Population-Wide Genomic Screening: Clinical Outcomes, Economic Value, and Ethics Considerations in Familial Hypercholesterolemia

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A dissertation

submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

University of Washington

2021

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Program Authorized to Offer Degree:

Public Health Genetics

University of Washington

Abstract

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Population-wide genomic screening is one of the great promises of precision medicine with opportunities to improve patient health outcomes, lower healthcare costs, and prevent disease. This dissertation examines population-wide genomic screening effects, economics, and ethics through the use case of familial hypercholesterolemia (FH) and bundled genomic screening. In Chapter 1, we performed a longitudinal statistical analysis estimating the effect of disclosure of pathogenic genetic variants for FH on individuals' low-density lipoprotein (LDL) cholesterol levels and trajectories. We used electronic health records from individuals with variants from FH associated genes (LDLR, APOB, and PCSK9) identified in a cohort of more than 190,000 patients within the Geisinger MyCode Community Health Initiative. When individuals in the United States with an FH variant receive their genetic return of results (ROR), there may be a reduction in their LDL cholesterol levels and LDL cholesterol level trajectories over time attributable to ROR, suggestive of a beneficial clinical effect. As interest in population genetic screening implementation continues

to grow, future studies should aim to include larger populations affected by FH and improved study designs for better insight into the true effect sizes of ROR on LDL cholesterol. Chapter 2 builds on this analysis, utilizing a decision-analytic model to estimate the clinical and economic outcomes of population-wide FH genomic screening versus no genomic screening in age-based cohorts from 20 to 80 years old. We found that population FH screening is not cost-effective at current genomic screening costs. However, reducing genomic testing costs or including FH testing within a broader multiplex screening panel may improve clinical and economic value. Finally, Chapter 3 evaluates at what age a bundled population genomic screen should take place from a utilitarian and principlist perspective. Our analysis found that a pragmatic approach considers engaging in a utilitarian analysis first due to the likelihood that health systems may have to weigh their actions in a very similar manner. Principlism can support and supplement analyses undertaken with a utilitarian perspective by identifying areas of concern based on discordance from proposed age recommendations. However, it is apparent that no matter what age a bundled population genomic screen takes place, there are going to be explicit and implicit trade-offs between conditions, dimensions, and principles.

TABLE OF CONTENTS

List of Figures

List of Tables

ACKNOWLEDGEMENTS

It has been challenging and exciting to engage with these topics of study while pursuing my PhD. I could not have completed this process without help from so many different people throughout the journey. First, I'd like to acknowledge the limitless support and love I received from my family: my parents, Kristen and Jeff, for always pushing me to strive for something greater than myself and to approach life with curiosity and kindness no matter the situation; and my siblings, Joseph and Audrey, for always providing a listening ear, reminding me not to take myself too seriously, and encouraging me and inspiring me through their own accomplishments.

Additionally, the exceptional mentorship and respect given to me by outstanding faculty, whom I have trained under, engaged with, and learned from both within and outside of the academic arena. I am appreciative of the grace, support, and guidance provided by my committee members (Dr. David Veenstra, Dr. Stephanie M. Fullerton, Dr. David Crosslin, Dr. Aasthaa Bansal, and Dr. Ken Thummel) due to their interest in my work and their engagement and feedback during an unprecedented period of societal changes throughout the pandemic. I also specifically acknowledge my Chair, Dr. David Veenstra, whose support allowed me the opportunity to continue to pursue my academic goals and whose guidance helped me to navigate the twists and turns of the rigorous scientific process. I am privileged to consider him a mentor and friend.

I acknowledge my friends, classmates, and colleagues, who I was fortunate to engage with during coursework, research projects, and outside of the academy. Your varied perspectives, criticisms, and own personal successes all provided inspiration to continue my own work while refining how to translate and communicate its implications. Specifically, I want to thank Dr. Greg Guzauskas, an alumnus of the Institute for Public Health Genetics and collaborator in the Rational Integration of Clinical Sequencing (RISE) project, for always being willing to answer my questions, provide thoughtful feedback, and share his own personal experience, both successes and challenges, to my benefit.

Finally, I'd like to acknowledge my partner, Shira, who completed this journey with me step-by-step and never flinched in the face of its chaos. She challenges me to think broadly, speak thoughtfully, and to continue to pursue making an impact in all that I do. Simply put, she believed in me when I was most uncertain, and her unwavering support pushed me through my toughest challenges while completing this degree. I am forever thankful for her assistance during the low and high points and look forward to our many future successes.

Chapter 1. INTRODUCTION

Population-level genomic screening is one of the ultimate promises of precision medicine because it can identify patients with unknown disease risk, provide assistance with the management of treatments and therapies to increase a patient's health, and potentially lower healthcare system costs by reducing cases of preventable disease.[1,2,3,4,5,6] Some of the most impactful and clinically informative genetic tests are those that look at disease risk for a known familial pathogenic variant. More specifically, population-level screening that utilizes highly penetrant monogenic risk factors is highly preferable. Genetic risk factors with high penetrance indicate that a large percentage of individuals with the monogenic variant, variation in a single gene, will exhibit or experience the disease.[7] The potential health improvement of population genomic screening would be mediated through preventative clinical actions such as drug treatment or surgery, changes in clinical screening protocols, leading to lowered incidence of high impact and high cost health events.[8,9] However, it is unclear if these benefits are actually realized, and if so to what extent they are realized, when implementing population-level genomic screening compared to more specialized, less populous genomic applications or to current clinical practices and guidelines.[10,11]

The Centers for Disease Control (CDC) has developed a list of Tier 1 Genomic Applications for screening that have clinical interventions or therapies that can reduce the diseases' associated mortality and morbidity: hereditary breast and ovarian cancer (HBOC), Lynch syndrome (LS) and familial hypercholesterolemia (FH). These are strong candidates for the implementation of

genetic screening because identifying individuals with increased risk has the potential for a large public health impact.[12]

Realizing the public health importance and potential impact of diseases classified as Tier 1 Genomic Applications, the focus of this dissertation will be FH. Heart disease is the leading cause of death for both men and women in the United States.[13] FH is a common monogenic genetic condition, with a prevalence of ~1/250, that increases individuals' cardiovascular risk primarily due to elevated low-density lipoprotein (LDL) cholesterol levels along with independent risk associated with having an FH variant.[14,15,16] Individuals affected with FH have a significantly higher risk of experiencing a cardiovascular event such as a myocardial infarction (MI) due to an inability of their body to appropriately manage LDL cholesterol levels. In addition to having an increased risk of experiencing a cardiovascular event, they also may experience these events earlier in their life when compared to individuals who are not affected by FH.[17] For the purposes of this dissertation I will focus on heterozygous FH, as homozygous FH is exceedingly rare.

FH is underdiagnosed and many affected individuals aren't aware they are at elevated risk of cardiovascular disease.[18,19,20] For example, a recent study found a third of patients with an FH variant are not on statin therapy, and only half on statin therapy are at their target LDL level.[21] Additionally, there is a limited amount of information that exists on the effect of returning genomic results on FH patients' therapeutic status and achievement of target LDL levels in the United States. Much of the existing literature has utilized data from European countries such as the Netherlands or Norway.[22,23,24,25] These countries have different health system structures and

population demographics when compared to the United States that limit the generalizability of these findings. Furthermore, much of the literature consists of studies employing designs using a variety of descriptive and naive statistics techniques that are limited in their ability to address temporal trends associated with LDL levels, therapy adherence, and age.[26] As a result, these studies also struggle to appropriately address differences between subjects' baseline LDL levels or other covariates and require more complex statistical methods to account for observations that tend to be correlated within individuals.

It has been documented that the cost of next-generation sequencing technologies has dropped dramatically in recent years, there is still significant uncertainty surrounding the likely economic value of population-level genomic screening.[27,28] The economic value is not solely driven by the price of next-generation sequencing technologies, it is also a result of the clinical utility and patient behavior related to receiving genetic return of results. The large upfront cost of testing also poises questions about the timeline for evaluating value and whether benefits or cost-savings will accrue in the short or long term for patients engaging in population genomic screening protocols. Patient behavior and decision making related to achieving clinical targets and goals provided by clinical guidelines are also not well understood which may be drivers of population genomic screening's economic value.[29] Previous decision analytic models have examined various forms of cascade screening or pediatric screening for FH and no recent studies have assessed the economic value of population-wide or universal screening in adults.[30] The literature contains limited analyses utilizing a United States perspective instead with perspectives from countries such as the UK, Spain, the Netherlands, and Australia. Currently there is a gap in the literature surrounding adult population wide genomic screening of FH in the United States.

Finally, decision-making surrounding genomic screening has frequently focused on considerations related to independent conditions associated with monogenic, highly penetrant variants. However, most genetic testing now involves multigene testing, whole exome sequencing, or whole genome sequencing, making it possible, and likely, that future screening will involve testing that simultaneously evaluates multiple disease risks (referred to here as 'bundled screening').[31,32] There are a variety of different considerations regarding implementation of bundled population genomic screening and the age at which bundled screening should be implemented. There has been little focus specific to such bundled screening activities and, therefore, no analysis to guide their implementation, particularly in health systems.

This dissertation aims to address several challenges associated with FH population genomic screening: 1) identifying the effect of returning FH results on patient behavior and outcomes, 2) understanding the long-term economic value of FH population wide genomic screening, and 3) the age at which bundled screening should be implemented.

Concluding comments and impressions can be viewed in the final chapter of this dissertation.

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Chapter 2. IMPACT OF POPULATION-WIDE GENOMIC SCREENING ON LDL CHOLESTEROL LEVELS AND TRAJECTORIES FOR FAMILIAL HYPERCHOLESTEROLEMIA

2.1 ABSTRACT

Objective: Estimate the effect of disclosure of pathogenic genetic variants for familial hypercholesterolemia (FH) on individuals' low-density lipoprotein (LDL) cholesterol levels and trajectories.

Methods: After a cohort of more than 190,000 patients within the Geisinger MyCode Community Health Initiative were sequenced, variants from FH associated genes (*LDLR, APOB,* and *PCSK9*) were returned to patients and clinicians. We fit a linear mixed effect model and utilized within-subject study design to estimate the effect of FH variant disclosure on individuals' LDL cholesterol levels and trajectories. We used a 2-year (24 month) pre- and post-disclosure time window. Data were collected from electronic health records within Geisinger Health.

Results: A total of 115 patients were included in the analysis with mean age of 63 (SD 16) years old, 68/115 (59%) were female, and 114/115 (99%) were white. Patient comorbidities and clinical attributes at time of return of results (ROR) included hypertension (90/115, 78%), 69/115 (60%) hypothyroidism, 25/115 (22%) diabetes, 56/115 (49%) have ever smoked, 15/115 (13%) past MI, 11/115 (10%) past Stroke, and 51/115 (44%) previous FH diagnosis. At the time of ROR 83/103 (81%) had used a statin and 13/115 (11%) had a documented statin allergy. The

effect of ROR status was not statistically significant and indicated a lower LDL cholesterol level (beta = -7.73, 95% CI [-21.00, 5.53], p = 0.253). The interaction effect of time (Centered Date (Months)) on ROR status is not statistically significant and estimates a decrease in LDL cholesterol (beta = -0.52, 95% CI [-1.49, 0.46], p = 0.297)

Conclusion: When individuals in the United States with either a likely pathogenic or pathogenic FH variant receive their genetic ROR, there may be reduction in their LDL cholesterol levels and LDL cholesterol level trajectories over time attributable to ROR and suggestive of a beneficial clinical effect. As population genetic screening implementation continues to grow, future studies should aim to include larger populations affected by FH over time and improved study designs to provide better insight into the true effect sizes of ROR on LDL cholesterol.

2.2 INTRODUCTION

Heart disease is the leading cause of death for both men and women in the United States.[1] Familial Hypercholesterolemia (FH) is a common monogenic genetic condition, with a prevalence of ~1/250, that increases individuals' cardiovascular risk primarily due to both elevated low-density lipoprotein (LDL) cholesterol levels and independent risk associated with having an FH variant.[2,3,4]

Individuals with untreated FH may have a 20 times higher life risk of coronary heart disease when compared to general population risk.[5] Individuals affected with FH also have an increased risk of experiencing a cardiovascular event earlier in their life when compared to individuals who are not affected by FH.[6] Thus, FH requires early, aggressive, and sustained lipid-lowering therapy, once it is diagnosed.[7]

FH is underdiagnosed and many affected individuals aren't aware they are at elevated risk of cardiovascular disease.[8,9,10,11] For example, a recent study found a third of adult patients with an FH variant are not on statin therapy, and only half on statin therapy are at their target LDL level.[12] Healthcare systems in the United States and countries abroad have begun to implement population genomic screening for various conditions including FH.[13,14,15] These screening programs are intended to inform individuals of their increased genetic risk and allow for preventative services, increased surveillance activities, and therapeutic interventions. However, population genomic screening programs are still in the early stages of implementation, evaluation, and adoption. As a result, there is limited information on the effect of returning genomic results on FH patients' LDL cholesterol levels and their LDL cholesterol trajectory post return of results (ROR) in the United States.

As the availability of genetic screening for the identification of individuals with FH increases it will be crucial to better understand the effect of genetic ROR on LDL cholesterol levels. There have been previous reports looking at clinician and patient behaviors surrounding initial participants who received FH results from the Geisinger MyCode Community Health Initiative (MyCode), but these used mainly descriptive and native statistical methods. The objective of this study is to utilize longitudinal data to evaluate the effect of ROR on FH individuals' LDL cholesterol levels and trajectories over time. We fit a linear mixed effect model utilizing a within-subject study design and used health data, from electronic health records within MyCode, pulled for a period 2 years (24 months) before and after individuals received their results.

2.3 METHODS

2.3.1 *Study Design and Setting*

We utilized a within-subject study design using retrospective observational data to evaluate the effect of genetic ROR on individuals LDL cholesterol levels and trajectories. Various health data was used from Geisinger Health System (GHS) electronic health records (EHR). GHS is a regional, integrated health system that serves over 3 million patients throughout central, south-central, and northeastern Pennsylvania and southern New Jersey. GHS launched the MyCode Community Health Initiative (MyCode) to link patients' genetic information and EHR data for broad research use.[16] The MyCode Community Health Initiative, with more than 190,000 patient participants, is the largest data source of its kind capturing longitudinal clinical information

including FH diagnosis and patient's EHR. MyCode research protocols have been explained in more depth in previous publications.[17,18,19]

The MyCode cohort's 190,000 participants consented to include their genomic and clinical data in a biorepository. The data in the biorepository consists of data such as patients' electronic health record (EHR), exome sequencing, and associated variant classification data. Patients began receiving their ROR in 2014 and the GHS MyCode Community Health Initiative includes ~190 patients with FH variants that are classified as either pathogenic or likely pathogenic according to the American College of Medical Genetics and Genomics criteria.

2.3.2 *Study Cohort*

The study population included all adults in the MyCode cohort with FH-associated variants who had received their genetic ROR.[15] Individuals were excluded from the study cohort if they: 1) did not have data related to LDL cholesterol levels within the pre- and post-ROR period, 2) withdrew from the MyCode cohort, or 3) died. The study population consisted almost exclusively of individuals with European ancestry, older mean and median age, and a high co-morbidity index.

2.3.3 *Data Sources*

Various sources of health data were pulled for a period 2 years (24 months) before and after the individual received their results. The data sources utilized were the Geisinger EHR and Surescripts Network Alliance (Surescripts), a health information network that links EHR,

pharmacy, and other health data from various sources. EHR data was collected for MyCode participants and included demographics, diagnoses of co-morbidity, prescriptions written, lipid panels, variant classification, and documentation of statin allergies. Prescription adjudication data (Surescripts) was utilized to supplement EHR prescription information when prescribed by clinicians outside of the Geisinger network.

