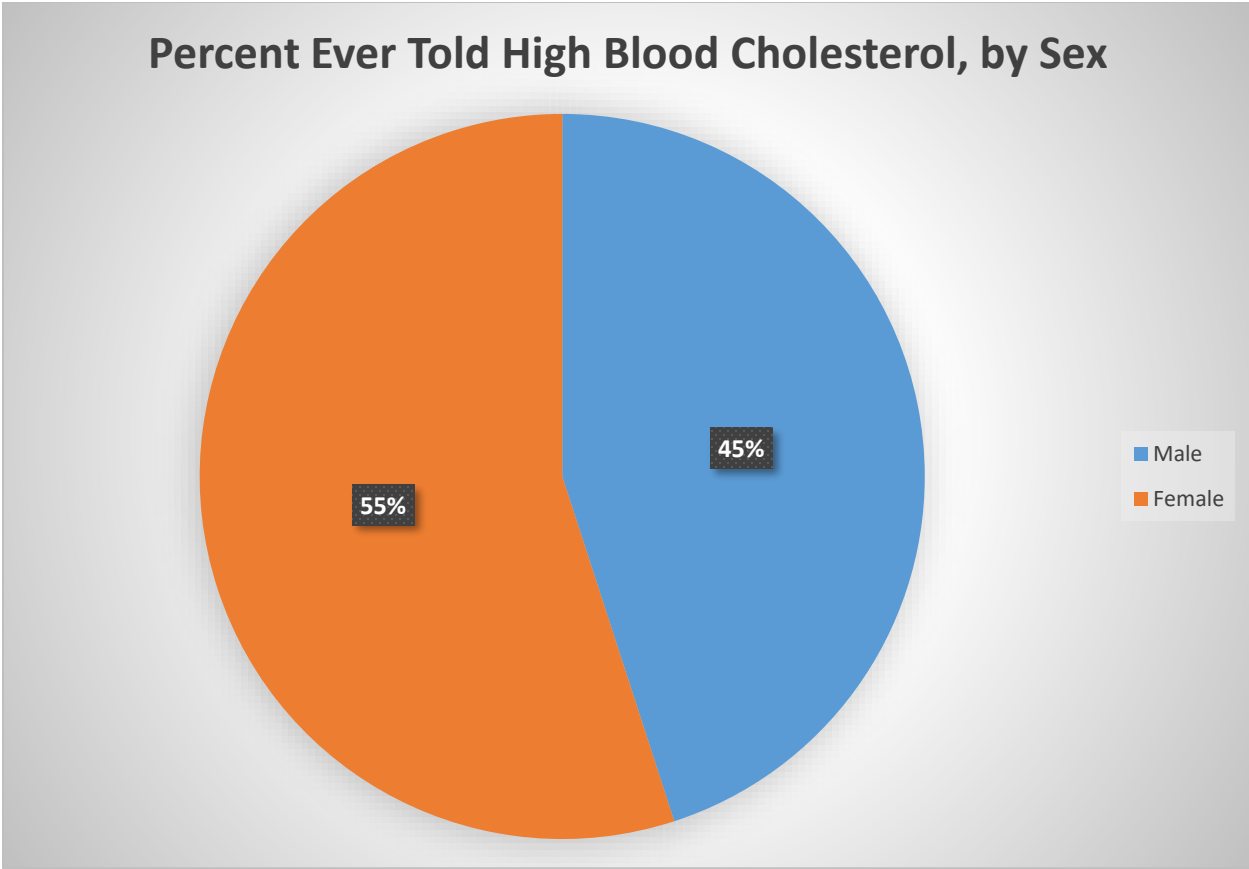


Figure 7. Percent Responded “Yes” by Sex, Respondents: 245,065

For the racial/ethnic grouping, the highest percentage was 38.21% of “White only, NH” and the lowest percentage was in “Hispanic” at 29.07% (Figure 8). The greater percentage of individuals identifying as White NH, responding “Yes” may be due to the fact there is a much large number of these individuals participating in the survey.

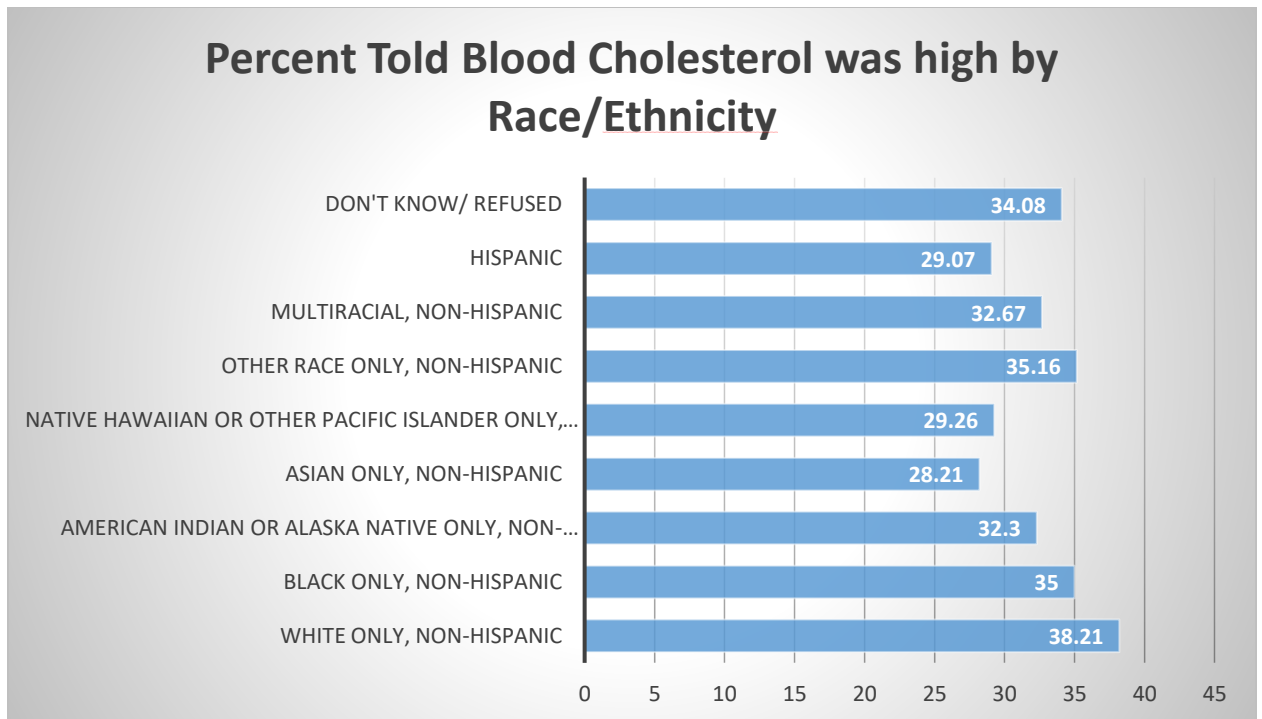


Figure 8. Percent “Yes” to Told Blood Cholesterol was High by Race/Ethnicity, 245,065 Respondents

Texas was the state with the highest reported percent of respondents who answered “Yes” to had “Ever been told their blood cholesterol was high”, at 39% (Figure 9). The states with the lowest reported percent of respondents who answered “Yes” to “Ever been told their blood cholesterol was high” were California and Minnesota at 31% (Figure 9). All the percentages of respondents answering “Yes”, however, were significant percentages of these states’ respondents.

