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# Cost-effectiveness of cascade genetic testing for familial hypercholesterolemia in the United States: A simulation analysis

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ABSTRACT

*Objective* There is no coordinated cascade testing program for familial hypercholesterolemia (FH) in the U.S. We evaluated the contemporary cost-effectiveness of cascade genetic testing relatives of FH probands with a pathogenic variant.

*Methods:* A simulation model was created to simulate multiple family trees starting with progenitor individuals carrying a pathogenic variant for FH who were followed through several generations. This approach allowed us to examine a family tree that had grown sufficiently to have large numbers of relatives across multiple degrees of relatedness. The model estimated costs and life years gained (LYG) when cascade genetic testing was implemented for relatives of FH probands identified through standard care who were at or older than designated age thresholds (5, 10, 15, 20, 25, 30, 35, 40). Costs were valued in 2018 U.S. dollars. Future costs and LYG projected by the model were discounted at an annual rate of 3%.

*Results:* For 1st degree relatives, cascade testing at every age threshold resulted in a positive number of average LYG per person, though this number decreased as testing was started at higher age thresholds. Testing was not cost-effective if initiated at an age threshold of 40 and older but was cost-effective at younger age thresholds, with a discounted cost per LYG per person of less than $50,000. For 2nd degree relatives, testing was cost-effective with a screening age threshold of 10 but no longer cost-effective at a threshold of 15 or higher. In more distant relatives, cascade genetic testing was not beneficial or cost-effective.

*Conclusions:* Based on our simulation model, cascade genetic testing for FH in the U.S. is cost-effective if started before age 40 in 1st degree relatives and before age 15 in 2nd degree relatives.

## 1. Introduction

Familial hypercholesterolemia (FH) is an autosomal dominant disorder associated with an increased risk of premature coronary heart disease (CHD) due to lifelong elevated levels of low-density lipoprotein-cholesterol (LDL-C) [1,2]. The estimated prevalence of heterozygous FH is approximately 1:250. Nearly 20 million people are affected worldwide but more than 90% remain undiagnosed [3]. Early detection and treatment can reduce risk of adverse outcomes such as myocardial infarction and sudden cardiac death in those with FH.

Current guidelines recommend cascade testing of family members of patients with FH [4], given the significant public health implications. Prior studies have utilized economic models to evaluate the cost-effectiveness of cascade testing programs in several European countries [5–8]. However, a coordinated testing program for FH does not currently exist in the U.S., though some have been evaluated [9–11]. A previous cost-effectiveness analysis in a U.S. setting in 2014 only assessed a male population and found that cascade genetic testing was not cost-effective [12]. There have been significant developments since, including marked reductions in the cost of genetic testing due to advances in next generation sequencing and availability of statins as generic medications [13].

Given the public health burden of FH, there is an urgent need to conduct a contemporaneous analysis of the cost-effectiveness of cas-