2.3.4 *Study Design and Outcomes*

This is a retrospective observational study that utilized a within-subject design to evaluate the effect of genetic ROR on individuals LDL cholesterol levels and trajectories (Figure 2.1). Individuals were treated as their own control within this study design. We considered employing a between-subject design with a comparison group consisting of individuals who had either (1) received a clinical diagnosis of FH, (2) met criteria for clinical diagnosis but who had not received a clinical diagnosis, and (3) received their genetic ROR starting in 2019 based on a secondary analysis compared to the primary analysis returned starting in 2014. We chose a within-subject study design due to concerns related to the proposed comparison groups for the between-subject study design being clinically different, potential confounding related to individuals having a family history, and differences in the effects of variants identified in the secondary analysis compared to the primary analysis.

The main outcomes of the study were 1) effect of ROR status on LDL cholesterol, and 2) LDL cholesterol trajectories over time after ROR. LDL cholesterol measurement dates were centered around each individuals' date of ROR and were transformed into months pre- or post-ROR as a

continuous variable. LDL cholesterol trajectories were estimated through an interaction term between the ROR status and the transformed centered dates in months. These trajectories represent the average change of LDL cholesterol over time according to ROR status controlling for the effects of the model covariates.

We examined several covariates' associations with the effect of ROR on LDL cholesterol, specifically age at ROR, sex, BMI, variant classification (likely pathogenic or pathogenic), race (white or African American), hypertension status, hypothyroidism status, diabetes status, smoking status (ever), previous FH diagnosis, previous MI, previous stroke, statin use, and statin allergy status. These were selected based on their relationship as potential secondary causes of hypercholesterolemia or association with LDL cholesterol levels based on review of the America Heart Association Heart Disease and Stroke Statistics, insight from expert clinical opinion, and broader review within the literature.[21,22,23,24,25,26,27] Comorbidities such as hypertension, hypothyroidism, diabetes, smoking status, previous MI, and previous stroke were all coded as binary variables based on information in the EHR.

2.4 Statistical Analysis

We performed descriptive analyses on patient demographics and pre-and post-ROR LDL cholesterol levels. Pre- and post-ROR LDL cholesterol were represented as means and standards deviations. Categorical and demographic variables are reported at the time of ROR. As noted previously, the time-period is defined by a 2-year (24 months) window pre- and post-ROR.

We fit a linear mixed model to predict LDL cholesterol levels with age at ROR, sex, BMI, variant classification, race, hypertension, hypothyroidism, diabetes, smoking, previous FH diagnosis, previous MI, previous stroke, statin use, statin allergy, ROR status and time (centered months from ROR). (formula: LDL Cholesterol ~ Age at ROR + SEX + BMI + VARIANT CLASSIFICATION + RACE + HYPTERTENSION + HYPOTHYROIDISM + DIABETES + SMOKER + FH DIAGNOSIS + MI + STROKE + STATIN + STATIN ALLERGY + ROR * Centered Date (Month)). The model included Patient ID as a random effect via random intercept (formula: ~1 | RISEPT_ID). We obtained fixed effects parameters by fitting the linear mixed effects model. 95% Confidence Intervals (CIs) and p-values were computed using the Wald approximation (Table 2.3).

The linear mixed effect model was fit utilizing R-Studio.[28] A random sample of 50 individuals' pre- and post-ROR LDL cholesterol levels are plotted over time to show the variation between patients and for each patient over time (Figure 2.2). As result, we couldn't perform a repeated measure ANCOVA or MANCOVA analysis due to methodological limitations that subjects should be observed at the same time points and the need to meet the compound symmetry assumption where patterns of association are the same for a subject at different time points. The differences between the pre- and post-ROR groups on the primary outcomes, LDL cholesterol levels post-ROR and LDL cholesterol trajectories by month (mg/dl), were tested as a fixed effect within the linear mixed-effects model with time as a continuous variable. The linear mixed effect model included both fixed and random factors.

2.5 RESULTS

2.5.1 *Demographics*

A total of 115 patients met the appropriate inclusion criteria (Table 2.1). The mean age was 63 (SD 16) years old, 68/115 (59%) were female, and 114/115 (99%) were white. Patient comorbidities and clinical attributes at time of ROR included hypertension (90/115, 78%), 69/115 (60%) hypothyroidism, 25/115 (22%) diabetes, 56/115 (49%) have ever smoked, 15/115 (13%) past MI, 11/115 (10%) past Stroke, and 51/115 (44%) previous FH diagnosis. At the time of ROR 83/103 (81%) had used a statin and 13/115 (11%) had a documented statin allergy. An unadjusted analysis found the average LDL cholesterol level in the Pre-ROR period was 145 (SD 67) mg/dl and the average LDL cholesterol level in the post-ROR period was 133 (SD 60) mg/dl.

2.5.2 *Linear Mixed Effects Model*

Model fit was evaluated using AIC and BIC. When comparing models with the same data, the model with the smaller AIC and BIC is preferable. Utilizing AIC and BIC we found the model fit with random effects including only a random intercept for Patient IDs was optimal (Table 2.2). Additionally, utilizing Restricted Maximum Likelihood (REML) rather than Maximum Likelihood (MLE) led to lower AIC and BIC and therefore the best model fit. The explanatory power for the fixed effects alone (marginal R^2) was 0.19. A QQplot of the residuals indicates that the data is fairly normally distributed (Figure 2.3).

2.5.3 *Fixed Effects*

The effect of ROR status was not statistically significant and negative (beta = -7.73, 95% CI [-21.00, 5.53], t(383) = -1.14, p = 0.253) indicating a ~8 mg/dl lower LDL cholesterol level for individuals post-ROR when controlling for all other covariates. The effect of time (Centered Date (Months)) was not statistically significant and positive (beta = 0.03, 95% CI [-0.64, 0.70], t(383) = 0.10, p = 0.922). However, the small co-efficient indicated minimal change in LDL cholesterol levels over time when controlling for all other covariates. The interaction effect of time (Centered Date (Months)) on ROR status is not statistically significant and negative (beta = -0.52, 95% CI [-1.49, 0.46], t(383) = -1.04, p = 0.297) estimating a ~6 mg/dl decrease in LDL cholesterol for individuals 12 months after ROR controlling for other covariates.

2.5.4 *Random Effects*

The random effects, a random intercept for the Patient IDs, presented a variance of 3278 (SD 57.25). The residual variance was 1085 (SD 32.94). As a result of this, about 75% of the total variance of LDL cholesterol levels is due to the patient IDs (ICC 0.75) and LDL cholesterol is highly correlated by patient IDs. The random effects appear to be normally distributed (Figure 2.4).

2.6 DISCUSSION

We studied the impact of ROR on LDL cholesterol levels and trajectories of individuals who participated in a population genomic screening program in the United States. The effect of ROR led to a reduction in individuals' LDL cholesterol levels compared to pre-ROR LDL cholesterol

levels. Additionally, individuals' LDL cholesterol level trajectories over time were lower after ROR. While ROR for genetic FH indicates lower LDL cholesterol values and trajectories over time, the lack of statistical significance and poor statistical power raises concerns if the true effect of ROR is captured.

Guidelines indicate that individuals with FH should target a 50% reduction in LDL cholesterol level or <100 mg/dl in various cases.[29] Realizing many individuals affected by FH can have LDL cholesterol levels >190 mg/dl, the magnitude of our results indicate LDL cholesterol level reduction from ROR may not be large enough to achieve recommended targets for individuals with high LDL cholesterol levels.[30] Additional research focused on younger adults my impact the effect size of ROR as our analysis consists of an older population (63 years old at ROR (SD 16)). Larger reductions in LDL cholesterol levels may be possible with the introduction of PCSK9 inhibitors and is an area for potential future work in conjunction with genetic ROR.[31]

Utilizing longitudinal analysis focused on LDL cholesterol level trajectories in a study cohort from the United States is a novel contribution to the literature. However, the lack of statistical significance and large confidence intervals for most of the model coefficients indicates that future analysis is necessary. As population genetic screening implementation continues to grow, larger studies of individuals affected by FH over time can provide improved insight into the true effect size of ROR on patient LDL cholesterol levels and trajectories over time.

Much of the existing literature evaluating individuals with genetically confirmed FH has utilized data from European countries such as the Netherlands or Norway and found relative success with individuals utilizing lipid lowering therapy but challenges achieving LDL cholesterol level targets.[32,33,34,35] These countries have different health system structures and population demographics when compared to the United States that limit the generalizability of these findings. A limitation of these previous studies is the lack of techniques to address temporal trends associated with LDL levels, therapy adherence, and age.[36] As a result, these studies also struggle to appropriately address differences between subjects' baseline LDL levels or other covariates and require more complex statistical methods to account for observations that tend to be correlated within individuals.

2.7 LIMITATIONS

There are several important limitations to this work. One limitation is missingness of data or imbalance of LDL cholesterol measurements within individuals because of utilizing observational, longitudinal data. However, the use of a linear mixed effect model was intended to address this concern because the number of measurements for each subject and the spacing between time intervals does not need to be equal.

A second limitation is that a with-in person study design is unable to control for time varying confounders because individuals act as their own control. Utilizing an individual as a case and control limits the ability to control for confounding such as a potential pre-treatment effect. This study design, being non-randomized, is not able to assess temporal trends related to known or

unknown time-specific effects for a certain duration or measure. However, utilizing a within-subject study design mitigates concerns about different FH variant effects because individuals will act as their own case and control group. This should limit potential confounding related to varied effect sizes because of different FH variants in this analysis.

A third limitation is the lack of diversity represented within our study population. The study population consists almost exclusively of individuals who identified as white (99%) which is a result of the regional population served by GHS consisting of more than 95% of individuals with European ancestry.[37] This impedes our ability to estimate the effect of ROR in non-white individuals and limits generalizability of our analysis to broader populations with diverse ethnic, cultural, and racial representation. Furthermore, this identifies a dire need for more diverse representation of individuals included in genetic research and more specifically for future analyses to focus on populations more inclusive of individuals with non-European ancestry.

A final limitation is the number of individuals and individual LDL cholesterol observations included in the study. The amount of data is further constrained by the time intervals selected for the pre- and post- ROR periods. The study is notedly underpowered (ROR status; power = ~30%, 506 observations).[38] However, the within-subject design provides improved statistical power for the study compared to between-subjects study designs referenced earlier. Everyone who has been identified with an FH variant was included if there was sufficient data in the pre- and post-ROR time intervals. This is a strength realizing at the time of this study only ~160 individuals had any data within MyCode after FH ROR.

2.8 CONCLUSION

When individuals in the United States with either a likely pathogenic or pathogenic FH variant receive their genetic ROR, there may be reduction in their LDL cholesterol levels and LDL cholesterol level trajectories over time attributable to ROR and suggestive of a beneficial clinical effect. As population genetic screening implementation continues to grow, future studies should aim to include larger populations affected by FH over time and improved study designs to provide better insight into the true effect sizes of ROR on LDL cholesterol.

2.9 TABLES & FIGURES

Table 2.1: Characteristics of FH Patients

Characteristic	**Study Population (n=115)**
Age at ROR (mean (sd))	63 (16)
Male (no.(%))	47 (41%)
White (no.(%))	114 (99%)
Risk Factor (no.(%))	
Hypertension Status	90 (78%)
Hypothyroidism Status	69 (60%)
Diabetes Status	25 (22%)
Smoking Status (Ever)	56 (49%)
Previous MI	15 (13%)
Previous Stroke	11 (10%)
Previous FH Diagnosis	51 (44%)
Statin Use (n=103)	83 (81%)
Statin Allergy	13 (11%)
Cholesterol (mg/dl) (mean (sd))	
Pre-ROR LDL (n=218)	149 (65)
Post-ROR LDL (n=201)	133 (60)

Notes: sd, standard deviation; FH, familial hypercholesterolemia; ROR, return of results; MI, myocardial infarction; LDL, low-density lipoprotein cholesterol

Table 2.2: AIC and BIC Model Comparison Values

Model	AIC	BIC	Degrees of Freedom
M.1	4219.876	4419.823	50
M.2	4207.325	4415.270	52
M.3	3838.191	4038.138	50
M.4	3831.866	4039.810	52
M.5	4206.306	4282.286	19
M.6	4201.444	4285.421	21
M.7	4111.861	4187.841	19
M.8	4107.474	4191.452	21
M.9	4207.597	4287.576	22
M.10	4202.159	4290.135	20
M.11	4105.503	4185.481	22
M.12	4100.672	4188.648	20

Table 2.3: Model Results

	LAB RES VAL NUM		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	159.46	0.49 – 318.42	**0.049**
Age_ROR	-0.77	-1.65 – 0.10	0.083
SEX	-23.00	-51.22 – 5.23	0.110
BMI	-0.45	-2.32 – 1.42	0.637
CLASSIFICATION	14.98	-22.83 – 52.79	0.437
RACE	28.46	-96.51 – 153.43	0.655
HYPERTENSION	35.50	1.56 – 69.43	**0.040**
HYPOTHYROIDISM	-16.01	-44.87 – 12.86	0.277
DIABETES	11.11	-19.10 – 41.32	0.471
SMOKER	-4.26	-31.84 – 23.32	0.762
FH DIAGNOSIS	7.88	-19.57 – 35.33	0.574
MI	-24.26	-63.47 – 14.96	0.225
STROKE	30.96	-12.44 – 74.35	0.162
STATIN	-1.95	-51.02 – 47.12	0.938
STATIN ALLERGY	36.92	-3.95 – 77.80	0.077
POST ROR	-7.73	-21.00 – 5.53	0.253
CENTERED DATE	0.03	-0.64 – 0.70	0.922
POST ROR * CENTERED DATE	-0.52	-1.49 – 0.46	0.297
Random Effects			
σ^2	1084.51		
$\tau_{00\ RISEPT\_ID}$	3277.88		
ICC	0.75		
Marginal R^2 / Conditional R^2	0.187 / 0.798		