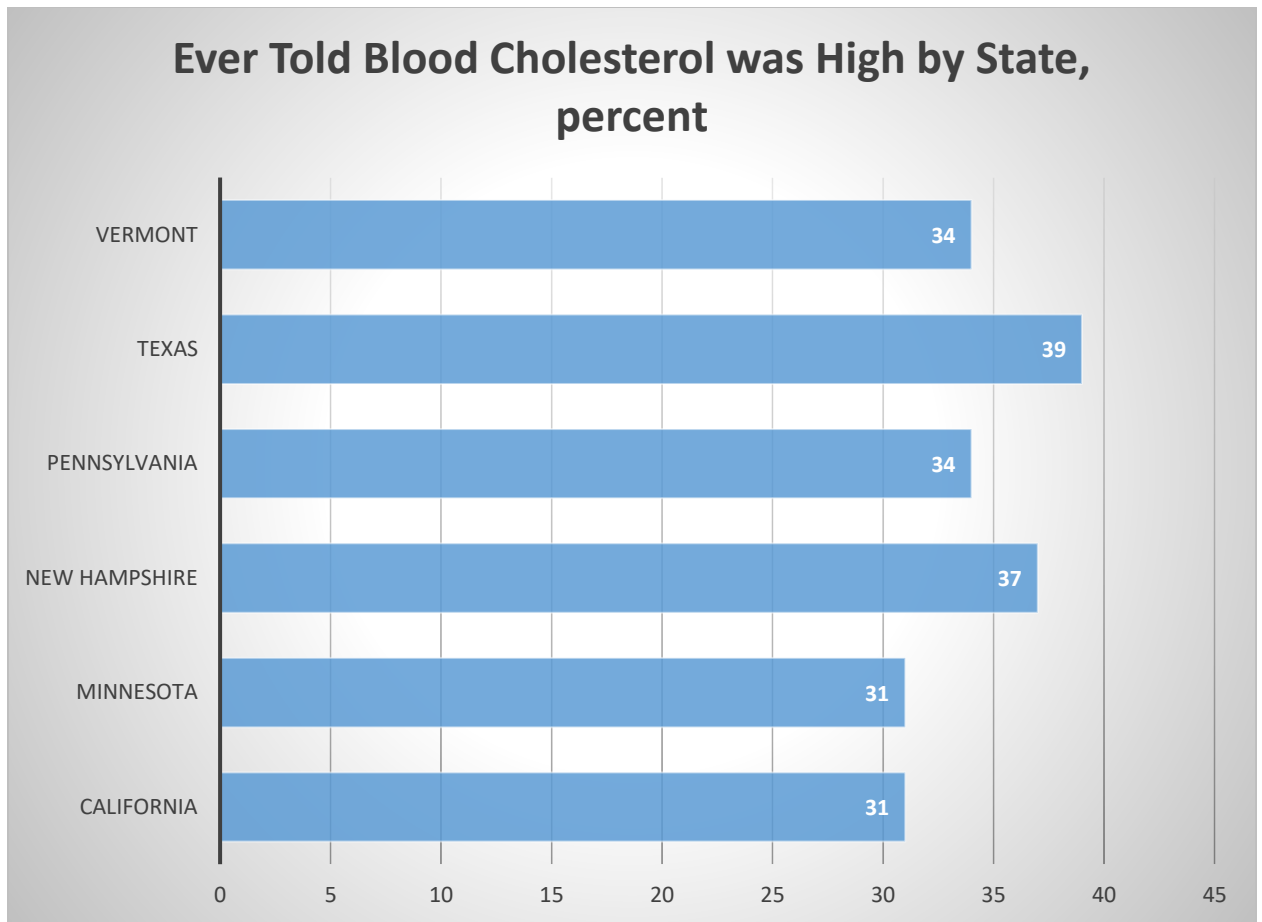


Figure 9. Yes"to Ever Told Blood Cholesterol was High by State

Of the initial 418,268 respondents, 143,613 were asked if they were “Currently taking medication for high cholesterol”. A majority of the participants responded “Yes” at 63.84% or 92,042 respondents. The respondents who answered “No” were numbered at 51, 571 or 35.77% (Figure 10). The rest of respondents answered either “Don’t know”, “Refused”, or were not asked.

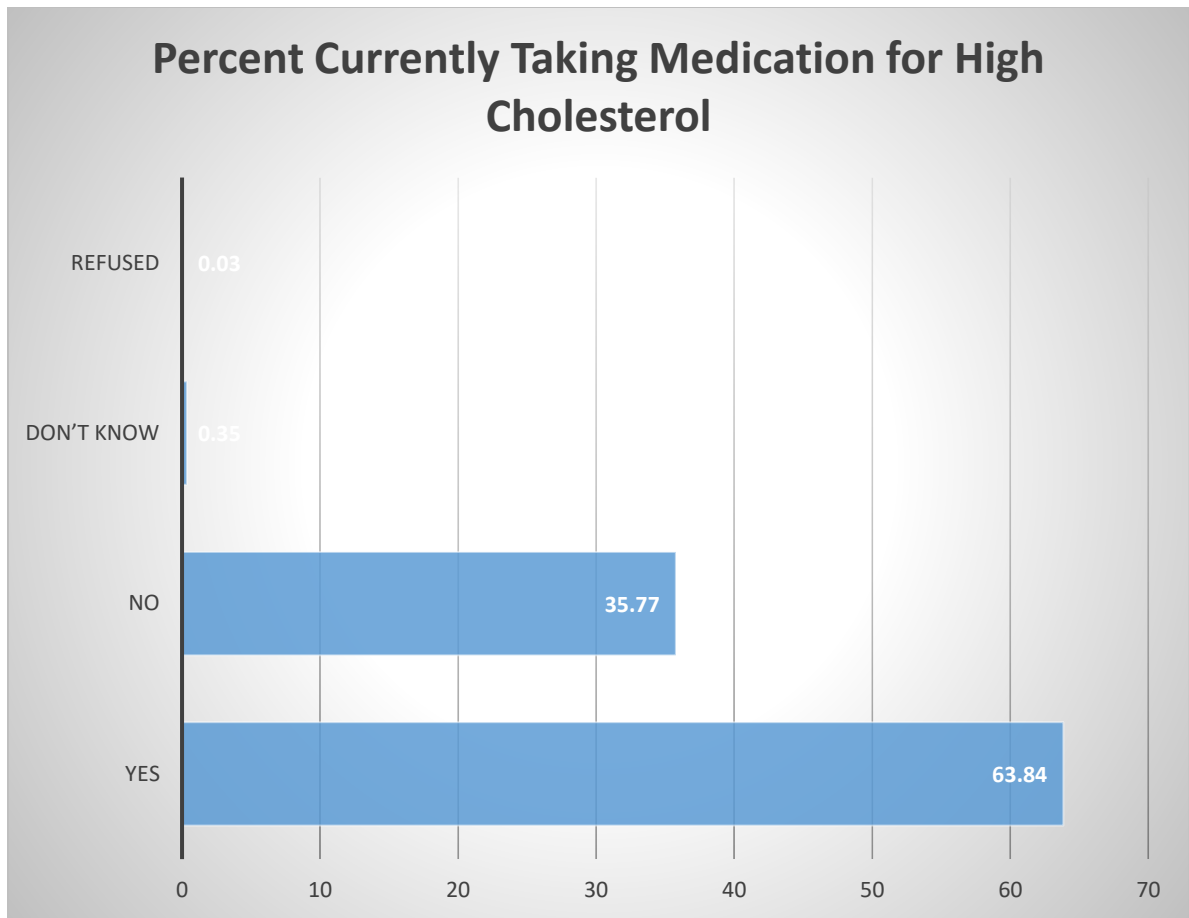


Figure 10. “Currently taking medication for high cholesterol” Responents: 144,169

A majority in all of the racial/ethnic groups responded yes to taking cholesterol medication. This is indicative of the prevalence of high cholesterol interventions across different racial and ethnic groups. In this survey the highest percent of “Yes” responses was 68% of the respondents who identified as, “Black only, NH” and were asked this question. The lowest percent was 53% in was in the respondents who identified as “Hispanic” and were asked this question (Figure 11).