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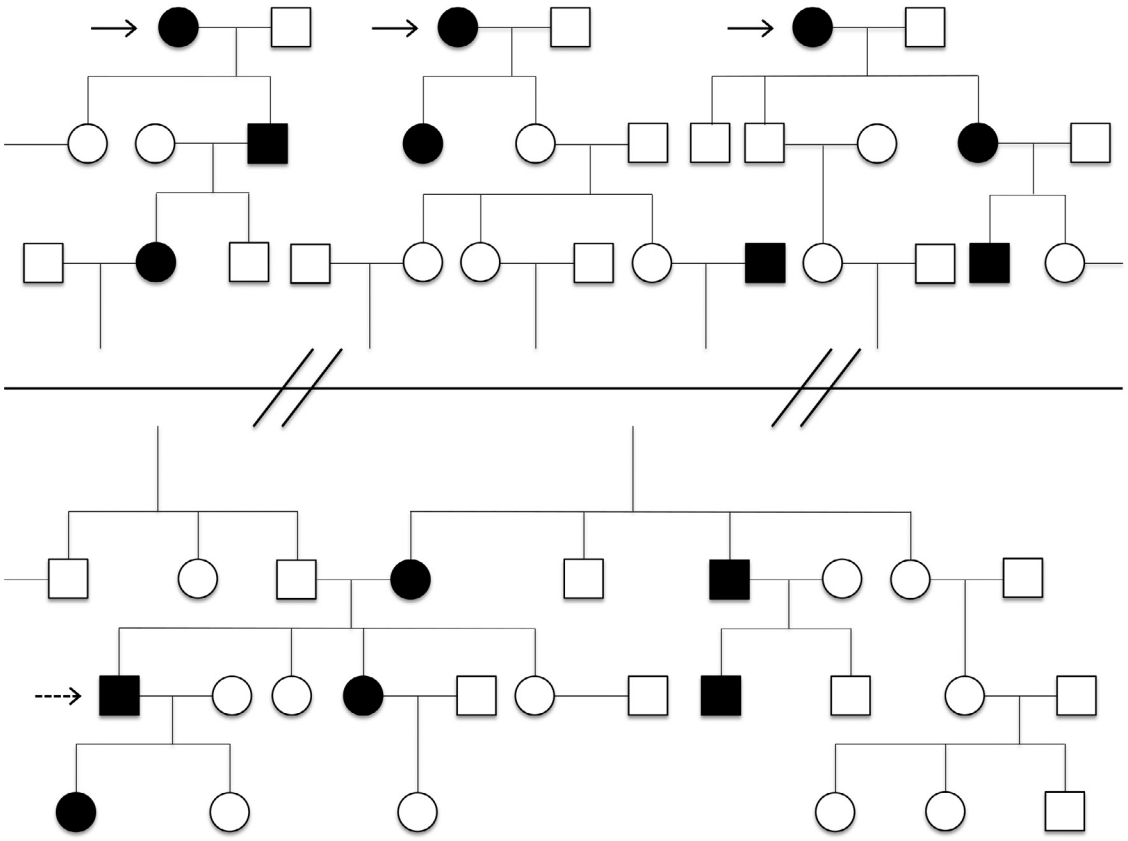


**Fig 1.** Simulation of family trees arising from a progenitor population (solid arrows) that has familial hypercholesterolemia (FH). Once a proband (dashed arrow) is identified through standard care, cascade testing of his/her relatives is initiated. Circles depict women. Squares depict men. Solid circles/squares depict FH positive individuals.

cade genetic testing in family members of patients with an identifiable pathogenic variant. Using a novel simulation approach, we attempted to provide an updated and comprehensive estimate regarding the cost-effectiveness of cascade genetic testing for FH and assess whether it is affected by the age at which testing is initiated in family members or the degree of relatedness to the proband. We followed the CHEERS guideline for reporting economic evaluations [14].

## 2. Methods

### *2.1. Simulation model*

There is not enough empirical data to estimate the number of pathogenic variant-carrying relatives of an FH proband in order to determine the cost-effectiveness of cascade testing family members. Therefore, we generated simulated family trees where the pathogenic variant was transmitted in an autosomal dominant mode through generations, using Arena® version 14.0 simulation software (Rockwell Automation, Coraopolis, PA) (**Fig. 1**). The creation of these simulated family trees used multiple sources of information including the United States Census Bureau Fertility Data [15] (see **Supplemental Methods** for more details). The model evaluated three populations: (1) a model validation population with an FH negative progenitor population used to validate the simulation model output against actual life expectancy (LE) and family size statistics from historical data; (2) a simulated population with an FH positive (FH+) progenitor population where cascade testing is not implemented to identify patients with FH; (3) a simulated population with an FH+ progenitor population where cascade testing is implemented and patients with FH are identified and treated.

The simulation model followed randomly generated family trees based off U.S. Census information, with each family tree starting with an FH+ female. Every year from 1900 to 1999, 10 FH+ females, which is hereafter referred to as the progenitor population, were “born” into the simulation, resulting in 1,000 family trees per simulation run. The simulation was then run with 50 replications to account for variation, resulting in 50,000 family trees for analysis. The year 1900 was chosen because according to U.S. census information, women are largely done having children by the age of 40, and there is good census information regarding children born to mothers starting in 1940. The simulation model assumed that the progenitor population would survive until age 40. This was done to reduce the size and complexity of the simulation model by reducing the number of replications needed to generate a sufficient number of FH+ descendants in the model for statistical analysis. The progenitor population was not used in any analysis.

The children of the progenitor population, and all subsequent offspring, were generated using the U.S. Census information for the number of children born to women at various ages. If the simulated female offspring did not live until age 40, their offspring were adjusted accordingly. For example, if the female only lived until age 30, her offspring would be modeled off known census information for a female at age 30. We could not find information regarding the number of children born to men. However, there is U.S. Census information regarding the likelihood of marriage for men as well as the age differences between males and females. If a male married, we modeled their offspring using their spouse. If a married male was FH negative, we still modeled their offspring in order to complete the family tree for accurate cost analysis.