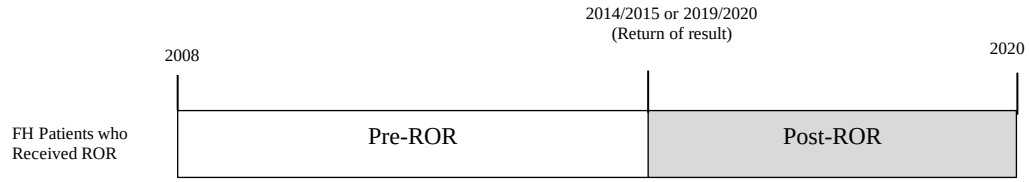

Figure 2.1: With-in Person Study Design

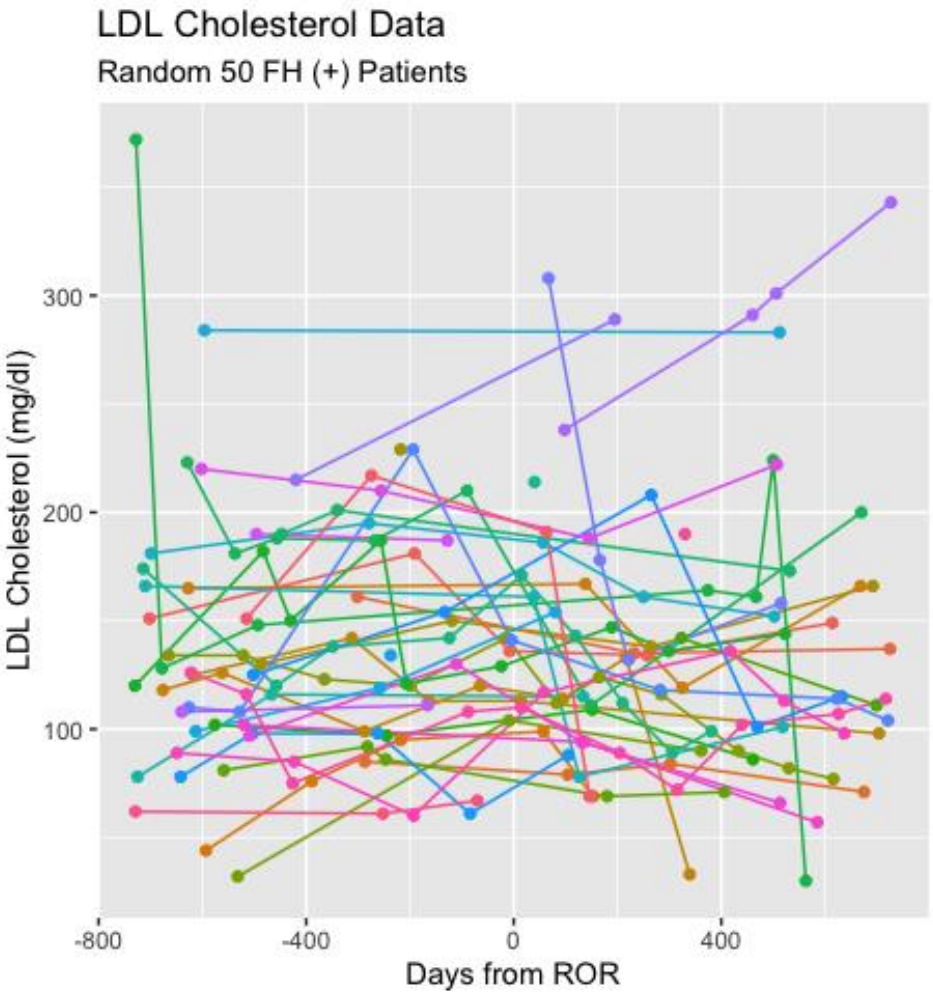

Figure 2.2: LDL cholesterol Levels by Center Date (Month)

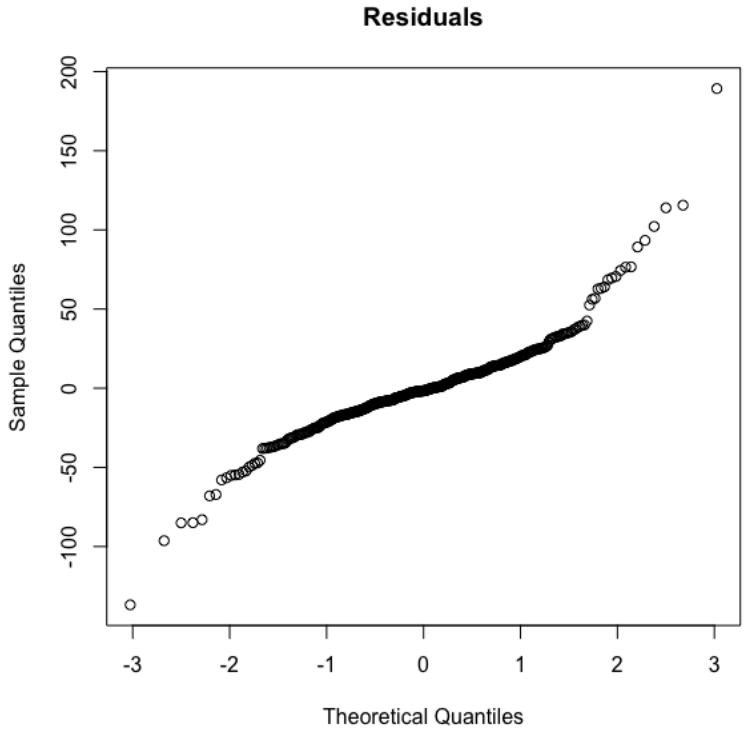

Figure 2.3: QQ Plot for Residuals

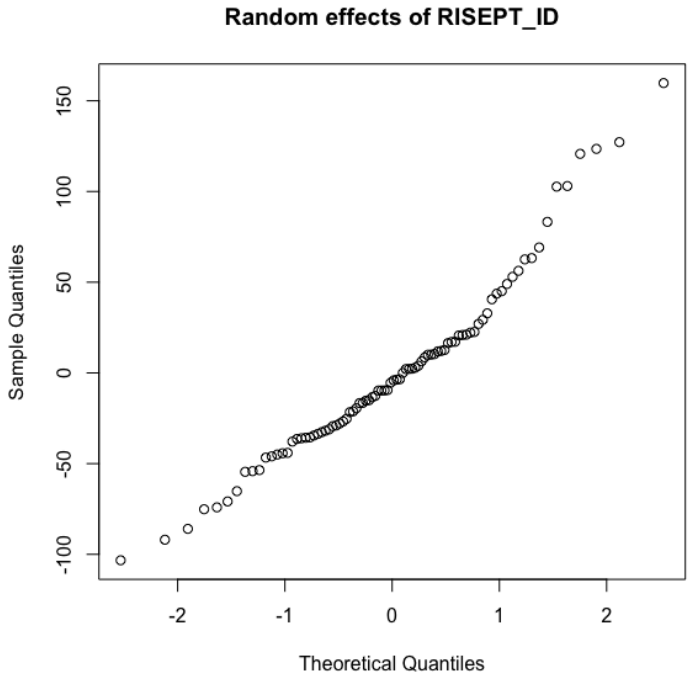

Figure 2.4: QQ Plot for Random Effects

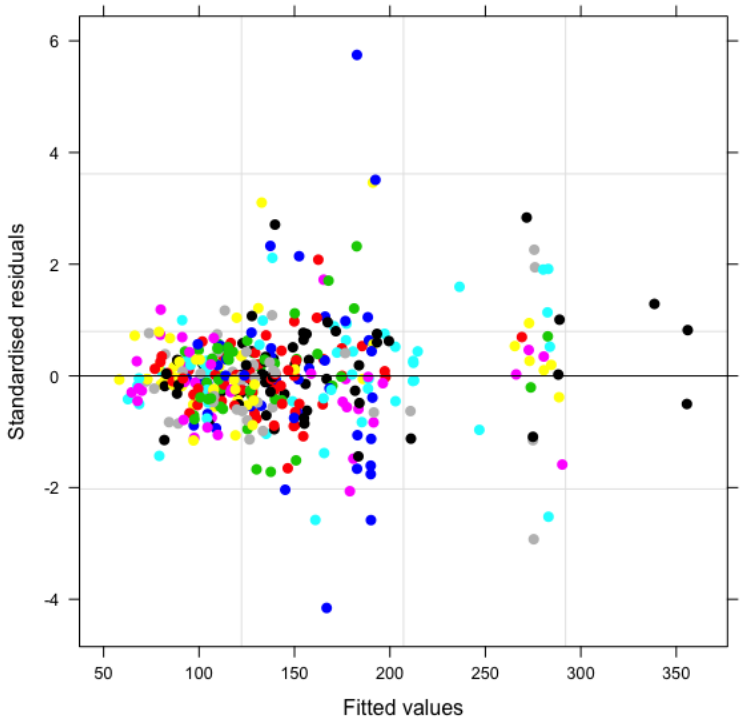

Figure 2.5: Standardized Residuals by Patient ID

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Chapter 3. COST-EFFECTIVENESS OF POPULATION-WIDE GENOMIC SCREENING FOR FAMILIAL HYPERCHOLESTEROLEMIA IN THE UNITED STATES

3.1 ABSTRACT

Importance: Population genomic screening for Familial Hypercholesterolemia (FH) in unselected individuals can prevent premature cardiovascular disease such as myocardial infarction (MI) and ischemic stroke by identifying high-risk patients and utilizing statin therapy to manage their lipid levels.

Objective: Estimate the clinical and economic outcomes of population-wide FH genomic screening versus no genomic screening.

Methods: We developed a decision tree and 10-state Markov model evaluating the identification of patients with an FH variant, treatment status, low-density lipoprotein (LDL) cholesterol levels, MI, and stroke to compare the costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness of population-wide FH genomic screening. FH variant prevalence (0.4%) was estimated from the Geisinger MyCode Community Health Initiative (MyCode). Test costs were assumed to be $200. Age and sex-based estimates of MI, recurrent MI, stroke, and recurrent stroke were obtained from Framingham Risk Equations. Additional, independent risk associated with FH variants was derived from *Khera et al*., a retrospective analysis of 26,025 participants

screened for FH. Distributions of individuals on vs. off treatment and on vs. off LDL target were fitted between ages 20 through 80 years old from *Abul-Husn et al.*, retrospective analysis of 50,726 individuals from MyCode, and *Holven et al.,* a retrospective analysis of 714 adult FH subjects in Norway. Costs and utility estimates were from published literature. Sensitivity and threshold analyses were conducted to evaluate model assumptions and uncertainty.

Results: FH screening was most effective at younger ages; screening unselected 20-year-olds lead to 111 QALYs gained per 100,000 individuals screened at an incremental cost of $20M. The incremental cost-effectiveness ratio (ICER) was $181,000 per QALY, and there was a 38% probability of cost-effectiveness at $100,00 per QALY willingness-to-pay threshold. Model drivers were relative risks of MI for FH positive individuals with both on and off target LDL levels, prevalence of FH, FH test cost, and the effect of genomic screening. A genomic testing cost of $100 resulted in an ICER of $91,000 per QALY.

Conclusion: Population FH screening is not cost-effective at current genomic screening costs. However, reducing genomic testing costs or including FH testing within a broader multiplex screening panel may improve clinical and economic value.

3.2 INTRODUCTION

Familial Hypercholesterolemia (FH) is one of the most commonly inherited cardiovascular conditions, with a prevalence of ~1/250, and increases individuals' cardiovascular risk due to lifetime exposure to elevated low-density lipoprotein (LDL) cholesterol levels as well as independent risk.[1,2,3] FH results from pathogenic variants in the *LDLR*, *APOB*, and *PCSK9* genes.[4,5] Individuals with untreated FH may have a 20 times higher life risk of coronary heart disease when compared to general population risk.[6] Individuals affected by FH are also at risk of experiencing cardiovascular events or death earlier in their life when compared to individuals with similar LDL cholesterol levels.[1,7,8,9]

FH is underdiagnosed and many affected individuals aren't aware they are at elevated risk of cardiovascular disease.[10,11,12] For example, a recent study found that roughly a third of patients with an FH variant were not on statin therapy, and only half on statin therapy were at their target LDL level in the United States.[13] FH can be diagnosed through clinical diagnosis and genetic testing. Guidelines recommend FH genetic testing where FH is definite, or probable based on clinical diagnostic criteria per the American College of Cardiology expert consensus panel and International FH Foundation.[14,15] However, there is not consensus regarding the diagnostic criteria for FH affecting adults in the United States which has led to chronic under diagnosis and treatment of patients with FH.[16]

FH is listed as a Tier 1 Genomic Application as identified by the Center for Disease Control and Prevention (CDC) based on its potential for significant positive impact on public health.[17]

A recent call to action by the global FH community identified the need for research on the value and cost associated with screening programs for FH.[18] While previous studies have evaluated the cost-effectiveness of identification of first-degree relatives through cascade or opportunistic screening with affected individuals, few studies have focused on screening an unselected population.[19,20,21,22] The objective of this study was to evaluate the cost-effectiveness of population-wide genomic screening for FH in the United States using a decision-analytic model and estimates from US data sources including the Geisinger MyCode Community Health Initiative.

3.3 METHODS

3.3.1 *Population Screening Model*

We developed a decision tree plus Markov model to compare (a) population screening for FH in an unselected population versus (b) no population screening (Figure 3.1). The decision tree distributed individuals between carrier/noncarrier status, on/off LDL cholesterol target levels, therapeutic status, and previously affected by MI or stroke among Markov health states in the first model cycle. The Markov model was then used to simulate the cohort's treatment, LDL-cholesterol levels, clinical events, health-related quality of life, and healthcare costs over a lifetime. The population screening model outcomes included lifetime costs, life years, and quality-adjusted life years (QALYs). We used a U.S. health care sector perspective, i.e., focused

on direct medical costs only, and all costs and health outcomes were discounted by 3% per year.[23] The model was developed in Microsoft® Excel®.

The decision tree accounted for (1) individual screening participation, (2) carrier/noncarrier status, (3) previous MI or stroke, and (4) known/unknown hyperlipidemia status. The Markov model included health states for pre-MI and pre-stroke (off treatment & on target LDL levels, off treatment & off target LDL levels, on treatment & off target LDL levels, and on treatment & on target LDL levels), single-cycle health states for MI and stroke, post-MI and post-stroke health states (on/off target LDL levels), and all-cause death. The proportion of these pre-MI and pre-stroke health states is age dependent. The treatment of interest for the model is statin therapy to lower and/or manage individuals' LDL cholesterol levels.[24] The model utilized annual cycles, and patients transitioned to another state or stayed in their current state each year as depicted by the arrows in Figure 3.1.

3.3.2 *Clinical Parameters*

The prevalence of pathogenic FH variant carriers (0.4%) was based on data from the Geisinger MyCode Community Health Initiative, consisting of more than 190,000 participants electronic health records (EHR) and genomic screening results in Pennsylvania and New Jersey.[25] Annualized, age, sex, and cholesterol-based estimates of MI, recurrent MI, stroke, and recurrent stroke probabilities were derived from the Framingham Heart Study's 10-year cardiovascular disease risk equations.[26,27,28] We used relative risks for MI based on LDL cholesterol levels and FH variant status (FH variant, 190-220 mg/dl: 2.86; FH variant, <130 mg/dl: 1.61) calculated

from *Khera et al.*, who conducted a retrospective analysis of 26,025 participants screened for FH and found that FH carriers had increased cardiovascular risk for any observed LDL cholesterol level.[1] These relative risks were applied to probabilities derived from Framingham Heart Study's risk equations for individuals affected by FH to appropriately estimate additional independent risk associated with FH variants.

The calculated baseline Framingham and FH risk adjusted probabilities were compared to the results of *Luirink et al.* and United States general population probabilities to validate the estimates.[29] *Luirink et al.* performed a follow-up study of statin therapy in 214 children with genetically confirmed FH (98%) and their 156 affected parents who did not have access to statin therapy until later in life, i.e. after 39 years old, finding the cumulative incidence of cardiovascular events and cardiovascular death for children with FH was lower than their affected parents (1% vs 26%; 0% vs 7%, respectively). We used the Kaplan-Meier curve for affected parents without access to statin therapy to calculate annual probabilities of cardiovascular events by age for comparison.