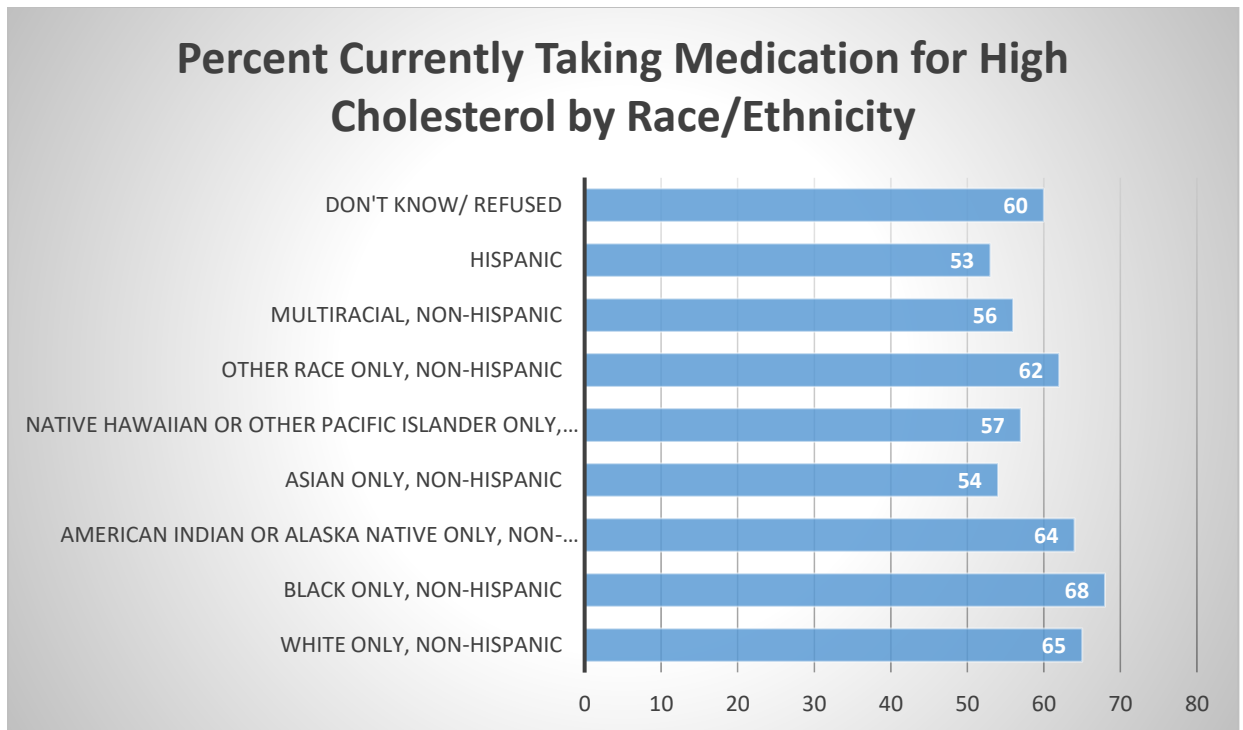


Figure 11. Percent by Race/Ethnicity who responded "Yes", Respondents: 144,169

Slightly more men, at 66% who were asked, “Currently taking medication for high cholesterol” responded “yes” than women at 61%, (Figure 12). This may be indicative of the disparities between men and women and statin use described earlier in this essay (Nanna et al., 2019).

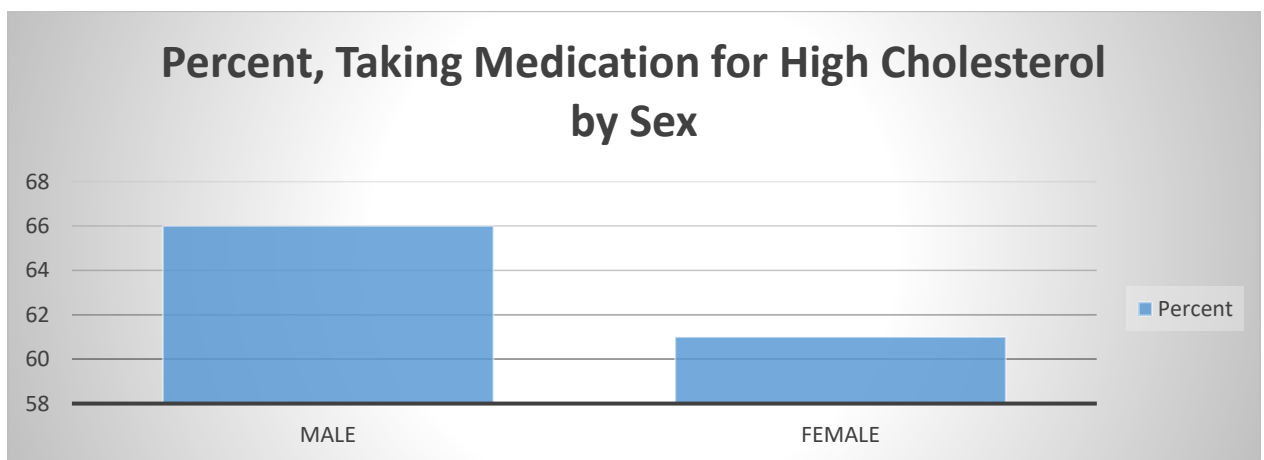


Figure 12. Percent by Sex who responded "Yes" Respondents : 144,169

A majority of the respondents from the six states of interest who were asked this question, reported taking medication for high cholesterol. The state with the highest percentage of respondents who were asked this question and responded “Yes” was New Hampshire at 66% and the lowest was California at 52% (Figure 13). Again, these are demonstrative of how prevalent the use of medication is for the treatment of high cholesterol.