Each family tree was then followed through 8 generations, with approximately 6 million simulated individuals at the end. A 50% probability of inheriting an FH variant was incorporated. The 1999 to 2012 United States National Health and Nutrition Examination Surveys reported a prevalence of 0.40% (95% confidence interval (CI) 0.32-0.48%) for FH in the U.S. [16]. During model building, it was determined that

there needed to be a 0.5% chance of an individual within the simulated family tree marrying someone outside with FH in order to maintain the estimated prevalence in the general population.

The model was initially run with all women in the progenitor population as FH negative in order to validate the simulation model output against actual LE and family size statistics from historical data [17]. After validation, the progenitor population was set as FH+ because we were only interested in the future offspring of an FH+ individual. The model was also validated by comparing the number of children born to women, as well as the number of individuals alive at a given age in our simulation, with national averages.

Life years gained with cascade testing was determined based on LE data extrapolated from a United Kingdom (UK) cost effectiveness analysis, which has detailed information regarding LE at various ages for the general population as well as FH individuals who are treated and untreated [7,18]. Assuming that LE for both the UK and U.S. populations have a similar mathematical function, the UK general population data were transformed to mirror the U.S. general population, and this function was then applied to the UK FH treated and untreated populations to obtain estimated LE for the U.S. FH treated and untreated populations, respectively.

Our simulation evaluated the potential benefit of cascade testing by comparing the average LE in a simulated population where cascade testing is implemented and patients with FH are treated, to the average LE in a simulated population where patients with FH are not treated. We refer to the latter population as the baseline state. We acknowledge that in practice, some patients with FH (with or without a clinical diagnosis) may receive treatment for hypercholesterolemia in the baseline state where there is no cascade testing. Therefore, our simulation assumed that 17% of FH patients in the baseline state would be treated with a lipid-lowering therapy by the age of 60 based on the National Health and Nutrition Examination Survey data showing that 17% of adults aged 40-59 take cholesterol-lowering medications [19]. Though this estimate reflects treatment in the general population, it would be expected that in the baseline state, without targeted testing programs, the proportion of FH patients that are treated should be similar to the proportion for the general population.

### 2.2. Cascade genetic testing of relatives

The identification of probands with FH in the year 2018 was presumed to occur through standard care. Therefore, there were no costs associated with identifying a proband. The model then looked at extended family members with various degrees of genetic relatedness including 1$^{st}$-degree relatives, 2$^{nd}$-degree relatives, 3$^{rd}$-degree relatives, and up until 6$^{th}$-degree relatives (**Supplemental Table 1**). The model was also run with different age thresholds at and above which genetic testing would be initiated for these family members (ages 5, 10, 15, 20, 25, 30, 35, 40).

If a simulated family member of a proband with FH was alive in 2018 and at or older than the designated age threshold above which genetic testing would be initiated, genetic testing was performed on that individual. If that individual were FH+, then he/she would begin treatment. Because our estimated LE for the FH treated population in the U.S. was modeled from data from the FH treated population in the UK, our simulation incorporates the effects of real-world treatment patterns, compliance, and achievement of therapeutic targets (or lack thereof) and the effects of outcomes such as cardiovascular events on LE.

The family tree of the proband was then followed for 30 years and any family members that reached the age threshold were tested. For example, the family tree of a proband identified in 2018 would be followed until 2048. We also ran the model following a family tree for 40 years but found there were almost no additional cases identified. Family members who were over the age of 45 at the time the proband was identified were excluded from the cost-benefit analysis because of lack of census information on how changes in their LE might affect future populations. Additionally, when we modeled U.S. life expectancy for FH+ individuals using UK life expectancy models [18] and adjusted for years of life gained with treatment for people in this age group who had not been previously identified as having FH, the results suggested that the gains in life expectancy for individuals with FH who were treated compared to untreated would be marginal after age 45.