The distributions of individuals on vs. off treatment and on vs. off LDL cholesterol target levels were fitted in linear fashion between ages 20 through 80 years old using estimates from *Holven et al. and Abul-Husn et al.*[12,30] *Holven et al.* performed a retrospective analysis of 714 adult FH subjects (>18 years old) from 3 different regional specialized lipid clinics in Norway to evaluate LDL-cholesterol target achievement pre- and post-genetic confirmation of FH. We used the pre-treatment lipid levels of the 469 normal risk-FH patients (defined as lower pre-treatment total

cholesterol, LDL cholesterol, and Lp(a) levels, earlier diagnosis of FH, lower prevalence of males, smokers, hypertension, and lower body mass index compared to very-high-risk FH patients; average age at FH diagnosis: 21.2 (11.0)) to calculate the distribution of individuals on and off LDL cholesterol target levels for the 20-year-old cohort. We assumed that no individuals were on statin therapy in the 20-year-old cohort. Transition probabilities between pre-MI and pre-stroke health states depicted by the arrows in Figure 3.1 were fit to match the distribution of individuals on/off treatment and on/off LDL cholesterol target levels found by *Abul-Husn et al.* in a 61-year-old cohort (No Treatment, On Target; 11%; No Treatment, Off Target: 31%; Treatment, Off Target: 31%; Treatment, On Target: 27%). After age 61 transition probabilities between pre-MI and pre-stroke health states only included non-adherence moving individuals off of treatment based on input from clinical experts and lack of available clinical data sources. The distribution of individuals previously affected by MI or stroke was determined by age- and sex-based cumulative incidences among a general population.[31]

The effect of population genomic screening on patients' therapeutic status and achievement of LDL cholesterol target levels was informed by *Holven et al.*, which found that 86% of individuals with normal-risk FH utilized statin therapy after receiving their genetic return of results (ROR).[32] This study was performed with a Norwegian population which employs a different health system, has different cultural and social norms regarding healthcare, and different healthcare utilization compared to the Unites States. We consulted with clinical experts and assumed that for a 20-year-old cohort the proportion of FH affected individuals on statin therapy was 60% in the United States. We estimated the effect of genomic screening was an

absolute 30% increase in FH individuals on statin therapy and at target LDL cholesterol levels. We assumed this absolute effect decreased in linear fashion as the age of the cohort increased to account for different health choice timing and changes in the distribution of individuals in the pre-MI and pre-stroke health states resulting in a smaller effect in older cohorts (Figure 3.5). We performed a retrospective, longitudinal study with 115 individuals affected with FH (average age at diagnosis: 63 (SD 16)) from the Geisinger MyCode Community Health Initiative to evaluate the effect of genetic ROR on LDL cholesterol levels and trajectories (Spencer et al, unpublished results, 2021). We found genetic ROR had a small effect on lowering LDL cholesterol level (approximately 20 mg/dl) which, in conjunction with expert clinical opinion, informed our assumption that older cohorts experience a smaller absolute effect on the proportion of individuals on statin therapy and at LDL cholesterol target levels.

3.3.3 *Quality-of-Life (Utility) Parameters*

We assumed a health state utility of 1.0 for healthy patients in the pre-MI and stroke health states. We assigned dis-utilities for MI and stroke health states during the year in which they occur.[32,33] The utilities for post-MI and post-stroke were obtained from published literature.[34] We assumed no disutility associated with statin therapy.

3.3.4 *Cost Parameters*

All costs were in 2021 U.S. dollars. Based on testing options available to the public we modeled a population screening test cost of $200.[35] Costs associated with experiencing an MI, experiencing a stroke, the post-MI health state, the post-stroke health state, and statin therapy

were derived from published sources.[36,37] Post-MI and post-stroke costs continued as individuals survived in either health state.

3.3.5 *Analysis*

We calculated lifetime MI and stroke incidence, costs, life years, and QALYs for population-wide FH genomic screening in an unselected, general population versus no FH genomic screening. The incremental cost-effectiveness ration (ICER) was calculated as the incremental difference in cost divided by the incremental difference in QALYs between strategies. We report results for a 20-year-old and 35-year-old cohort consisting of both males and females, representative of a general population in the United States.[38]

We performed two scenario analyses varying the test cost to $150 and $100, respectively. We also performed one-way and probabilistic sensitivity analyses to evaluate the effect of uncertainty in parameters on the model results. One-way sensitivity analysis involves varying a single parameter at a time to its upper or lower value while all other parameters remain constant. Probabilistic sensitivity analysis varies all parameters simultaneously and randomly over 1,000 simulations based on distributions assigned to each parameter.

3.4 RESULTS

3.4.1 *Base Case*

Screening unselected 20-year-olds for FH lead to 111 QALYs gained per 100,000 individuals screened at an incremental cost of $20M versus no screening, resulting in an ICER of $181,000

(Table 3.2). Screening unselected 20-year-old males for FH lead to 116 QALYs gained per 100,00 individuals screened at an incremental cost of $20M versus no screening, resulting in an ICER of $172,000. Screening unselected 20-year-old females for FH resulted in 106 QALYs gained per 100,000 individuals screened at an incremental cost of $20M versus no screening, resulting in an ICER of $190,000.

Screening unselected 35-year-olds for FH lead to 84 QALYs gained per 100,000 individuals screened at an incremental cost of $20M versus no screening, resulting in an ICER of $234,000 (Table 3.2). Screening unselected 35-year-old males for FH lead to 90 QALYs gained per 100,000 individuals screened at an incremental cost of $20M versus no screening, resulting in an ICER of $216,000. Screening unselected 35-year-old females for FH lead to 77 QALYs gained per 100,000 individuals screened at an incremental cost of $20M versus no screening, resulting in an ICER of $254,000.

3.4.2 *Sensitivity Analysis*

In the one-way sensitivity analysis for 20-year-olds, the ICER was most sensitive to the relative risk of MI for FH positive individuals with both on and off target LDL levels, the population prevalence of FH, FH test cost, and the effect of genomic screening on achieving target LDL cholesterol levels (Figure 3.2). For 35-year-olds, the ICER was most sensitive to the relative risk of MI for FH positive individuals with both on and off target LDL levels, the effect of genomic screening on achieving target LDL cholesterol levels, the population prevalence of FH, FH test cost, and the utility of the post-MI health states (Figure 3.2).

Probabilistic sensitivity analysis results are represented as cost-effectiveness acceptability curves (CEACs) which show the probability of the results being cost-effective at different willingness-to-pay thresholds. For 20-year-olds, FH population screening had a 1%, 38%, and 81% probability of being cost-effective at $50,000, $100,000, and $150,000 per QALY thresholds, respectively (Figure 3.6). For 35-year-olds, FH population screening had a 0%, 14%, and 57% probability of being cost-effective at $50,000, $100,000, and $150,000 per QALY thresholds, respectively (Figure 3.7).

3.4.3 *Scenario Analysis*

Effect of Test Cost: At the population level, the incremental impact of lower test costs was significant. When we changed the test cost to $150, the incremental cost of screening unselected 20-year-olds and 35-year-olds versus no screening was $15M per 100,000 individuals resulting in an ICER of $136,000 and $174,000, respectively. When we changed the test cost to $100, the incremental cost of screening unselected 20-year-olds and 35-year-olds versus no screening was $10M per 100,000 individuals resulting in an ICER of $91,000 and $115,000, respectively.

3.5 DISCUSSION

We conducted a cost-effectiveness analysis to estimate whether the health outcomes gained when implementing FH population genomic screening justifies its additional cost compared to no population genomic screening. Our model was informed by annualized, age, sex, and cholesterol-based estimates of MI, recurrent MI, stroke, and recurrent stroke risk, variant-

specific FH risk, and age specific uptake of statin therapy. We found that population genomic screening is not cost-effective in an unselected population between the ages of 20 and 75-years-old in the United States (Figure 3.3).

Our findings highlight that the cost-effectiveness of population genomic screening for FH dramatically improves when screening cohorts of younger patients compared to older patients. Individuals who are older when identified have less time in which to act and are not able to augment their previous cumulative LDL cholesterol exposure. Additionally, as the age of the cohort screened increases the proportion of individuals who are on statin therapy or that have high LDL cholesterol levels is likely larger, decreasing the impact and effect of population genomic screening efforts. Further research into the effect of population genomic screening on younger patients' therapeutic status and LDL cholesterol levels may improve the cost-effectiveness, which could suggest that adoption of population genomic screening of FH should be considered by policymakers willing to pay $150,000 per QALY.

Our results are the first to report on population-wide genomic screening for FH in the United States to our knowledge. *Pelczarska et al.* evaluated seven diagnostic strategies in Poland, including a universal screening strategy, in three populations including children, young adults, and individuals who experienced acute coronary syndrome.[22] However, universal screening strategies only employed genetic testing for individuals with definite/probable FH based on clinical diagnosis rather than population genomic screening.

Our scenario analysis lowering the test cost for a population genomic screen to $100 resulted in screening being cost-effective. Thus, lowered costs of testing have the potential to significantly affect the cost-effectiveness of population genomic screening of FH and increase its value at commonly accepted willingness-to-pay thresholds in the United States. Another approach is bundled screening that includes additional CDC Tier 1 Genomic Applications such as Hereditary Breast and Ovarian Cancer (HBOC) and Lynch Syndrome (LS). Our previous analysis of population genomic screening for HBOC indicated that screening at younger ages lead to improved health outcomes and greater cost-effectiveness similar to FH.[39] Utilizing a single test to screen for multiple conditions would defray testing costs, a primary driver of our FH results, and potentially boost the clinical and economic value of population genomic screening. As a result, a bundled screen may improve cost-effectiveness and future research should prioritize analysis of the cost-effectiveness of multiplex population genomic screening that includes additional conditions such as HBOC and LS in the United States.

When screening 20-year-olds we found that the ICER was most sensitive to the relative risk of MI for FH positive individuals both on and off target LDL levels, the population prevalence of FH, FH test cost, and the effect of genomic screening on achieving target LDL cholesterol levels. The additional risk affecting individuals with FH compared to individuals with similar LDL cholesterol levels has clear clinical impact. Future studies might estimate relative risk through stratified analyses by age, family history, or other features from clinical diagnostic criteria that were limited due to data constraints. Research identifying additional variants of significance or sources of polygenic cardiovascular risk may increase and amplify the impacts of population

genomic screening. Future studies might identify age and time varying effects of population genomic screening on therapeutic status and achievement of LDL cholesterol level targets which may impact estimates of clinical and economic value for different aged cohorts.

Our analysis has limitations. First, there is limited US data regarding FH genomic screening, LDL cholesterol levels and treatment effects for young adults, and long term clinical behavior and disease management for the FH patient population, which required use of estimates from populations based in European countries.[12,32] FH populations in the United States and Europe are possibly different due to varied ancestry, social and cultural norms, and associated screening effectiveness, but we made reasonable assumptions with the data available and insight from clinical expertise. Second, there are gaps in understanding the effects that population genomic screening has on FH patients' utilization of statin therapy and achievement of LDL cholesterol target levels. We performed a retrospective, longitudinal analysis using Geisinger's MyCode Community Health Initiative to inform assumptions about the model's effect from population genomic screening. Finally, our model only considered population genomic screening for FH, but it is likely that a screening program would include other Tier 1 genomic applications which could improve clinical benefit and economic value. The value of FH screening should be evaluated in the context of a broader multiplex screening panel.

In conclusion, population FH screening presents the best value in younger populations and is not cost-effective at current genomic screening costs. However, the model indicates reducing

genomic testing costs and/or including FH testing within a broader multiplex screening panel may lead to screening being cost-effective.

3.6 TABLES & FIGURES

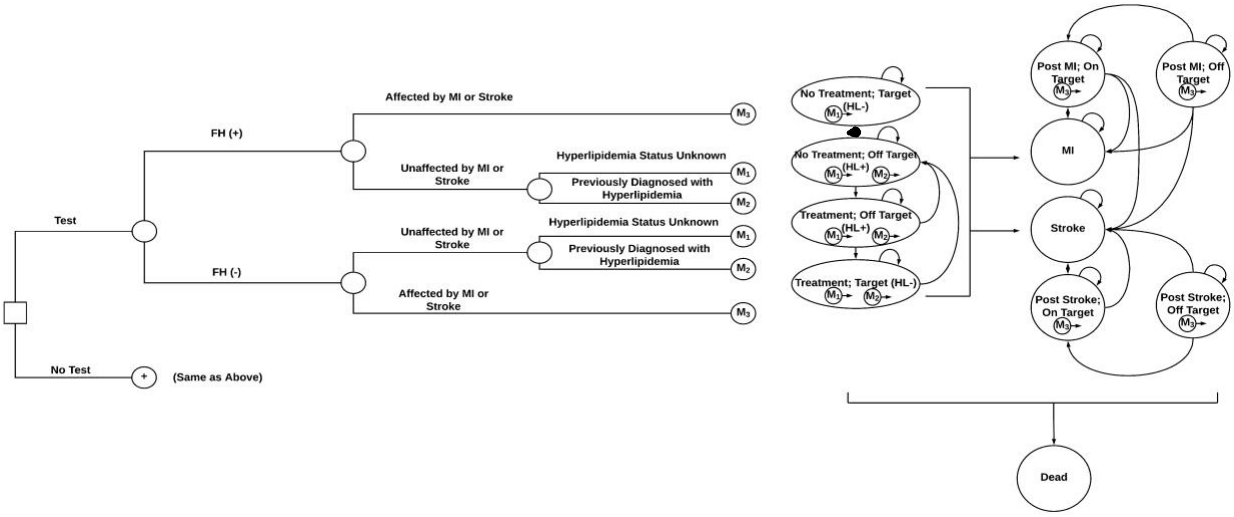

Figure 3.1: Model Schematic

Table 3.1: Model Parameters

MI & STROKE PARAMETERS - MARKOV MODEL TRANSITIONS					
Parameter	Default	< Range >		Distribution	Source
Baseline Cardiovascular Risk					
Post MI to Stroke	0.0145	0.0116	0.0174	Beta	SEER
Proportion of CV Events MI	0.7900	0.6320	0.9480	Beta	AHA
Proportion of CV Events Stroke	0.2100	0.1680	0.2520	Beta	AHA
Proportion of fatal MI	0.2400	0.1920	0.2880	Beta	AHA
Proportion of fatal Stroke	0.2100	0.1680	0.2520	Beta	AHA
Recurrent CV Event RR	1.4400	1.1520	1.7280	Log-Normal	Jernberg
Relative Risk (MI)					
FH(-), <130 mg/dl	1.0000	0.8000	1.2000	Log-Normal	Calculated from Khera et al.
FH(-), 160-190 mg/dl	1.8281	1.4625	2.1937	Log-Normal	Calculated from Khera et al.
FH (+), <130 mg/dl	1.6054	1.2844	1.9265	Log-Normal	Calculated from Khera et al.
FH (+), 190-220 mg/dl	2.8630	2.2904	3.4356	Log-Normal	Calculated from Khera et al.
Test Effect Size (by age)					
20-40	0.3000	0.2400	0.3600	Beta	Assumption
40-50	0.2000	0.1600	0.2400	Beta	Assumption
50-70	0.1500	0.1200	0.1800	Beta	Assumption
70+	0.0500	0.0400	0.0600	Beta	Assumption
Test Effect on Treatment Proportion Size (by age)					
20-40	0.6000	0.4800	0.7200	Beta	Assumption
40-50	0.6000	0.4800	0.7200	Beta	Assumption
50-70	0.6000	0.4800	0.7200	Beta	Assumption
70+	0.6000	0.4800	0.7200	Beta	Assumption
MI & STROKE PARAMETERS - UTILITIES					
Parameter	Default	< Range >		Distribution	Source
Health States					
PreCVD	1.00	0.80	1.00	Beta	Assumptions
Stroke Post	0.70	0.56	0.84	Beta	Lin et al.
MI	0.87	0.69	1.00	Beta	Galper et al.
Stroke	0.33	0.26	0.39	Beta	Gandra et al.
MI Post	0.74	0.59	0.89	Beta	Lin et al.
Statins	1.00	0.98	1.00	Beta	Chen et al.
MI & STROKE PARAMETERS - Costs					
Parameter	Default	< Range >		Distribution	Source
Costs					
Genetic Test	$ 200.00	$ 160.00	$ 240.00	Normal	Pandya et al.
Statins	$ 312.00	$ 249.60	$ 374.40	Normal	Pandya et al.
General Practitioner Screening	$ 75.00	$ 60.00	$ 90.00	Normal	Pandya et al.
Fatal MI	$ 20,491.00	$ 16,392.80	$ 24,589.20	Normal	O'sullivan et al.
Nonfatal MI	$ 72,711.00	$ 58,168.80	$ 87,253.20	Normal	O'sullivan et al.
Fatal Stroke	$ 12,446.00	$ 9,956.80	$ 14,935.20	Normal	O'sullivan et al.
Nonfatal Stroke	$ 23,974.00	$ 19,179.20	$ 28,768.80	Normal	O'sullivan et al.
Post Stroke	$ 2,472.00	$ 1,977.60	$ 2,966.40	Normal	O'sullivan et al.