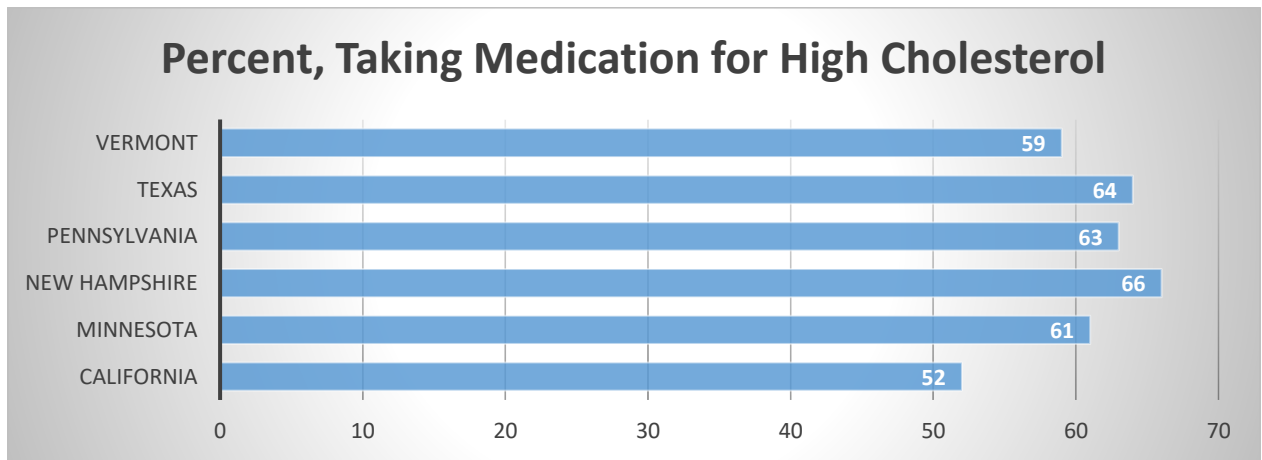


Figure 13. Percent of "Yes" responses by State, Respondents: 144,169

The BRFSS survey data demonstrates how prevalent high cholesterol is in the population. About 30% of respondents from the various racial or ethnic groups who were asked if they were “Ever told blood cholesterol was high”, and the percentages appear similar for the six states identified as potential pilot states for an FH cascade screening program by the FH Foundation and included in the policy analysis portion of this paper. While not a majority, these percentages are significant portions of the respondents to the question. A sizeable majority of the 144,169 respondents asked whether they are “Currently taking medication for high cholesterol” responded “yes”. This is representative of the importance of medication in controlling cholesterol levels. For those undetected FH cases, this kind of intervention could be lifesaving (Raal, Hovingh, & Catapano). The higher percentage of men, compared with women in respondents who were asked

whether they were “Currently taking medication for cholesterol” is indicative of the issue of men being prescribed or maintaining statins more often than women (Nanna et al., 2019). While outside the scope of this assessment, statistical tests could be run in the future on the responses to the BRFSS survey questions related to cholesterol and cholesterol medications to determine if any differences between groups are statistically significant.

4.2 Policy Analysis

Policy analysis was completed for California, Minnesota, New Hampshire, Pennsylvania, Texas, and Vermont. The goal of this analysis was to determine whether there were any state policies in place that would be a barrier to a cascade screening program or a facilitator of such a program. This analysis did not include federal policies such as HIPAA and GINA, but state policies related to these were assessed.

To date, only one of these states has received previous funding for their public health department through a CDC Cooperative agreement to fund public health genetics programs outside of newborn screening (CDC - Public Health Genomics and Precision Health Knowledge Base (v7.3), 2020). Minnesota was funded in 2003 and decided to incorporate genetic risk factors into their chronic disease prevention health plan. Some of the objectives included in their plan were to promote referral and payment for genetic risk assessment (St. Pierre et al., 2014). While this funding occurred some time ago, programs implemented at that time could help lay the foundation for future public health genetics programs, including a cascade screening program for FH.

For the state policies, all six states had several policies that fell under “Genetics Statutes”. Many of these directly related to their state’s newborn screening programs and address methods

of reporting, criteria for reporting, and linkage to services. All of the states also had statutes in place addressing genetic discrimination as it applies to insurance and workplace discrimination. Texas was unique in that it had a statute establishing a genetics council with the purpose of increasing the use of genetics in the realm of public health (*76(R) SB 602 Enrolled version - bill text*, 1999).

All six states had statutes that fell under “Communicable Disease Statutes”. A communicable disease can be defined as an illness caused by an infectious agent and occurs through either direct or indirect contact with an infected individual (Definitions for consideration, 2012). These statutes typically set up infrastructure for mandatory reporting as well as protecting the privacy of affected individuals as long as the need for privacy did not interfere with public safety. Although FH is not considered a communicable disease, as a heritable disease much like a communicable disease, it is passed from one person to another through genetic mechanisms.

Each state had several privacy statutes. California in particular had several, one an expansion of HIPAA protections and many others regarding consumer privacy and electronic health records and reporting (*Code Section Group*, n.d.). All six states had statutes regarding breaches of health data. Vermont had a privacy statute that particularly addressed sharing health data. The statute makes an exception to disclosing private health care data to avert a “serious risk of danger” (*Act 53: Vermont's Consent to Share Health Data Policy*, 2020).

Several but not all states had statutes that fell under the category of “Public Health Surveillance/Expansion”. Both Vermont and New Hampshire have statutes regarding the establishment of chronic disease prevention programs. The premise of Vermont’s “Blueprint for Health” statute was to establish infrastructure for care of chronic diseases (*18 V.S.A. § 703*, 2011). The primary components of this statute were, identifying individuals, evidence based clinical practice guidelines, and collaboration of healthcare providers. Minnesota and Vermont both use

language in their cancer registry statutes that establish a population-based registry to report on disease prevalence (*Office of the revisor of statutes; 18 V.S.A. § 152, 1993*). Pennsylvania had a statute called “Peyton’s Law” addressing the death of a public-school student from cardiac arrest. The statute makes a provision for electrocardiogram testing to prevent another death from a similar manner (*Bill information - Senate BILL 836; regular Session 2019-2020*).

The statutes that fall into the four categories outlined above for these six states are summarized in Table 3 and Table 4. A summary of each state’s policies and a preliminary assessment of whether they would support or impede a cascade screening program being established are covered in subsequent sections. This analysis focuses specifically on policies in these four categories, but there may be additional policies not identified for the purpose of this analysis. While this policy analysis provides a preliminary assessment, further analysis and advice from legal counsel is warranted prior to and during the implementation of a cascade screening program. Additionally, an analysis of federal policy has been previously undertaken by the FH Foundation and is not reported here.

Table 3. Statutes by State

	Genetics Statutes	Communicable Disease/ Reporting Statutes	Privacy Statues	Public Health surveillance/expansion Statue
California	DIVISION 106. PERSONAL HEALTH CARE (INCLUDING MATERNAL, CHILD, AND ADOLESCENT) [123100 - 125850] (Division 106 added by Stats. 1995, Ch. 415, Sec. 8.), § 6523. Prenatal Birth Defects Screening Laboratories and Analytical Methods., Department Authority and Purpose for the Newborn Screening Program,	REPORTABLE CONDITIONS: NOTIFICATION BY LABORATORIES,	California Constitution, Article 1 – Declaration of Rights, Information Practices Act (IPA) (1977, Confidentiality of Medical Information Act (CMIA), Physical Safeguards Statute,	
Texas	Texas Administrative Code section 1, Senate Bill 602, House Bill 39	Tex. Health and Safety Code § 81.041	Medical Records Privacy Act - Senate Bill 11, Texas Medical Privacy Act	House Bill 2085
New Hampshire	RSA 141-H:2 Conditions of Genetic Testing, RSA 141-H:4 Use of Genetic Testing in Health Insurance, Birth Conditions Program (several statutes)	RSA 141-C:10 Disclosure; Confidentiality, RSA 141-C:26 Ethics Committee	MEDICAL RECORDS AND PATIENT INFORMATION (several statutes included),	Chapter: Chronic Disease Prevention: RSA 141-B:9 Confidentiality,