### 2.3. Outcome variables

Outcome variables of interest included the average number of life years gained per person in a simulated population where cascade testing is implemented and patients with FH are treated compared to a simulated population where patients with FH are not treated. For an FH+ individual under treatment, the average life expectancy is greater than the average life expectancy for an FH+ individual not under treatment. However, it is possible for the FH+ population under treatment to have a worse outcome compared to the FH+ population not under treatment because of random variation since all life expectancies are based on probability distributions. For example, by chance, we might have an iteration of the simulation where on average, the simulated population where patients with FH are not treated lives longer than the simulated population where patients with FH are treated. We accounted for this by running many replications of the simulation model, which reduces the confidence interval around the estimate and thus minimizes the effect of random variation. If testing and treatment start at a later age, the benefit of treatment is small and we are more likely to encounter simulations where there is no benefit to treatment and the confidence interval shows a negative effect of treatment. Because this had no context within the model, it was displayed as 0 and implies that any benefit of treatment is not statistically detectable. In our simulation, a positive number of average life years gained, with a confidence interval did not include 0, indicated group benefit with testing.

We also evaluated the average discounted cost in U.S. dollars per life year gained per person. The cost-effectiveness threshold that was used was $50,000 per life year gained per person. As a quality-adjusted life year (QALY) is equivalent to 1 year in perfect health, if the quality of the life years gained in our simulation was at least 50% of perfect health, our results would show that testing would be cost-effective with a threshold of $100,000 per QALY that is typically used [20,21]. Testing for a group was not cost-effective when the average cost per life year gained per person or lower/upper bound of the confidence interval was noted to be greater than $50,000 per life year gained per person or to be infinite.

### 2.4. Costs

Costs included in the simulation are from the health care provider's perspective and are restricted to direct costs of medical care. Input costs are displayed in **Table 1**. In terms of genetic testing, most laboratories now offer next generation sequencing targeted panels for FH index cases at an out-of-pocket cost of less than $500. Subsequent testing for a pathogenic variant in relatives is typically cheaper [13]. In our model, the genetic testing cost used for family members was $250, which is a conservative estimate, as it may be offered free for family members of identified probands within a 90-day period [22]. This cost was applied to all family members of an FH proband as part of the cascade testing process.

Family members of the proband with a negative FH test did not incur additional costs above what is expected in the baseline state where cascade testing is not implemented and FH patients are not identified and treated. For family members identified to have FH, additional costs considered in the model included lipid panels, ECG, stress tests, cardiac computerized tomography (CT) scans for coronary calcium scoring, lipoprotein (a), alanine aminotransferase/aspartate aminotransferase (ALT/AST), and clinical consultation with a specialist. Some of these

**Table 1**
Simulation input costs for those who have a positive genetic test for FH.

| Test or Office Visit | Cost in 2018 U.S. Dollars | First Year | | Subsequent Years | | Proportion Receiving |
|---|---|---|---|---|---|---|
| | | Yes/No | Number of Tests | Yes/No | Number of Tests | |
| FH Genetic Test* | $250.00 | Yes | 1 | No | 0 | 100% |
| Lipid Panel | $26.46 | Yes | 3 | Yes | 1 | 100% |
| ECG | $25.84 | Yes | 1 | No | 0 | 100% |
| Stress Test | $75.18 | Yes | 1 | No | 0 | 25% |
| CT Coronary Calcium | $99.21 | Yes | 1 | No | 0 | 25% |
| Lipoprotein (a) | $17.23 | Yes | 1 | No | 0 | 100% |
| ALT/AST | $12.93 | Yes | 2 | Yes | 1 | 100% |
| Specialist Visit | $179.63 | Yes | 1 | Yes | 1 | 100% |
| Lipid-Lowering Therapies | Cost in 2018 U.S. Dollars** | Proportion of Patients | | | | |
| | | Month 0 | Month 6 | Month 12 | Subsequent Years | |
| Statins Only | $91.03 | 74% | 25% | 25% | 25% | |
| Statins + Ezetimibe | $230.16 | 0% | 45% | 23% | 23% | |
| Statins + Ezetimibe + PCSK9 Inhibitors | $12,601.54 | 0% | 0% | 22% | 22% | |
| Statins + PCSK9 Inhibitors | $12,462.41 | 0% | 4% | 4% | 4% | |
| PCSK9 Inhibitors Only | $12,371.80 | 3% | 3% | 3% | 3% | |
| Ezetimibe Only | $139.13 | 13% | 3% | 3% | 3% | |
| PCSK9 Inhibitors + Ezetimibe | $12,510.51 | 0% | 10% | 10% | 10% | |
| No Lipid-Lowering Therapies | $0 | 10% | 10% | 10% | 10% | |