Table 3.2: Model Results for Ages 20 and 35

Cohort of 100,000 20-year-olds				
	Cost	**QALYs**	**Life Years**	**ICER**
Test	$2,449,000,000	2,616,492	2,711,663	
No Test	$2,429,000,000	2,616,381	2,711,594	
Incremental	**$20,000,000**	**111**	**69**	**$181,000**
Cohort of 100,000 35-year-olds				
	Cost	**QALYs**	**Life Years**	**ICER**
Test	$3,378,000,000	2,224,944	2,343,758	
No Test	$3,358,000,000	2,224,860	2,343,704	
Incremental	**$20,000,000**	**84**	**54**	**$234,000**

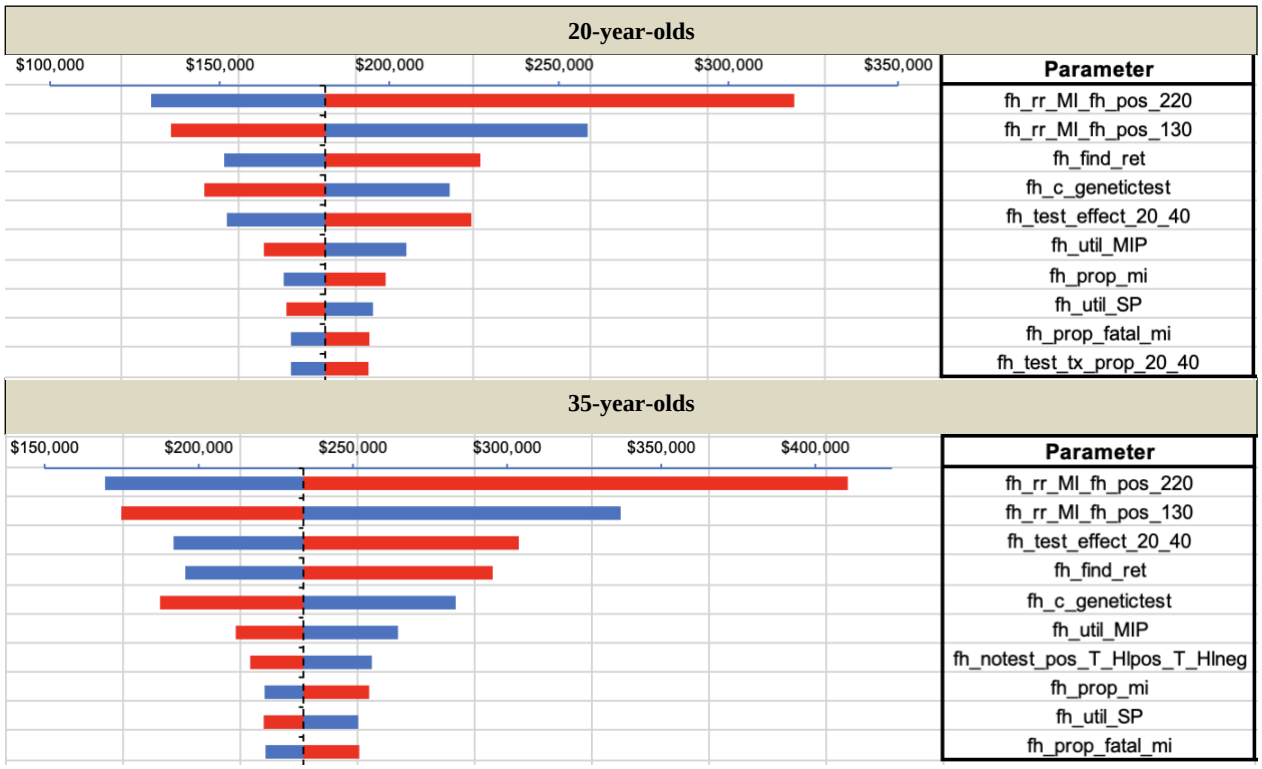

Figure 3.2: One Way Sensitivity Analysis for 20-year-olds and 35-year-olds

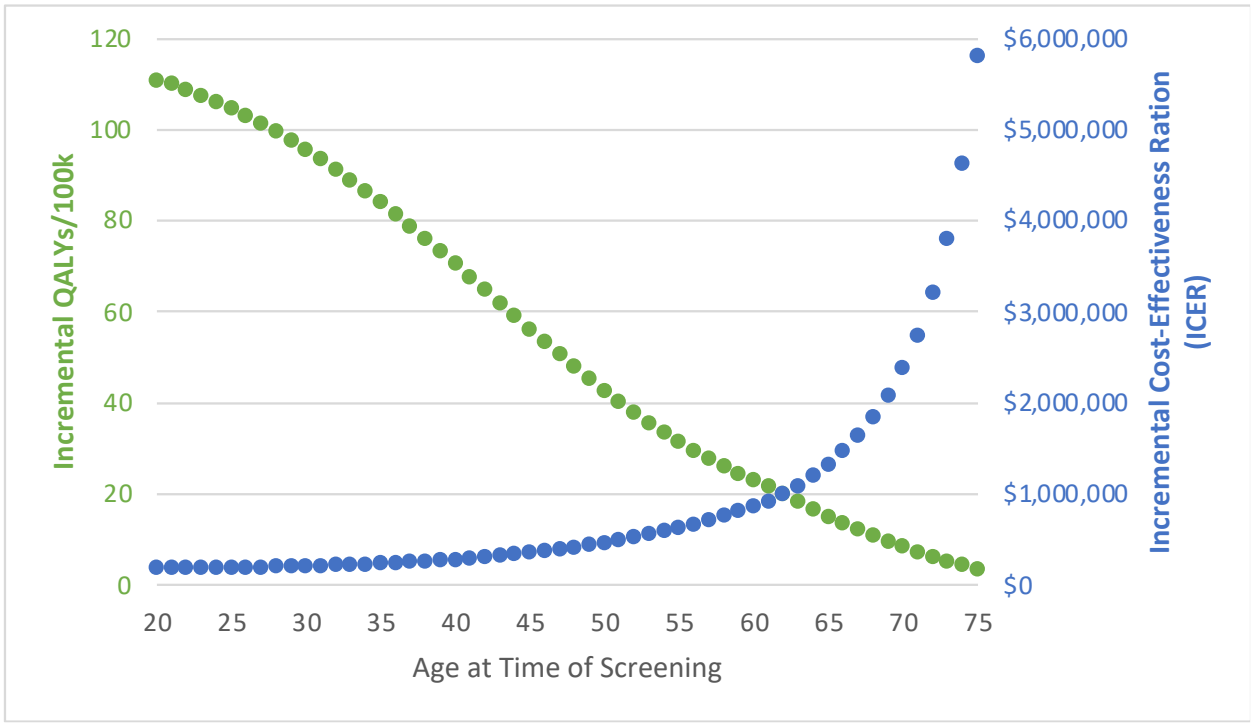

Figure 3.3: Base Case Results by Age of Genomic Screening

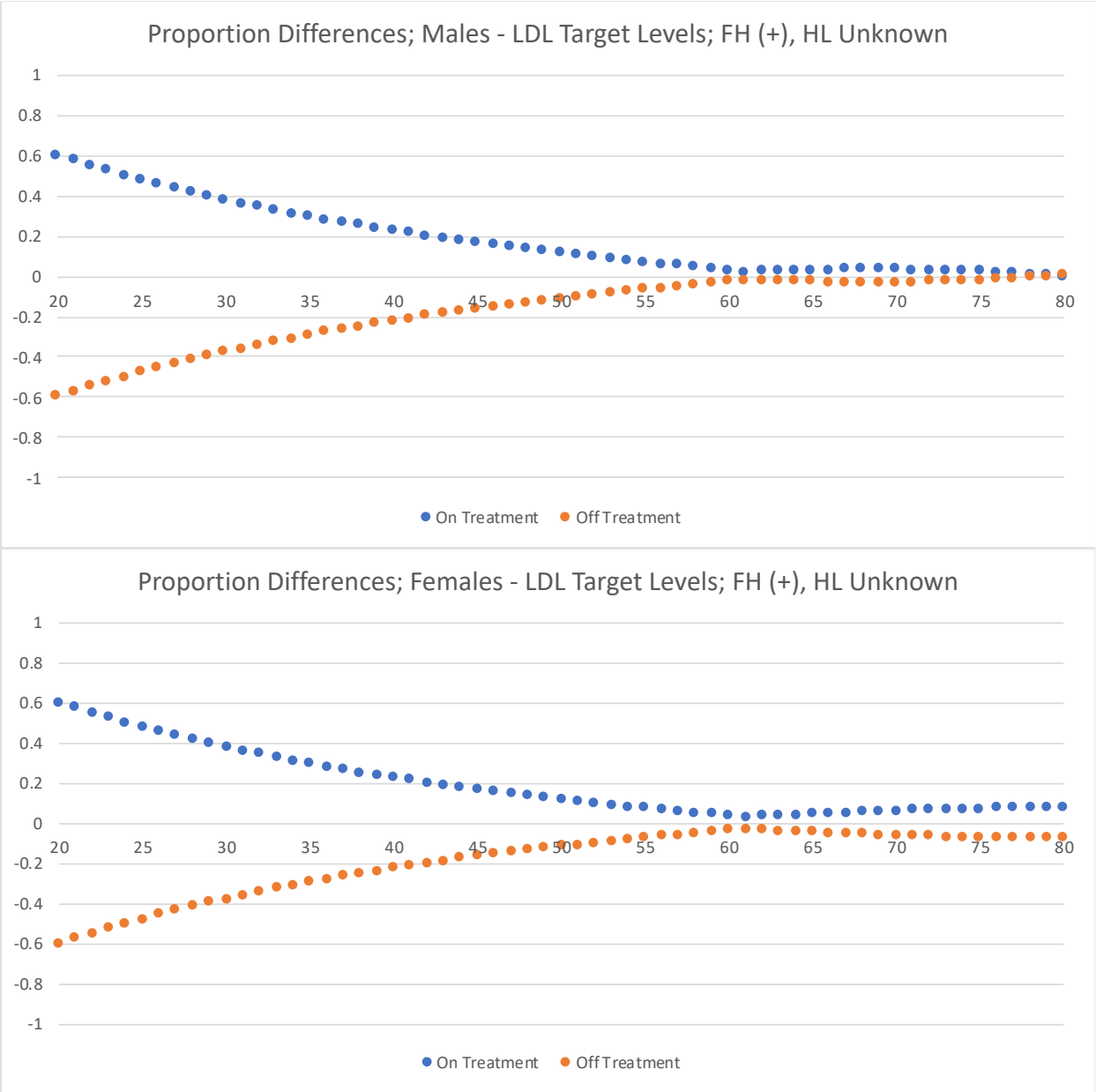

Figure 3.4: Treatment Proportion Differences at Age of Screening between 20-80 years old

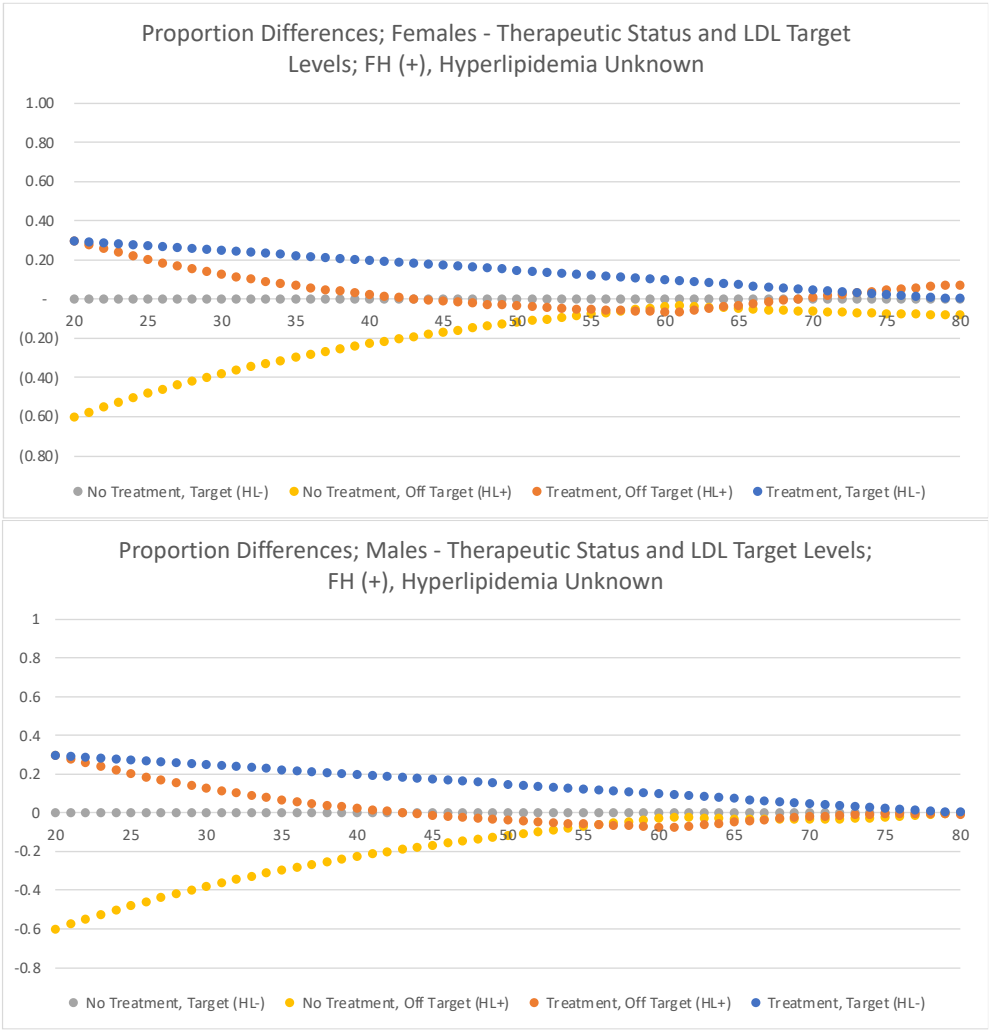

Figure 3.5: Estimated Effect of Screening on Therapeutic Status and LDL Cholesterol Target levels by Age at Time of Screening; Proportion Difference between Test and No Test Arm