Table 4. Statutes by State, continued

	Communicable Disease/ Reporting Statutes	Privacy Statues	Public Health surveillance/expansion Statue	Genetics Statutes
Pennsylvania	Disease Prevention and Control Laws (several statutes)) PRIVACY OF CONSUMER HEALTH INFORMATION (several statutes) and Breach of Personal Information Notification Act	Peyton's Law	NEWBORN CHILD TESTING ACT - NEWBORN CHILD SCREENING AND TESTING
Vermont	Communicable Disease Testing	Healthcare Privacy, Security Breach Notice Act , CT 53: VERMONT'S CONSENT TO SHARE HEALTH DATA POLICY	Cancer Registry (several statutes), Blueprint for Health: ch 13. § 703. Health prevention; chronic care management	Newborn Screening Rule, § 9332. Genetic testing; limitations,
Minnesota	Adverse Reporting Laws (several statutes under this), CHAPTER 4605, COMMUNICABLE DISEASES	Government Data Practices Act, 62J.498 HEALTH INFORMATION EXCHANGE., Minnesota Health Records Act	CANCER SURVEILLANCE SYSTEM; PURPOSE., 4605.7046 SENTINEL SURVEILLANCE, RSA 420-G:11-a Development of a Comprehensive Health Care Information System	144.91 POWERS AND DUTIES. (of the health commissioner regarding genetics), Treatment of Genetic Information Held by Government Entities and Other Persons, 72A.139 USE OF GENETIC TESTS. 144.671

4.2.1 Texas

The Texas administrative code consists of all the state agency rules (*Texas Secretary of State*, n.d.). The covered entities described in the Texas administrative code includes people or

persons who handle private health information in a nonprofit aspect or governmental aspect (*77(R) SB 11 Enrolled version - bill text, 2001*). Section one of Texas' Administrative Code addresses genetics services in the public health sphere, particularly the disclosure of public health information. This section states, "A covered entity may use or disclose protected health information without the express written authorization of the individual for public health activities or to comply with the requirements of any federal or state health benefit program or any federal or state law." (*77(R) SB 11 Enrolled version - bill text, 2001*). This exception to the law is justified through the understanding that this information is important for preventing or controlling disease and allowing for the development of public health surveillance and interventions (*77(R) SB 11 Enrolled version - bill text, 2001*). If a cascade screening program were to be implemented in Texas, this code may be used as evidence of general support for such a program as it meets the criteria of sharing health information with the goal of surveilling the prevalence of a chronic disease and aids in not only spreading awareness but can lead to the development of targeted public health programs and interventions (*77(R) SB 11 Enrolled version - bill text, 2001*). Identifying asymptomatic carriers of disease can improve clinical outcomes for those affected and ultimately lessen the burden of disease on the community (*For public health and healthcare providers, n.d.*). Ultimately the FH Foundation intends to share this information with the permission of the affected patients.

In Senate Bill 602, there was an attempt to establish a membership and the powers of an interagency council for genetic services. The purpose of the statute in regard to public health agencies was to act as an educated body in regard to developing policies on genetics as well as to promote a statewide database, coordinating statewide human genetics services, and identifying entities that serve individuals affected or at risk of having children with genetic disorders (*76(R)*

SB 602 Enrolled version - bill text, 1999). Unfortunately, it was difficult to determine whether the council is still functional, such a council could be instrumental in developing and encouraging the use of cascade screening to identify family members of index patients with FH throughout Texas.

A major concern in the use of genetics to identify disease is the concern of discrimination in employment and insurance coverage. With the expansive prevalence of FH, uncovering those with the condition would rightly bring up the concern of health coverage. House Bill 39 prohibits the use of genetic testing to discriminate in health insurance coverage (*75(R) HB 39 Enrolled version - bill text, 1997*). In House Bill 2085, Texas amended its health and safety code, directing the Texas Board of Health to plan to create a council on CVD, aimed at reducing the mortality, morbidity, and economic burden of CVD (*76(R) HB 2085, n.d.*). With regard to FH, this amendment of the code could have allowed for the council to support the development of FH screening in Texas and encouraged the education about FH in cardiovascular health materials. Unfortunately, this amendment only included funding until 2011, but does show previous interest of the state in supporting programs around CVD (*76(R) HB 2085, n.d.*). According to the Texas Health and Safety Code 81.041, regarding communicable disease, such diseases are required to be reported to the department of health and can never be made public (*Health and safety code chapter 81. communicable diseases, n.d.*). This health code defines a communicable disease as, “an illness that occurs through the transmission of an infectious agent or its toxic products from a reservoir to a susceptible host, either directly, as from an infected person or animal, or indirectly through an intermediate plant or animal host, a vector, or the inanimate environment” (*Health and safety code chapter 81. communicable diseases, n.d.*). Although genetically transmitted diseases are not considered under communicable diseases in Texas, an argument can be made that causal alleles are directly transmitted from person to person and can potentially be managed under the statutes

and health codes in a similar way as the reporting and management of communicable diseases. In contact tracing of a communicable disease, when a case is identified, they are asked to provide contact information for potential cases they may have exposed to disease. Cascade screening takes a similar approach but with first and second-degree relatives of identified cases.

Texas' current policies and statutes are amenable to the establishment of a cascade screening program for familial hypercholesterolemia. Section one of the Texas administrative code makes an allowance for sharing protected health information, particularly genetic information (*77(R) SB 11 Enrolled version - bill text, 2001*). Despite not maintaining the council, the state at one point sought to have a body of experts in genetics with the goal in mind of coordinating statewide genetics resources and identifying persons at risk of genetic diseases, among other goals (*76(R) SB 602 Enrolled version - bill text, 1999*). The health and safety code was amended with the aim of tackling the burden of CVD in the state (*76(R) HB 2085, n.d.*). The establishment of an FH cascade program encompasses multiple goals previously supported in the state, which clearly are of significance to the legislative body. There is already a protocol and infrastructure in place for tracing communicable diseases as well as for identifying new individuals with genetic conditions, such as newborn screening, and reporting this genetic information (*76(R) SB 602 Enrolled version - bill text, 1999*). Cascade screening encompasses a similar concept to contact tracing with a focus on familial diseases, which are covered under the health codes regarding protected genetic information.

4.2.2 California

The constitution of the state of California, describes the authority, structures, and functions of government for the state of California” (*Code section group, n.d.*). Article 1, section 1

guarantees all residents of the state the right to privacy (*Code section group*, n.d.). This right to privacy was expanded upon in 1977 through the Information Practices Act (IPA). The IPA limits the collection, management, and disclosure of personal information by state agencies (*Federal and state health laws*, 2020). This amendment was passed in response to the increased use of computers and the threat to privacy rights. The act limits the collection and retention of personal information by public agencies to what is necessary to “accomplish the agencies specific goals” (*Federal and state health laws*, 2020). Should a cascade screening program be implemented in California, the parameters outlined in this law could serve as a guide for the appropriate collection and retention of personal information by the cascade screening program. Although the FH Foundation is not a public agency, the guidelines of this act could still be referenced as guidance in California.

The Confidentiality of Medical Information Act (CMIA) limits the disclosure of patient medical information to healthcare providers, health plan providers, and contractors (*Federal and state health laws*, 2020). Using this definition, the FH Foundation, through licensed healthcare providers such as doctors or genetic counselors, may be authorized to disclose medical information. As far as the release of medical information to patients is concerned, California has a statute in place addressing this. Health and Safety Code 123148 states, upon patient request test results must be delivered either orally or in written form. For electronic delivery, prior consent must be obtained from the patient in accordance with CMIA regulations (*Federal and state health laws*, 2020). With this patient consent, it would be possible to make contact via the internet with relatives, who could then decide whether or not to pursue screening.

The Hereditary Disorders Act explicitly states all participation in genetic screening with the exception of phenylketonuria (PKU) is voluntary. This act provides a uniform, statewide policy regarding genetic screening programs to prevent any abuses in genetic screening (*Hereditary*

Disorders Act, 1995). Should the FH Foundation enact a cascade screening program in California, the policy can provide guidance on how they can operate in the state.

Under the California Code of Regulations, Title 17, Section 2505, laboratories are required to report results suggestive of communicable disease to the health department. Although genetic diseases are not explicitly considered communicable diseases in the state of California, the state may decide to collect this information to measure the burden of disease in the state.

California also has its own version of GINA, called the California Genetic Information Nondiscrimination Act (*CalGINA*, 2011). This law expands GINA protections to fair housing, receipt of emergency medical services, access and accommodation in business and professions, mortgage lending, and participation in state funded programs (*The California genetic Information Nondiscrimination act (CalGINA) Q and A*, 2013). This law protects California residents who may participate in the cascade screening program from discrimination in multiple areas which may encourage participation in this state.

The statutes and policies of California are favorable to the development of a cascade screening program for familial hypercholesterolemia. The Hereditary Disorders Act provides guidance on how a genetic screening program is to be operated within the state (*California Legislative Information, 2001*). While a cascade screening program may be both similar to and different from other genetic screening programs, one similarity to newborn screening programs is that it would be linking people to genetic services and alerting them to risk for a genetic condition. Article 1 of the state constitution as well as the IPA clearly state the privacy rights and exceptions guaranteed in California. The CMIA addresses the disclosure of protected medical information in state (*Federal and state health laws, 2020*), and FH Foundation would want to make sure they are operating within these parameters. The protections offered by CalGINA may also encourage

California residents to seek out cascade screening as they would not have to fear discrimination based on their results (*The California genetic Information Nondiscrimination act (CalGINA) Q and A*, 2013).

4.2.3 Minnesota

The state of Minnesota has statutes that seem to support the possibility of the establishment of a cascade screening program. Under the Minnesota Government Data Practices Act, health records may be released to an external researcher for scientific purposes. The statute specifies that health records generated on or after January 1, 1997 can be released only after disclosing the request for release in writing to the patient and receiving their permission (*Research Department, Minnesota House of Representatives, 2018*). Minnesota also has a Health Information Exchange program aimed at accelerating efforts to use health information to improve the coordination of health services to reduce, among other things, chronic disease (*Ch. 256b mn STATUTES - revisor.mn.gov*, 2020). This program could potentially be applied to the FH Foundation's proposed cascade screening program as they are an organization aimed at addressing CVD that is caused by Familial Hypercholesterolemia. Additionally, ways to integrate this health information into patients' health profiles could be explored, ultimately raising awareness about FH and improving the health of those affected in Minnesota.

Another potentially informative statute is the Cancer Surveillance System. This statute establishes a statewide cancer surveillance program to monitor trends, accurately target intervention resources, inform health professionals, and promote research to better control disease (*144.671 CANCER SURVEILLANCE SYSTEM*, 2020). Although this statute is specific to cancer, this may provide a precedent that could be applied to FH, as it is a genetic cause of a common

chronic disease just as cancer can be caused by multiple inherited genetic conditions, and these are often quite prevalent in most populations.

Minnesota's Sentinel Surveillance statute, states that the health commissioner may select a "disease or syndrome" for which surveillance would achieve significant public health purposes for a disorder that has significant morbidity and mortality (*4605.7046 SENTINEL SURVEILLANCE*, 2015). This statute in particular could be applied to FH, as it has significant associated morbidity and mortality (Allard et al., 2014).

Under the Communicable Diseases statute, persons required to report such diseases or syndromes are described as a healthcare practitioner or facility such as a clinic and these are required to report to the health commissioner. The criterion for such diseases includes having serious morbidity or mortality and that reporting of the disease "is necessary to monitor, prevent, or control the disease or syndrome to protect public health". This statute states that a disease meeting this criterion requires a specific, planned mechanism of surveillance (*4605.7080 NEW DISEASES AND SYNDROMES; REPORTING AND SUBMISSIONS*, 2005). Although heritable diseases are not necessarily classified as communicable, this language could be applied to a chronic disease like FH. In this circumstance, cascade screening could be considered as a specific planned mechanism for disease surveillance. Minnesota's Adverse Reporting Law states that the duties of the health commissioner include monitoring implementation strategies in other states regarding reportable events and establishing a reporting system compatible with other states, in order to share information effectively (*144.7067 COMMISSIONER DUTIES AND RESPONSIBILITIES*, 2020). This correlates to the FH Foundation's goal of having an interstate cascade screening program. Although this statute doesn't directly apply to heritable diseases, the language of the statute could be applied similarly.

One of the many duties and powers of the health commissioner outlined is the authority to establish a program in the field of human genetics, with the aims of disseminating information to professionals and laypeople and reduce the manifestation of inherited genetic conditions (*144.7067 COMMISSIONER DUTIES AND RESPONSIBILITIES*, 2020). Although the cascade screening program would be operated by the FH Foundation, states often collaborate with or outsource to non-for-profit organizations to accomplish their goals or missions (*The Nonprofit Sector and Government: Clarifying the Relationship*, 2002). Minnesota also has a statute regarding the treatment of genetic information which states that genetic information can only be collected and disseminated with the written informed consent of the individuals involved (*Minnesota House of Representatives; Research Department*, 2018). Again, this would be addressed in the registration process for the cascade screening program. Under this same statute Minnesota explicitly states that genetic tests taken by individuals or their relatives cannot be used for health insurance ineligibility (*Minnesota House of Representatives; Research Department*, 2018).

Minnesota has several statutes in place that could facilitate the implementation of a cascade screening program for FH. The Minnesota Government Data Practices Act and the Treatment of Genetic Information Held by Government Entities and Other Persons statute both outline how genetic information is to be collected and shared in the state (*Office of the revisor of statutes*, n.d.). Neither of these seem to be a probable impediment to a cascade screening program. The language used in the cancer surveillance program statute provides guidance in monitoring and targeting resources to better understand and control the prevalence of a chronic disease (*Office of the revisor of statutes*, n.d.). The communicable disease statute calls for the establishment of a planned and specific mechanism of surveillance to monitor and control a disease of significant morbidity and mortality (*Office of the revisor of statutes*, n.d.). Cascade screening in FH targets first-degree

relatives of identified index cases and screens them either for genetic marker indicative of FH or cholesterol levels of a certain threshold or both (Alonso et al., 2020). One of the powers of the state commissioner of health defined under Minnesota's health statutes is the authority to establish a program in the field of human genetics, with the goal of disseminating information to professionals and laypeople and reduce the manifestation of deleterious genes (*Office of the revisor of statutes*, n.d.). This is exactly the goal of the FH Foundation's cascade screening program. Often, government will use an external organization to accomplish its goals (*The Nonprofit Sector and Government: Clarifying the Relationship*, 2002). The state commissioner of health clearly has the authority to work with the FH Foundation to establish a cascade screening program in Minnesota.