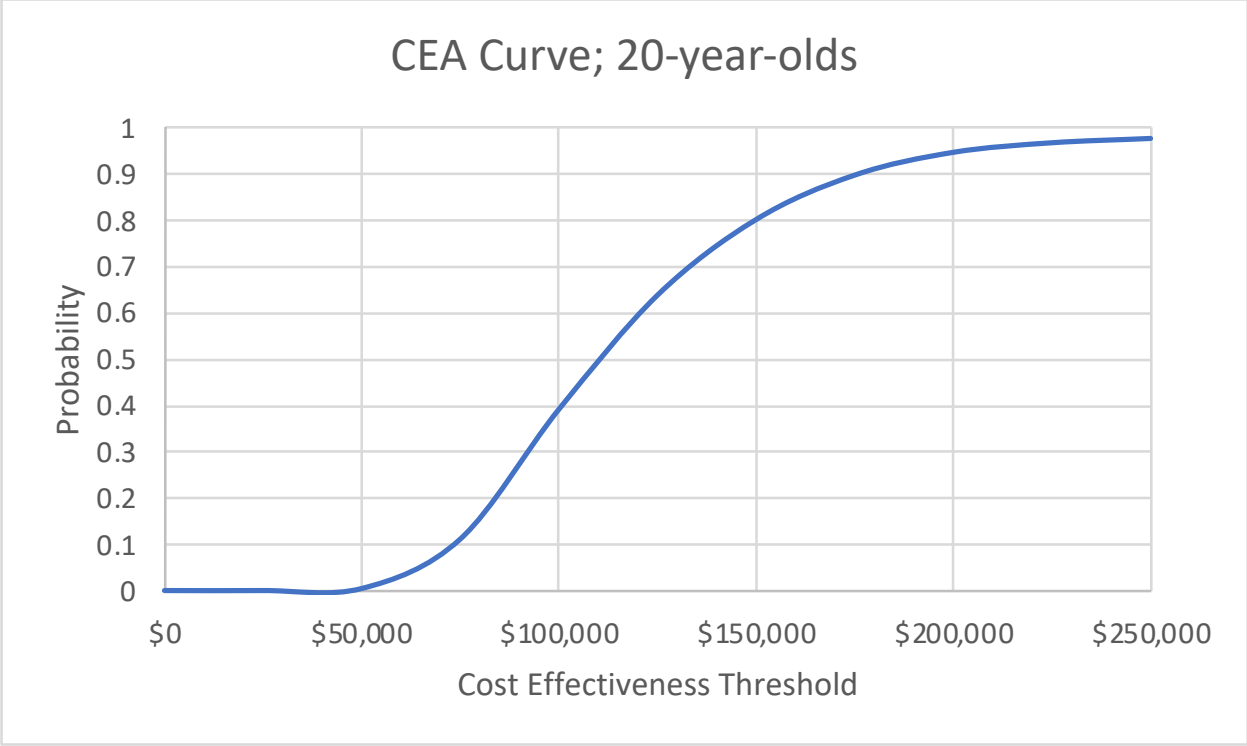

Figure 3.6: CEA Curve; 20-years-olds

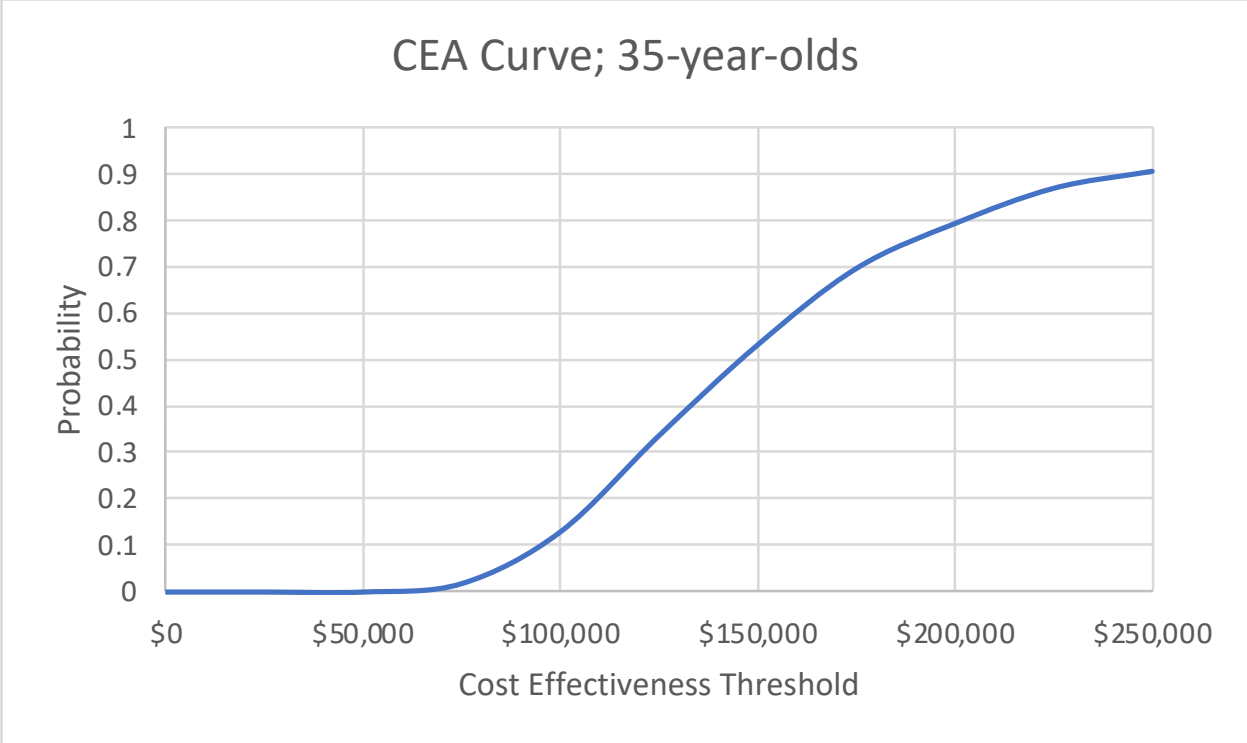

Figure 3.7: CEA Curve; 35-years-olds

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Chapter 4. BUNDLED POPULATION GENOMIC SCREENING… BUT AT WHAT AGE?: UTILITARIAN AND PRINCIPLIST PERSPECTIVES

4.1 ABSTRACT

Objective: Evaluate at what age a bundled population genomic screen should take place from a utilitarian and principlist perspective.

Methods: We identified three dimensions via targeted literature review, clinical, non-clinical, and family planning, to evaluate bundled population genomic screening. A narrow bundle use case was used, consisting of the CDC Tier 1 Genomic Applications familial hypercholesterolemia, hereditary breast and ovarian cancer, and lynch syndrome, for analysis of whether to engage in bundled screening "At Age of Majority" or "After Age of Majority" from the utilitarian and principlist perspectives. Utilitarianism claims that an act is morally right if and only if it maximizes the good or utility for the largest number of people. Principlism applies four ethical principles, autonomy, justice, beneficence, and non-maleficence, to claim the morality of an action. Clinical dimensions were considered for the utilitarian analysis while the principlist analysis evaluated non-clinical and family planning dimensions.

Results: We recommended that the age at which a bundled population genomic screen should take place is "After the Age of Majority" for the narrow bundle use case from the utilitarian perspective. The principlist approach identified trade-offs that may exist between principlist and

utilitarian recommendations, along with how actions taken to mediate ethical concerns may be at the cost of different principles.

Conclusion: A pragmatic approach considers engaging in a utilitarian analysis first due to the likelihood that health systems may have to weigh their actions in a very similar manner. Principlism can support and supplement analyses undertaken with a utilitarian perspective by identifying areas of concerns based on discordance from proposed age recommendations. However, it is apparent that no matter what age a bundled population genomic screen takes place there are going to be explicit and implicit trade-offs between conditions, dimensions, and principles.

4.2 INTRODUCTION

Population-level genomic screening for future disease risk is one of the ultimate goals of precision medicine.[1] Highly penetrant monogenic risk factors have been the focus over the past decade, and more recently genome-wide polygenic risk scores (PRS). Decision-making surrounding genomic screening has frequently focused on considerations related to independent conditions. However, most genetic testing now involves multigene testing, whole exome sequencing, or whole genome sequencing, making it likely that future screening will involve simultaneous testing for multiple disease risks (referred to here as 'bundled screening').[2,3] There are a variety of different considerations regarding implementation of bundled population genomic screen including the conditions included, the cost, who covers the cost, and who should perform a bundled population genomic screen. To date, there has been little focus specific to such bundled screening activities and so no analysis to guide their implementation, particularly in health systems.

The gene-disease pairs currently prioritized for population screening by the Centers for Disease Control and Prevention (CDC) are designated Tier 1 Genomic Applications. These are defined as including (1) genes with high penetrance (likelihood that a genotype will lead a disease phenotype), (2) that are associated with diseases associated with high mortality and/or morbidity, (3) with established and effective preventative intervention(s) for individuals carrying the gene, and (4) a knowledge base regarding the gene and condition associated with pathogenic and/or likely pathogenic variants.[4,5] These criteria assist with identifying genes and associated

conditions that have the potential for significant positive impact on public health if identified and utilized for preventative health services. Typically, considerations for responsible implementation are described on a disease-specific basis. In this analysis I will focus instead on considerations surrounding the implementation of a bundled screen of current Tier 1 Genomic Applications, including Familial Hypercholesterolemia (FH), Hereditary Breast and Ovarian Cancer (HBOC), and Lynch Syndrome (LS).

Evidence shows that accepted screening practices utilizing medical history fail to identify a large majority of individuals with monogenic risk for cancer and/or heart disease.[6,7] This suggests a significant opportunity for positive impact on patient health and overall clinical benefit through utilization of population genomic screening Pediatric and newborn population genomic screening have been discussed in much length but there is currently limited guidance related to the age of screening for adult populations as seen in "*A Proposed Approach for Implementing Genomics-Based Screening Programs for Healthy Adults"* by the National Academy of Medicine. [8,9,10,11,12] Realizing the impact of age of onset and current poor identification processes for these medically actionable conditions, attention and guidance related to timing of screening is increasingly important as screening efforts are likely to continue to expand. As result, the focus of this analysis will be:

At what age *should* a bundled genetic population screen take place?

Age of screening is important when considering implementation of a bundled population genomic screen because of the interaction between the age of onset for conditions included within the bundled screen and the degree to which treatment or intervention is tied to the age of the patient. The purpose of this analysis is not to provide a recommendation regarding a specific age to implement a population genomic screen but instead to assist with identifying the necessary components that require consideration when evaluating when to implement population genomic screening. While recommendations of the exact age for which to implement a bundled population genomic screen could be attempted for the 3 current Tier 1 applications, because the intention here is to explore considerations surrounding bundled screening more generally, I will instead explore the question of age in the context of providing screening "At Age of Majority" versus "After Age of Majority". This analysis will assist with identifying tradeoffs in relationship to broadening implementation of bundled population genomic screening in the context of an increase in the number of eligible conditions.

4.2.1 *At Age of Majority*

The age of majority in the United States is 18 years old and is the point in an individual's life where they are granted full legal and decision-making capacity.[13] This is the age at which they can vote, etc. and in many states also the age at which they can consent to medical care. As a result, this is likely the youngest age at which a patient could choose to voluntarily participate in a population genomic screening program and receive their applicable results.

4.2.2 *After Age of Majority*

"After Age of Majority" is referring to individual's 26 years and older. We are using this general cut-off in conjunction with how the U.S Department of Health & Human Services defines Young Adult Coverage related to health insurance. When individuals turn 26, they are no longer eligible to stay on their parent's health insurance plan and are forced to cycle off to establish coverage on their own behalf. We are using this distinction as a justification for the general bound defining "At Age of Majority" and "After Age of Majority".

4.2.3 *Use Case Definition*

The use case for analysis will focus on a "narrow bundle" utilizing the 3 current CDC Tier 1 Genomic Applications (FH, HBOC, & LS) due to the evidence regarding the potential for positive public health impact when applied in a population genomic screening program. As noted above, there will likely be additional Tier 1 conditions added over time and the characteristics of bundled screening highlighted in this analysis are intended to guide considerations for broadening a bundled population genomic screening program when this occurs. Additionally, for the purpose of this analysis, "population" will assume a demographically representative sample of the United States, which is important to note because the screening characteristics examined may differ depending on the population or sub-population being considered when evaluating implementation.

The bundled population genomic screen will include full sequence analysis of high penetrance genes and affiliated genetic return of pathogenic and/or likely pathogenic variants in those genes

related to FH, HBOC, and LS. Further, it will be assumed that patients will be offered the bundled population genomic screening in the context of a primary care wellness exam. We assume patients will also have access to these services through either insurance coverage and associated mechanisms or public health initiatives rather than paying for them completely out of pocket. Finally, it should be noted that health systems must consider implementation and/or adoption decisions in the context of budget constraints, fiduciary responsibilities, and complex regulatory landscapes but this analysis will be focused on evaluating ethical considerations related to the timing of population genomic screening.

4.3 Analysis Dimensions

Various dimensions related to bundled population genomic screening activities have been identified and selected for consideration based on a targeted literature review that included patient interviews and expert roundtable discussions.[14,15,16] Some explicit considerations identified were related to prevention, treatment, peace of mind, anxiety, worrying, and actions related to family and family members. For the purposes of this analysis, these dimensions will be sub-divided into three categories (1) Clinical, (2) Non-clinical, and (3) Family Planning for evaluating the benefits and harms associated with bundled population genomic screening.

4.3.1 *Clinical*

Clinical dimensions include aspects related to potential for effective disease prevention, appropriate treatment, and/or care management. When considering the prevention of disease this includes recommended prophylactic interventions and the degree that the recommended

treatment or intervention is dependent on timing. Appropriate treatment and care management will include the time sensitivity related to care, if there are recommendations and/or evidence identifying an optimal age for an intervention or care pathway, and if future care management involves additional screening, surveillance, or clinical activities.

4.3.2 *Non-Clinical*

Non-clinical dimensions include effects related to psychosocial effects, impacts affiliated with or because of bundled population genomic screening, and other experiences that patients face. These non-clinical dimensions may be difficult to quantify and/or highly personal to specific patients but require consideration because they can affect patient behavior, clinical utilization, and outcomes. Additionally, as more research is undertaken it is likely that a non-negligible contingent of individuals involved in a bundled population genomic screen may experience some sort of variant reclassification event or the identification of a new variant of significance. Variant reclassification can occur as underrepresented populations are included in research efforts or as the number of individuals sequenced for research purposes grows. Patients may exhibit behavior changes related to their genetic ROR such as obtaining life or long-term disability insurance, changes in work/life balance, or other broad personal decisions like taking a "bucket list" trip.

4.3.3 *Family Planning*

Family planning dimensions include actions or considerations related to conceiving, raising, or other actions related to children. The sex of the patient is also a component of family planning as it will impact the decisions and options available when an individual receives a positive genetic

result from a bundled population genomic screen. Individuals who do not already have a family may engage in clinical activities to eliminate or lower the likelihood of passing on a variant associated with a condition included with the bundled population genomic screening. In contrast, depending on the age in which bundled population genomic screening is implemented individuals may be actively family planning, trying to conceive, or pregnant which may affect their ability to engage in preventative actions or interventions related to conditions included in the bundled population genomic screen.

4.4 Narrow Bundle Conditions

Having identified dimensions for consideration related to bundled population genomic screening it is necessary to discuss them in the context of conditions included in the screen (Figure 4.1).