4.2.4 New Hampshire

In the state of New Hampshire, the Medical Records and Patient Information law's medical records section states, that all medical records are property of the patient (*RSA 332-I:1 Medical Records*, 2020). This same law states under its Patient Information section that confidential healthcare information cannot be revealed without the patient's consent except by law or in the interest of public welfare. This may not be applicable necessarily to a genetic screening program as consent would be obtained during the initial registration and given that patients have the outlined rights to their medical records, releasing them to the FH Foundation does not appear as though it would be problematic.

In New Hampshire's Communicable Disease chapter, under disclosure, any health care provider or any person with an individual afflicted with a communicable disease under their care is required to report to the health commissioner (*RSA 141-C:10 Disclosure; Confidentiality*, 2020). This same chapter also has a section on an ethics committee to advise the commissioner on how

to plan and address communicable diseases (*RSA 141-C:26 Ethics Committee, 2020*). This committee's advice and recommendations could be sought and applied to the ethics of a genetic cascade screening program for a heritable disease.

The conditions of genetic testing specified in New Hampshire stipulate that genetic testing results cannot be disclosed without the expressed written consent of the individual being tested (*RSA 141-H:2 Conditions of Genetic Testing, 2020*). New Hampshire also does not allow for health insurers to require genetic testing of those insured or the results of their relatives (*RSA 141-H:2 Conditions of Genetic Testing, 2020*). New Hampshire also has several statutes that address interaction of genetic screening programs, specifically newborn screening, with the state's public health programs. Under the section regarding access to health information under the Birth Conditions Program chapter, it is stated that healthcare providers, clinic sites, etc, should allow the state's health information exchange program access to identifiable information relating to occurrence of birth conditions (*RSA 141-J:3 Program Access to Health Information, 2020*). By definition FH is a condition one has from birth and so this statute could potentially guide consideration of a cascade screening program (Bourhairie et al., 2015). The statute also allows for contractors, which the FH Foundation may fall under, to share information with the state's health information exchange. However, a potential barrier may be that under the birth conditions program section on disclosure, it is stated that identifiable health information of New Hampshire residents may not be shared with similar programs in other states (*RSA 141-J:4 Program Ability to Share Data, 2020*). This barrier may be mitigated by the fact that the FH Foundation's cascade screening would be the same program operating in another state, but this particular policy should be very critically assessed by the FH Foundation prior to developing a cascade screening program in this state.

Under New Hampshire's Chronic Disease Prevention chapter related to cancer surveillance, they have established a registry for affected individuals. This registry is confidential, and identities cannot be released, except in the case of persons, "demonstrating a need related to health research... and release is conditionally on the identities remaining confidential" (*2015 new Hampshire Revised statutes :: Title x - public HEALTH :: CHAPTER 141-B - chronic disease PREVENTION, assessment and Control :: Section 141-B:9 - Disclosure; Confidentiality*). Confidentiality is difficult to achieve in a cascade screening program, however the concept of a disease registry can be considered as a guide for a cascade screening program for Familial Hypercholesterolemia. In order to accurately trace relatives and new cases, concepts could be adapted from already established registries. However, several considerations will need to be made including consent, when to include family members, and issues of anonymity.

There do not appear to be any significant barriers to implementing a cascade screening program in New Hampshire. The state does have its own privacy laws that build upon those established by HIPAA, however this should not be an issue as the patient's consent will be obtained during registration (*RSA 332-I:2 Patient Information, 2020*). New Hampshire also specifies that genetic testing information may not be shared without a patient's consent, which again would be obtained during registration (*RSA 141-J:3 Program Access to Health Information, 2020*). Under the statute describing the conditions of New Hampshire's Birth Conditions Program, health care providers and others defined must share identifiable health information related to the birth condition with the program. However, it will not share the information with any similar programs in another state (*RSA 141-J:3 Program Access to Health Information, 2020*). This issue could potentially be addressed by the fact that the FH Foundation would not share information with a "similar program" as it would be the same program. Although FH is a heritable disease, the

language of the statutes for communicable diseases may provide guidance, and the FH Foundation may want to consider how to address issues such as reporting of cases to the health department or may seek out a review by the ethics committee (*RSA 141-C:26 Ethics Committee*, 2020). The language used in New Hampshire’s cancer surveillance statute may provide guidance for FH surveillance. The goal of the cancer registry is to provide information relating to the incidence and diagnosis of cancer (*Statutes, codes, and regulations*, n.d.). This is the ultimate goal of the cascade screening program and any confidentiality requirements of this statute would be addressed when obtaining the patient’s consent during the registration process.

4.2.5 Pennsylvania

According to the Commonwealth of Pennsylvania’s Disease and Prevention Control Law’s section on the confidentiality of communicable disease reporting, nothing in the disease reports should be able to identify an individual (*CHAPTER 27. COMMUNICABLE AND NONCOMMUNICABLE DISEASES*, 2002). This same law also contains a section that requires individuals responsible for testing in a clinic who may uncover reportable information to fill out a reporting form to facilitate the sharing of information (*CHAPTER 27. COMMUNICABLE AND NONCOMMUNICABLE DISEASES*, 2002). The Disease and Prevention Control Law also specifies who is required to report “an infectious disease or condition” (*CHAPTER 27. COMMUNICABLE AND NONCOMMUNICABLE DISEASES*, 2002). Any health care practitioner or health care facility is required to report to the health department if an individual in their care has an infectious or communicable disease. This could be used as a guide in the case of the FH Foundation’s cascade screening program.

The Newborn Screening Act requires the testing of newborns for genetic conditions (*NEWBORN CHILD TESTING ACT - NEWBORN CHILD SCREENING AND TESTING Act of Jul. 4, 2008, P.L. 288, No. 36*). This law provides a legal precedence and significance of genetic testing to public health in the Commonwealth. The success and longstanding practice of newborn screening to uncover genetic conditions could serve as an example of a successful genetic screening program. Additionally, the infrastructure that has been developed around newborn screening can provide guidance for the development of a cascade screening program. Such a screening program has the potential to uncover many individuals unaware of their genetic risk for FH as well as bring awareness to the condition (Bourhairie et al., 2015).

Although it is not directly related to FH, Peyton's Law was passed to address the sudden cardiac arrest and death of a high school student. The law requires that families receive written information about the option of echocardiogram testing for student athletes in an effort to prevent death from sudden cardiac arrest (*Bill information - Senate BILL 836; regular Session 2019-2020*). Like cases of sudden cardiac arrest, often individuals affected with FH are unaware of their risk and can die relatively young from cardiac arrest among other causes (Ito et al., 2015). Screening individuals and connecting them to resources is a highly effective method to prevent cardiac deaths, and in Pennsylvania Peyton's Law illustrates the state's interest in public health programs to address these issues.