4.4.1 *Familial Hypercholesterolemia*

Receiving a positive genetic ROR leads to a recommendation of lipid lowering therapy (LLT) such as statins and in more severe cases possible PCSK9 or ezetimibe.[17] Individuals with FH benefit from engaging in LLT earlier in their life in an effort to limit or lower their lifetime exposure to low-density lipoprotein (LDL) cholesterol which is associated with early onset and increased risk for cardiovascular disease (CVD).[18] Statins are relatively well tolerated with minimal adverse events, are not particularly expensive, and are typically covered by health insurance.[19]

Non-clinical dimensions of FH may affect individuals in a variety of ways due to the complex nature of CVD risk. Lifestyle, environmental, and other factors can all affect the likelihood that an individual experiences CVD and LLT is intended to lower the increased risk of premature CVD that individuals with FH experience compared to the general population. However, this does not mean that the risk of experiencing CVD is eliminated so this may cause individuals mental distress or affect their quality of life if they are changing their behavior to minimize their risk of experiencing CVD. Additionally, there are noted quality of life dis-utilities experienced by individuals who do have CVD.[20],[21] For example, individuals who experience a severe heart attack may have to restrict the types of physical activities they engage in or other activities that they usually enjoy engaging in. The US Preventive Services Task Force (USPSTF) recommends that patients 40 years and older get screened for lipid disorders and take statins if they have more than a 10% 10-year risk of cardiovascular risk.[22,23]

Family planning dimensions associated with FH affect males and females in different ways. Women who are of childbearing age and are attempting or want to conceive are recommended to stop statin therapy. This phase of stopping LLT often persists through the period where a woman is trying to conceive, during pregnancy, and during the period of breast feeding or additional conception/family planning. Stopping or altering LLT in this way affects women's' ability to mitigate the risk of experiencing increased LDL cholesterol levels and CVD.[24,25] In contrast, males do not have these requirements and are able to more intentionally manage their risk of CVD via LLT during their reproductive years.

4.4.2 *Hereditary Breast and Ovarian Cancer*

The clinical dimensions of HBOC include increased and/or earlier surveillance and screening upon receipt of a positive genetic result.[26,27] Additionally, prophylactic surgeries may be recommended for risk reduction, including bilateral mastectomy and/or salpingo-oophorectomy. However, when an individual does engage in surgical interventions these have been shown to significantly lower future risks of developing either breast or ovarian cancer depending on the intervention undertaken.[28] Considerations regarding false positives and false negatives likely have large impacts on the effects of bundled genetic population screening. Individuals who undergo either a mastectomy or oophorectomy may face immense potential harm if they are subject to a false positive.[29] On the other hand, false negatives may lead to an increased incidence in preventable cancers due to less intensive or later surveillance engagement and fewer prophylactic interventions by patients.

Non-clinical dimensions of HBOC may present significant psychosocial impacts for patients, especially those that experience a false positive result, or the reclassification of a variant previously identified as being pathogenic or likely pathogenic.[30,31] Additionally, even for patients who are accurately identified there are well noted and abundant concerns regarding the effects, including physical, mental, and emotional, from undergoing either mastectomy or oophorectomy as a prophylactic intervention. These effects may be highly individualized and are potentially challenging to quantify broadly and accurately.[32]

The family planning dimensions of HBOC are nuanced and can lead to emotional distress.[33] Prophylactic interventions specifically may limit a family's ability to conceive a child. The timing associated with prophylactic interventions can be variable depending on the life stage of an affected individual and their associated personal and reproductive goals and desires. As a result of this females may choose to hold off from engaging in prophylaxis during their childbearing years but this may put them at increased risk of experiencing HBOC, as variant carriers have a lifetime risk of breast cancer between 45% to 75% compared to 13% for the general population.[34,35,36] It is also noteworthy that individuals, both male or female may engage in clinical activities to limit or eliminate the likelihood of passing down genetic variants associated with HBOC to their children. This may come at significant financial, emotional, or other costs. Concern with passing down these types of variants associated with increased risks is noted within the literature.[37,38,39]

4.4.3 *Lynch Syndrome*

Clinical dimensions of LS include both increased surveillance modalities and prophylactic surgeries for affected individuals. The focus of LS is often colorectal cancer, but it is important to note that affected individuals may also have increased risk for developing cancers that affect the endometrium, ovaries, stomach, small intestine, kidney, brain, liver, or prostate.[40,41] Surveillance specific to colorectal cancer includes engaging in colonoscopy at age 20-30 or 2-5 years prior to the earliest colon cancer diagnosis in a family depending on the variant, endoscopy at ages 20-30, and taking daily aspirin to reduce future risk.[42] If a polyp is identified, then the removal often will take place during the colonoscopy and/or endoscopy. If cancerous polyps are

identified, then considerations for colectomy are required as a form of prophylaxis. The ability to remove polyps during these procedures may also limit the need for prophylactic interventions. Furthermore, engaging in a colectomy does not always necessitate the full removal of the colon and may be either a subtotal or hemi colectomy.[43] Females and Males both experience increased risk of CRC because of LS. Females may experience increased risk of endometrial cancer.[44] Additional prophylactic considerations may include oophorectomy and/or hysterectomy.[45]

Non-clinical dimensions of LS include costs associated with false negatives or false positives for LS and considerations related to quality of life due to surveillance through colonoscopy and/or endoscopy.[46,47] Additionally, LS carriers suffer an increase in depression and anxiety scores after their disclosure. Genetic information may increase or create psychosocial burdens for carriers as they are encouraged to connect with their family members to share the results of their disclosure. Burden may also be associated with future screening and prevention recommendations.[48]

Family planning considerations associated with LS include actions associated with screening, prophylaxis, and pre-implementation genetic diagnosis. Engaging with increased surveillance or the removal of polyps for colorectal cancer should not interfere with family planning activities for either males or females.[49] Females who engage with either an oophorectomy or hysterectomy may be limited or incapable of conceiving a child depending on when they are required to engage with prophylaxis.[50] If a patient delays a prophylactic intervention this may lead to an instance of a preventable cancer and unnecessary risks. Patients have noted that they would consider preimplantation genetic diagnosis to prevent passing LS variants on to their offspring.[51]

The three dimensions will be used to identify benefits and harms along with ethical, clinical, and implementation trade-offs. This will take place through the vehicle of Utilitarian and Principlist analyses. To begin I will use Utilitarianism to evaluate the age at which a bundled population genomic screening, either "At Age of Majority" and "After Age of Majority", should take place.

4.5 UTILITARIANISM

Utilitarianism claims that an act is morally right if and only if it maximizes the good or utility for the largest number of people.[52] Utilitarianism is not focused on the distribution of benefits or to whom the benefits are distributed when utilizing a population genomic screen. For example, if 100,000 individuals are screened and only 10 people gain 15 years to live with others receiving no benefit this would be preferable to 100 people gaining an additional year to live. The 100 people get 100 additional years in the aggregate which is less than the 150 additional years of aggregate benefit from the 10-person scenario. This may affect groups of patients differently based on the distribution or general make up of a population. It is important to restate that for the purposes of this analysis I will be considering a population generally representative of the demographics of the United States.

In the context of utilitarianism, health economics and outcomes research (HEOR) such as a cost-utility analysis (CUA) can assist with providing insight into what actions maximize the benefit for a population.[53] More specifically, this type of evidence can impact the decision-making process when considering adoption or implementation decisions in a healthcare setting. For the

purposes of this analysis, the utilitarian perspective will focus on the clinical dimensions of a bundled population screen. This analysis will focus on the clinical benefits and risks related to surveillance, preventative therapeutics, or interventions, and/or the need for surgical prophylaxis. These clinical benefits and risks will need to be contextualized within the age of onset for disease. From a utilitarian perspective the bundle will in many ways be considered the sum of its parts, i.e., the combination of benefits resulting from the individual disease states or conditions (Figure 4.2).

FH is a condition that has an "early" age of onset insofar as the aggregate effects of increased lipid exposure begin prior to the experience of a cardiovascular event such as MI or Stroke.[54] As a result, surveillance and preventative intervention serve to provide meaningful benefit through actions such as lipid lowering therapy, cholesterol level screening, and other clinical actions. Research has shown that children undergoing population genetic screening is likely cost-effective and has benefit in a non-US setting.[55,56] Additionally, the Simon-Broome diagnostic criteria, which considers LDL cholesterol levels, clinical history, family history, and molecular diagnosis, can be applied to children under the age of 16 which indicates that there is value in early identification.[57,58] While there are potential side effects of lipid lowering therapy such as diabetes mellitus, and muscle pain or weakness, the overall safety profile of lipids suggests that they are relatively well received by most patients.[59] This leads to expectations for a comparatively large net benefit through preventative actions and surveillance. FH diagnosis does not have an associated prophylactic surgery that will affect the risk level of affected individuals but does have therapeutic options. Preliminary results from Spencer et al. indicate that

population genomic screening is more cost-effective for younger patients (20-year- old compared to 35-year-olds).[60] Lowering patients' cholesterol levels via statin use has high lifetime benefits and relatively low iatrogenic risks, screening at the "Age of Majority" is preferred.

HBOC recommendations include increased surveillance for affected individuals such as mammography or MRI. Estimates indicate that the majority of individuals with *BRCA* mutations will experience breast cancer diagnosis after the age of 30 so prophylactic surgery is recommended after this due to its invasive and irreversible nature.[61] Genetic testing for HBOC is recommended for women who have a family history or for women who are under 60-year-olds and have experienced triple-negative breast cancer.[62] The US Preventive Services Task Force found that there is additional need for research related to the optimal age for risk assessment and genetic screening for variants associated with *BRCA1/2*.[63] *Guzauskas et al.* found that population genomic screening was likely cost effective for 30-year-old women.[64] Due to the availability of increased surveillance, the majority of cancer diagnosis occurring after age 30, and recommendation of prophylaxis after age 30, screening "After the Age of Majority" is preferred.

Defining features of the LS clinical dimension include early engagement in surveillance for polyps which is a benefit to patients. If a patient with a polyp is identified, then this can be sent to pathology for analysis and can also be removed during a colonoscopy or endoscopy. This engagement with annual surveillance can significantly decrease the likelihood that a patient will experience late-stage cancer diagnosis or unknown cases of cancer.[65,66] Additionally, these types of surveillance activities are considered low risk activities. After a patient has a cancerous polyp

identified it may be necessary to consider a prophylactic surgery such as a colectomy or an oophorectomy if a patient is found to be affected by endometrial or ovarian cancers (recommended after childbearing has been completed). Individuals with LS are recommended to begin screening via colonoscopy annually or biannually at the age of 25 or 2-5 years before the youngest familial CRC diagnosis, consider annual endometrial sampling or transvaginal ultrasound (TVUS) if a women, or esophagogastroduodenoscopy (EGD) beginning at age 30 should be considered.[67,68,69,70] Realizing the availability of surveillance, the recommendation for screening activities to begin at age 25, and prophylactic interventions connection to surveillance, screening "After Age of Majority" is preferred.

For the purposes of this analysis, we will assume that the prevalence of conditions and variants within the population is relatively similar therefore allowing for a simpler evaluation of the bundled screen's benefit. However, as additional conditions are considered within a bundled screen the prevalence of the conditions may need to be considered in relationship to the benefits expected from engaging in the screening activities. Both HBOC and LS present a recommendation for "After the Age of Majority" while FH is "At Age of Majority" based on the analysis of clinical benefits, guidelines, and recommendations through the lens of utilitarianism. Therefore, it would be recommended that the "Narrow Bundle" be implemented and performed "After the Age of Majority". It is important to note that screening "After the Age of Majority" may result in possible negative effects for individuals who ultimately test positive for FH such as delayed lipid lowering therapy and associated increases in lifetime cardiovascular event risk.

As noted, the utilitarian approach puts specific focus on the clinical dimensions of a bundled population screen. However, there are additional dimensions that are not easily integrated into these considerations. These may include both the non-clinical and family planning dimensions previously discussed. To build on the utilitarian analysis the "narrow bundle" will also be evaluated utilizing the ethical framework of principlism.

4.6 PRINCIPLISM

Principlism is an analytical approach that applies four ethical principles to a consideration of the morality of an action. These four principles include respect for autonomy, justice, beneficence, and non-maleficence.[71,72] Respect for autonomy refers to an individual's ability to make decisions for themselves without coercion or other forms of pressure. The aim of this principle is to respect the wishes of the patient. Justice refers to considerations related to the fair distribution of the benefits and harms or costs of an action. Beneficence refers to acting to benefit others which may involve preventing harms or actively promoting some sort of specific benefit(s). Non-maleficence refers to not intentionally causing harm or avoiding actions that are expected to harm individuals. These four principles are all utilized to evaluate ethical questions and provide a normative answer in conjunction with trade-offs that may exist between the four principles.

Components of the non-clinical dimension that will be emphasized include psychosocial impacts, anxiety, and patient preferences/experience. The family planning dimension includes components such as patient sex, considerations related to conception, reproductive planning activities, and activities associated with raising a child. The analysis will identify areas of

potential discordance between the recommendation of implementing a Narrow Bundle population genomic screen “After the Age of Majority” that may require additional considerations in the context of responsible health system implementation (Figure 4.2).

4.6.1 *Respect for Autonomy*

Respect for autonomy is relevant to considerations surrounding family planning. Individuals who find themselves subject to a Tier 1 genetic risk, for example, may want to take steps to limit the likelihood of passing the risk variant to future offspring by engaging in preimplantation genetic diagnosis or related activities. In such cases, having the information at the “Age of Majority” may provide additional time for consideration and planning. A separate concern includes decisions regarding prophylactic or therapeutic interventions with respect to their timeline for attempting to conceive a child. An individual may wish to delay prophylactic intervention such as a mastectomy for HBOC or need to stop a therapeutic intervention such as statin therapy for FH when intending to conceive a child.[73,74] Implementing a narrow bundle population screen “After Age of Majority” therefore interferes with a patient’s autonomy by limiting their ability to make such decisions in a timely fashion.

Waiting until “After the Age of Majority”, especially in families with a history of a condition(s), may lead to unnecessary angst or anxiety related to not knowing their variant status within the non-clinical dimension. Individuals may want to engage in a narrow bundle population screen at the “Age of Majority” to have to ability to inform family members of potential risk earlier and engage in potential cascade screening activities. However, this may raise issues related to family

members' autonomy, insofar as it may not respect their right not to know their own genetic status.[75] Additionally, Individuals may not want to engage in a narrow bundle population screen if they feel that knowing a result will affect their identity. For example, clinical actions, such as mastectomy in females, have been noted to have a negative impact on self-image, body image, identity, or other factors.[76,77]

4.6.2 *Justice*

Justice considerations related to engaging in a narrow bundle population genomic screen "After the Age of Majority" include the likelihood of being affected by a condition in the bundle skews to a specific sex at the "Age of Majority", such that some demographic groups may be unfairly penalized. In our narrow bundle use case, for example, females may experience increased impact related to their family planning and non-clinical dimensions due to effects of prophylactic surgery such as mastectomy and/or oophorectomy.[78,79,80] Additionally, when a female becomes pregnant, they are not able to stay on statin therapy, increasing their risk of experiencing increased LDL cholesterol levels and/or a cardiovascular event. Stopping statin therapy can increase an individual's short-term and lifetime risk of experiencing a cardiovascular event. Engaging with a narrow bundle population genomic screen at the "Age of Majority" may give additional time to mitigate these potential harms associated with increased cardiovascular risk. Receiving this information earlier may also increase an individual's potential benefits through utilization of different family planning activities including when to attempt conception, how many children to have, and the timing between utilizing therapeutic interventions and conception(s).

While not necessarily discordant from the utilitarian recommendation of engaging in narrow bundle population genomic screen “After the Age of Majority”, it is important to note that there are potential harms that require consideration in the non-clinical dimension. For example, individuals who receive a prophylactic intervention may experience negative effects that are traditionally difficult to quantify or are extremely individualized such as identify conflicts, guilt, or anxiety. These non-clinical dimensions were not captured in the utilitarian analysis that utilized clinical dimensions to assess when a narrow bundle population genomic screen should be implemented.