Regarding privacy practices, The Privacy of Consumer Health Information statute governs how private personal health information about individuals is handled by those licensed to handle such information by the health department (*31 Pa. Code § 146b.1, 2021*). The stipulations of this may apply to the FH foundation and how they handle health information, particularly the relatives of recently identified cases, in the commonwealth of Pennsylvania. This statute also describes the

process of information disclosure for licensed entities. In Pennsylvania the licensed entity must first identify themselves, a description of the information being disclosed, a description of the party having the information disclosed to them and the purpose of the disclosure, and the signature of the subject of the information being disclosed (31 Pa. Code § 146b.1, 2021). The Breach of Personal Information Notification Act describes the consequences and penalties of breaching private information in the commonwealth of Pennsylvania (*Pennsylvania's breach of personal INFORMATION Notification Act: Wolf, Baldwin & Associates, P.C.: Pottstown Pennsylvania, n.d.*). The law requires a business or organization to inform individuals of any potential breaches and has a fine should the organization fail to inform affected individuals. This statute may apply to the FH Foundation as they would be responsible for personal health information and could potentially be held financially liable for a breach of information. As such, this would be an important policy for the FH Foundation legal team to consider more closely when considering a cascade screening program in the state.

The only significant barrier in Pennsylvania to the implementation of a cascade screening program could be the Privacy of Consumer Health Information statute. This statute requires the party disclosing personal health information to a third party to be licensed in Pennsylvania to do so, in addition to having the subject of the information's permission (31 Pa. Code § 146b.1, 2021). The communicable disease statutes require anonymity when disclosing information and mandatory reporting to the health department. While FH is not classified as a communicable disease, the reporting measures may still be applicable, particularly in maintaining anonymity (*CHAPTER 27. COMMUNICABLE AND NONCOMMUNICABLE DISEASES*, 2002). Ideally the FH Foundation would only be disclosing information to the first-degree relatives of the identified cases with the patient's permission. Peyton's Law requires electrocardiogram testing of student athletes to

prevent another sudden death from cardiac arrest (*Bill information - Senate BILL 836; regular Session 2019-2020*). Through cascade screening for FH, unaware individuals would be made aware of their condition and be able to seek out the necessary interventions. In this instance, the screening is specific to FH, nonetheless it furthers the efforts lawmakers in Pennsylvania have already taken to address sudden cardiac deaths in the commonwealth. Like every state in the U.S., Pennsylvania has its own newborn screening program and statutes. The goal of the program is to identify newborns with actionable genetic conditions and facilitate access to resources for the parents (*NEWBORN CHILD TESTING ACT - NEWBORN CHILD SCREENING AND TESTING Act of Jul. 4, 2008, P.L. 288, No. 36*). The existence of this law establishes the legal groundwork for a genetic screening program to identify individuals in the population that may be unaware of their condition. The primary difference is instead of screening the general population, the cascade screening program will only focus on identified cases and their first-degree relatives.

4.2.6 Vermont

Title 18 of Vermont's Health statutes, chapter 4 describes the establishment of a cancer registry. The goal of the registry is to have a uniform statewide population-based system and to determine the incidence of cancer in the state (*18 V.S.A. § 152, 1993*). Reporting of cancer cases to the state registry is required under the statute by any health care facility diagnosing or treating cancer. (*18 V.S.A. § 153, 1993*). This chapter also addresses disclosure of registry information. It protects individuals who report to the registry from any damages related to disclosure. A similar protection could be applied to those who participate in a FH cascade screening program. This statute related to the registry could provide a guide for establishing an FH cascade screening program and could help establish a better estimate of FH's prevalence in Vermont.

Vermont also had legislation regarding Blueprint for Health. This is meant to be the development of a chronic care infrastructure in Vermont (*18 V.S.A. § 703*, 2011). One of the tenets of the program was to have a process to identify individuals with or at risk for chronic disease. A cascade screening program for FH would do just that. Should such a program be implemented in Vermont, it would easily align with the health goals clearly already established in the state.

For communicable disease reporting, Title 18, Chapter 21, describes that health care workers who identify patients with such diseases are mandated to report them to the health department (*18 V.S.A. § 1141*, 2007). The language of this statute is directed more for infectious diseases such as a bloodborne pathogens.

The newborn screening statute's language mentions screening with the intent of identifying disease and accessing treatment to prevent death or disability (*Newborn Screening Program Rule*, 2019). The FH Foundation's cascade screening program would have similar goals of identification and connection to services. The newborn screening statute provides potential guidance standards for FH screening in Vermont. A particular program in Vermont that would aid in the implementation of a cascade screening is the Vermont Health Information Exchange. The Vermont Health Information Exchange was established by Act 53: Vermont's Consent to Share Health Data Policy. It is an aggregate of patient records from health care facilities and practices across Vermont. This was made in its language to be an opt out program to ensure more participants in the exchange (*Act 53: Vermont's consent to share health data policy*, 2020). This is demonstrative of Vermont's willingness for sharing health information and the amenability of their privacy laws in the exchange of health information.

According to Vermont's Healthcare Privacy statute, there are no restrictions on disclosures done to avoid serious danger or related to patient healthcare (*18 V.S.A. § 1882*, 2017). This statute

is very agreeable with the implementation of a cascade screening program. Although the patient's consent would be obtained prior to any release of information, this statute eases the process of reaching out to the first-degree relatives of any identified cases.

The various statutes in Vermont appear to be quite agreeable to a FH cascade screening program. The establishment of Vermont's cancer registry and newborn screening programs both provide precedence of initiatives regarding genetic screening, notification of disease status, and monitoring incidence of disease in the state. The cascade screening program has similar goals as Vermont's Blueprint for Health which also seeks to identify individuals with chronic disease and connect them to resources for management (*18 V.S.A. § 703, 2011*). The Vermont Health Information Exchange makes the process of ensuring patients as well as providers are aware of a patient's FH status efficient. Vermont's healthcare privacy statute is particularly friendly to the establishment of a cascade screening program, as it does not add any additional barriers to disclosing information to the relatives of the identified cases (*18 V.S.A. § 1882, 2017*).

5.0 Limitations and Conclusion

5.1 Limitations

There are some limitations with the BRFSS dataset utilized to determine prevalence of high cholesterol in the six states of interest covered in this report. The BRFSS is self-reported data, and it was not meant to directly assess the prevalence of FH. The dataset is likely not able to represent the true reality of the health disparities regarding cholesterol screening and treatment. BRFSS data in most states is only translated to Spanish outside the initial English questionnaire, which likely left out many in the surveyed states who are fluent in neither. Since the survey uses skip logic, some questions have more respondents than others.

In the analysis of state policies presented in this paper, it is important to note that there may be other state policies not mentioned in this essay that effect the implementation of a cascade screening program as well as national policies and statutes. All final decisions regarding the implementation of a cascade screening program should be made with the help of legal counsel.

5.2 Conclusion

There is evidence in the literature that CVD is a large burden on public health, in the United State in particular. The large, estimated prevalence of FH and its underdiagnosis is likely a large contributor to this burden. The existing disparities in the healthcare system and administration of care in the U.S. only compound these issues. Even so, the infrastructure to address these issues is

present. Within the language of the various statutes in the six states previously mentioned, there is guidance and infrastructure at the state level to coordinate an interstate cascade screening program. Many of these states already have statutes related to cancer registries and policies in place for contacting at-risk individuals, though this is typically in the context of the reporting of communicable diseases. However, the language in the statutes that established them could provide guidance for the FH Foundation's cascade screening program, which would have the goal of finding undiagnosed cases of FH.

Screening programs for FH have been shown to be successful in other settings. A cascade screening program in the US could go a long way in undoing some of the health care disparities that exist in the genetics and cardiovascular care received by minorities as well as women by bringing awareness to FH and its prevalence to not only patients but primary care providers, particularly in large states like Texas and California that are more demographically diverse than the nation at large.

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