4.6.3 *Beneficence*

The utilitarian analysis recommends that the narrow bundle population genomic screen take place “After Age of Majority” but it is necessary to consider that not all individuals may be best served by this approach, raising broader beneficence concerns. Individuals may feel they are being exposed to unnecessary screening, especially since many patients will likely not receive a positive result, but this contrasts with providing benefits to the population at large. It may be necessary to provide opt-out options for patients who do not feel they will benefit from a narrow bundle population genomic screen in conjunction with educational resources regarding the purpose and potential benefits of such a program.

Additionally, when implementing a narrow bundle population genomic screen in a health system it is necessary to ensure that the care provided because of genetic results being identified is

improved compared to not engaging in a screen. This will require clear training and familiarity with the clinical care pathways that providers should consider for individuals who receive genetic screening results. Provision of educational programs and access to genetic counseling can assist with balancing benefits against risks such as anxiety or psychosocial impacts. Intentional design, implementation, and utilization of these types of genetic counseling and education programs can improve impacts that individuals experience from narrow bundle population screen.

4.6.4 *Non-Maleficence*

Non-maleficence and beneficence may appear in discordance with one another. One example is an opt-out option for the narrow bundle population genomic screen, individuals may wish to opt-in to screening for a particular condition or disease prior to the recommended time of "After Age of Majority". For example, it appears that earlier FH screening has clinical and other benefits so a health system may need to consider options for a genetic FH screen for patients who have clinical or other reasons for requesting these actions. However, for the purposes of this analysis we are focused on a bundled screen so it is important to note that individual conditions within that bundle may challenge the timing of a screen doing no harm. An opt-in option, or an awareness that this may happen, would ensure that individuals and other stakeholders are able to act in way that limits patient harm while still enacting a pragmatic implementation of a narrow bundle population genomic screen.

Additionally, there is potential for undo harm to occur because of engaging in a narrow bundle population screen at too young an age. Specifically, the possibility of exposing individuals to information that leads to unnecessary prophylactic interventions such as a mastectomy, oophorectomy, or colectomy for either HBOC or LS would be doing undue harm. It is important to understand where non-maleficence may exist within a bundled screen as to identify explicit trades-offs and limit harms.

4.7 CONSIDERATIONS

Utilizing the lens of principlism when evaluating the question "At what age should a bundled genetic population screen take place?" allows for considerations outside of the clinical dimensions such as the non-clinical and family planning dimensions. This is important due to the focus utilitarianism places on the clinical outcomes when evaluating how to maximize the benefits of a bundled genetic population screen. The non-clinical or family planning dimensions may be difficult to quantify but can be highly impactful as shown above.

Principlism is not just useful for broadening the dimensions considered in relationship to the age for implementation pf a bundled genetic populations screen. It also provides a distinct approach to evaluate trade-offs that may exist and how actions taken to mediate concerns may be at the cost of different principles. For example, addressing an issue with respect to autonomy may raise concerns with regards to other principles such as non-maleficence. Specifically, by allowing an opt-in program, to respect patient's autonomy, a genetic population screening program may expose patients to undue harm and put a provider in at risk of failing in their duty to do no harm.

Similarly, justice considerations may run counter to respect for autonomy. Implementing a bundle population genomic screen fairly may, for example, require restrictions related to individuals' autonomy. This is not to say that it is not considered but that the respect for autonomy principle could be more fully fulfilled but would come at a cost to justice. An example of this is a bundle population genomic screen that is given universally at a certain age for purposes related to fair process and distribution of resources, but individuals may wish to utilize the screen at an earlier or later age, either for reasons of personal preference or other factors.

Furthermore, it is important to realize that while this analysis assumed that a population was representative of the US population this is not the case for many, if not most, health systems. As a result, when making decisions related to the age of implementation of a bundled genetic population screen it will be important to provide appropriate demographic and population preference information that can lead to important insights when utilizing a principlist approach including non-clinical and family planning dimensions.

4.8 RECOMMENDATIONS

For the narrow bundle population genomic screen use case described here consisting of FH, HBOC, and LS, we recommend that the age of implementation is "After the Age of Majority". This is because of the availability of cancer surveillance activities, recommendations for screening activities to begin at age 25, and prophylaxis to be considered after age 30 for HBOC and LS. However, it is important to remember that the purpose of this analysis was less about

providing an actual recommendation for what age a bundled population genetic should be implemented. This paper aims to assist health systems evaluating at what age a bundled genetic population screen should take place.

Furthermore, a pragmatic approach for answering this question engages the utilitarian approach first due to the likelihood that health systems may have to weigh their actions in a very similar fashion based on budget constraints, fiduciary responsibilities, and complex regulatory landscapes. Additionally, the clinical dimension may be more easily quantified when compared to non-clinical and family planning dimensions as noted previously. Realizing this, it appears that principlism can support and supplement analyses undertaken with a utilitarian perspective by identifying areas of concerns based on discordance from utilitarian recommendations and is specifically important in this case because it allows for consideration of non-clinical and family planning dimensions. It is also apparent that while the goal is to present an optimal age for the implementation of bundled population genomic screens there are likely going to be explicit and implicit trade-offs. This is further apparent from the paper's focus on bundled screening which will likely increase in capacity and clinical applicability over time.

4.9 FUTURE WORK

Future work in this space can assist with providing broader context for considerations of conditions not included as CDC Tier 1 genomic applications. These may have different dimensional considerations including prevalence, modes of inheritance, and condition characteristics such as age of onset, severity, and other components. Explicit evaluation outside

of a theoretical context focused on non-clinical and family planning dimensions would also add insight into how to address areas of ethical discordance more appropriately. This type of work may allow for more accurate assessment of individuals' preferences providing more appropriate and thorough considerations regarding when the age at which a bundled population genomic screen should be implemented.

4.10 TABLES & FIGURES

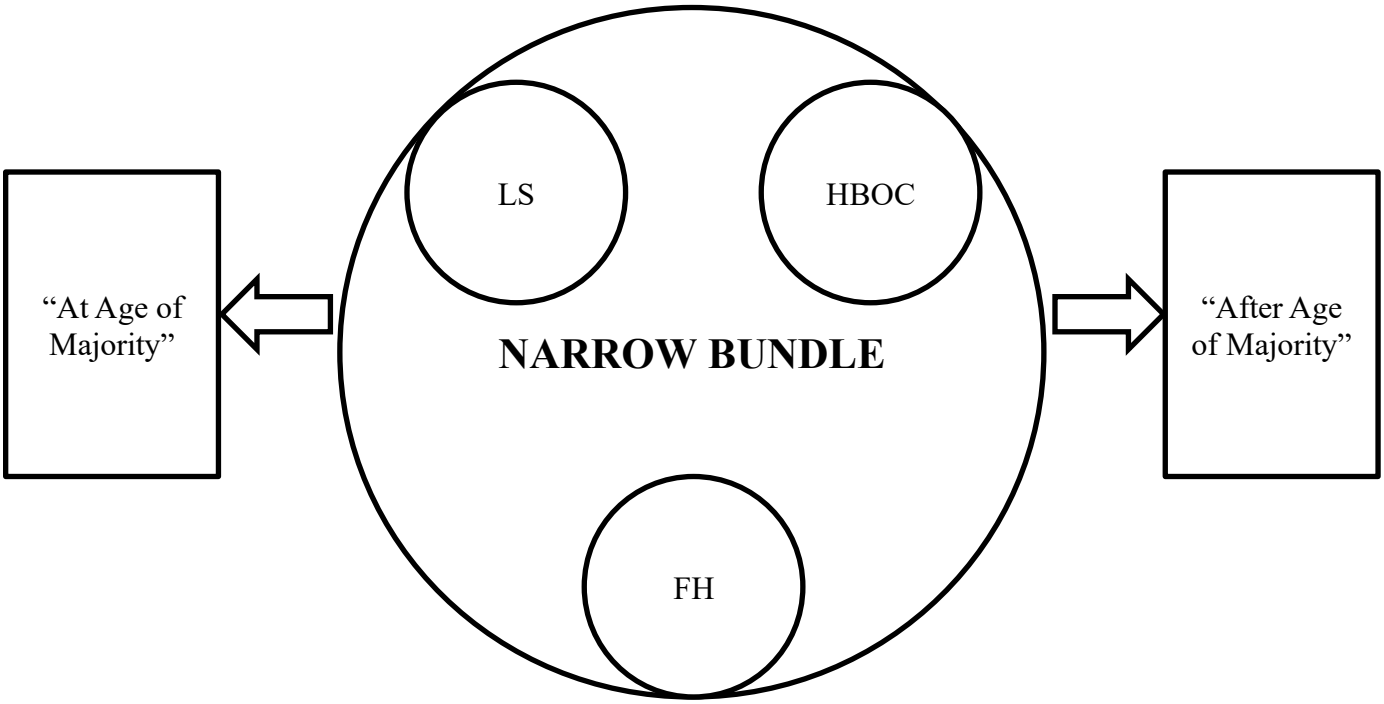

Figure 4.1: Narrow Bundle Use Case & Age

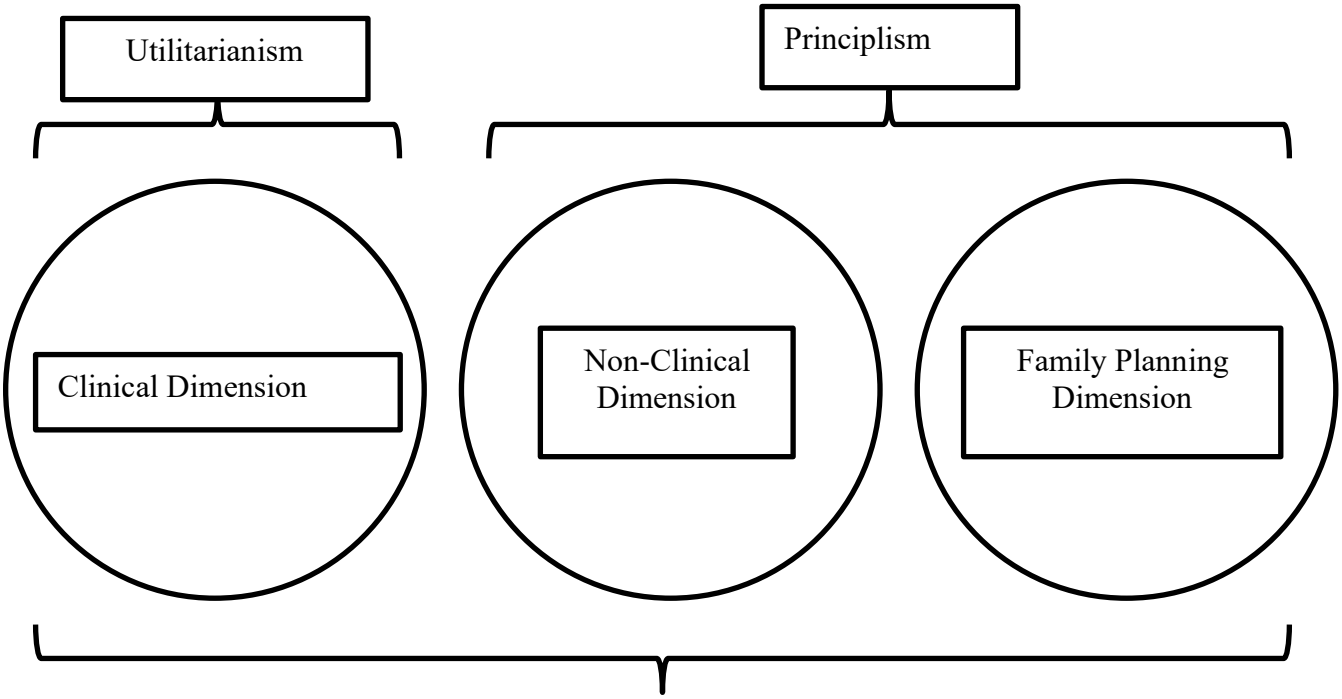

Figure 4.2: Analysis Dimensions

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Chapter 5. CONCLUSIONS

The contents of this dissertation have worked to evaluate population-wide genomic screening through an analysis of longitudinal patient data, decision modeling approaches, and normative ethical analysis with familial hypercholesterolemia and bundled screening as use cases. In the context of the effect of returning FH results to patients, we found that there may be reduction in LDL cholesterol levels and LDL cholesterol level trajectories over time attributable to ROR which is suggestive of a beneficial clinical effect. Our results were limited by a lack of statistical power and suggested positive trends in relationship to patients achieving target LDL cholesterol levels. As population genetic screening implementation continues to grow, our findings indicate that larger populations affected by FH and improved study designs should be included in future studies to provide better insight into the true effect sizes of ROR on LDL cholesterol.

The economic evidence suggests that at current genomic testing costs population FH screening is not cost-effective at a willingness to pay threshold of $150,000 per QALY. Genomic testing costs are a large driver in the results of our cost-effectiveness analysis along with the relative risk associated with having FH, FH population prevalence, and the effect size of ROR. Engaging with a population genomic screen at a younger age improved the overall cost-effectiveness and improved health outcomes for individuals affected with FH. While our results do not indicate cost effectiveness, reducing genomic testing costs or including FH testing within a broader multiplex screening panel may improve clinical and economic value for a population genomic

screen. These findings provide context for public health professionals and policy makers when considering preventative screening actions to reduce societal burden of cardiovascular disease.

While the first two analyses focused on FH, the results of the economic analysis indicated that considerations including multiple diseases or conditions in a population genomic screen had merit, especially in context of minimal population genomic screening guidance related to bundled screening within the literature. When considering the age at which a bundled screen should be implemented, we found that a pragmatic approach considers engaging in a utilitarian analysis first. It is likely that health systems weigh their actions and decision-making processes in a very similar manner opting to maximize the systems utility or benefit with less focus on the distribution of or individual considerations related to these benefits. Principlism can support and supplement analyses undertaken with a utilitarian perspective by identifying areas of concerns based on discordance from proposed age recommendations. However, it is apparent that no matter what age a bundled population genomic screen takes place there are going to be explicit and implicit trade-offs between conditions, dimensions, and principles. This analysis' use case was made up of HBOC, LS, and FH but it aims to provide an approach and framework for healthcare systems considering implementation of bundled screens with conditions including, but not exclusive to, CDC Tier 1 Genomic applications.

While the promise of population wide genomic screening is great, its true impact depends on variety of variables including patient's response to receiving their results, taking appropriate clinical action, and overall economic value. The analyses undertaken in this dissertation allowed

for estimates of the effect of returning FH results on patient's behavior and outcomes related to their therapeutic status and LDL cholesterol levels, the long-term economic value of FH population-wide genomic screening, and a framework for normative ethical considerations on implementation of bundled population genomic screening from a healthcare system perspective. This dissertation aims to better inform considerations about population wide genomic screening utilization and associated effects on patients' outcomes and behavior. We hope that this information will assist with future policy development and considerations for population genomic screening implementation and investment into high impact areas for future research.

VITA

Scott J. Spencer earned his BS in Molecular Genetics and Chemistry from The Ohio State University. Scott received his MPA at The Evans School of Public Policy and Governance with a focus in science policy and public finance, where he completed his Master's Capstone project, *Life Insurance and Long-Term Disability Insurance: The Genetic Information Nondiscrimination Act of 2008.* Scott concurrently earned his MA in Bioethics at the Department of Bioethics and Humanities at the University of Washington, where he completed his Master's thesis, *Ethics and Economics: Value-Based Pricing as a Tool for Justice in Cancer Treatment.* He also completed his PhD in Public Health Genetics investigating the effect, value, and ethics associated with population-level genomic screening. Scott has deep formal training in quantitative, computational, policy, behavioral and economic analysis. Additionally, his research interests intersect with entrepreneurship, commercialization for healthcare and precision medicine initiatives, digital health, and life sciences technologies.