*FH genetic testing was performed for all family members of an FH proband as part of the cascade testing process. Other items only apply to those who have a positive genetic test for FH.
**Listed costs for lipid-lowering therapies are annual costs.
Abbreviations: FH (familial hypercholesterolemia); ECG (electrocardiogram); CT (computerized tomography); PCSK9 (proprotein convertase subtilisin/kexin type 9)

items were only included as first-year costs, while others were also included in subsequent years. Estimates regarding the frequency of lipid panel and AST/ALT testing were obtained from a study on laboratory monitoring in patients on chronic statin therapy [23]. Coronary calcium scoring was included given its utility in risk stratification and informing decisions regarding intensity of treatment in FH patients [24]. All individuals received lipoprotein (a) testing as recommended by guidelines [25]. Additional costs included lipid-lowering therapies such as statins, ezetimibe, and PCSK9 (proprotein convertase subtilisin/kexin type 9) inhibitors. Estimates regarding treatment patterns were based on information from the CASCADE FH registry [26]. The timeframe over which treatment was escalated for those not at therapeutic targets was based on expert opinion. Costs of professional services including diagnostic tests and office visits were based on Medicare reimbursement rates [27], which is typically the standard practice at our institution [28]. Though Medicare costs may be a lower bound, they are generalizable. Costs of medications were obtained from the GoodRx website [29]. All costs were valued at constant 2018 U.S. Dollars and were ultimately recorded in the simulation using a 3% discounted rate for future costs.

## 3. Results

Our simulation demonstrated that cascade genetic testing for 1st-degree relatives was cost-effective, with an average discounted cost per life year gained per person and associated confidence interval of less than $50,000, using testing age thresholds of 5, 10, 15, 20, 25, 30, and 35 (See **central illustration** for a graphical display of our results. Please refer to **Supplemental Table 2** for more details). However, when testing was started at age 40 and above, the average discounted cost per life year gained per person and associated confidence interval was greater than $50,000. Cascade testing at every age threshold resulted in a positive number of life years gained per person, indicating benefit with testing. However, the average number of life years gained per person decreased when testing was started at higher age thresholds.

For 2nd degree relatives, cascade genetic testing using screening age thresholds of 5, 10 and 15 years of age resulted in a positive number of life years gained per person. However, when testing was started at older age thresholds, there was no statistically significant increase in life years gained per person. Cascade testing was cost effective, with an average discounted cost per life year gained per person and associated confidence interval of less than $50,000, using a testing age threshold of 10 but was not cost-effective using other age thresholds.

Simulation results for 3rd degree relatives, 4th degree relatives, 5th degree relatives, and 6th-degree relatives showed that cascade testing led to no benefit in terms of average life years gained per person except with testing of 3rd-degree relatives at an age threshold of 5, which resulted in a positive number of life years gained per person. Additionally, the discounted cost per life year gained per person with testing of these distant relatives at all age thresholds was not cost-effective based on a $50,000 per life year threshold.

## 4. Discussion

Our simulation provides a contemporaneous analysis of the cost-effectiveness of cascade testing in family members of FH probands identified through standard care. Early detection and treatment of individuals with FH, who are often asymptomatic, is critical to prevent adverse outcomes such as sudden cardiac death and myocardial infarction. European guidelines recommend that all patients with clinical and biochemical features of FH should be counseled about genetic cascade testing in their relatives [4]. In the Netherlands, cascade testing in families of FH probands with a pathogenic variant led to statin treatment of affected family members who were at risk of early CHD [30]. As a result, more than 70% of the estimated familial cases have been identified, in contrast to fewer than 15% in the U.S [4]. Although the Centers for Disease Control and Prevention has prioritized the detection of prevalent and actionable Tier 1 genetic disorders such as FH [31], no formal cascade testing programs currently exist in the U.S.

Our simulation model demonstrates that cascade genetic testing for FH in the U.S. would be cost-effective, with an average discounted cost per life year gained per person and associated confidence interval of less than $50,000, if started by age 35–40 for 1st degree relatives. This estimated range was derived from the finding that testing is cost-effective with screening age thresholds of 5, 10, 15, 20, 25, 30, and 35 but not cost-effective when testing is started at age 40 and above. For 2nd degree relatives, cascade testing was cost-effective using a screening age

threshold of 10 but was not cost-effective at higher age thresholds. Interestingly, testing using an age threshold of 5 was not found to be cost-effective, which makes the data for 2nd degree relatives more difficult to interpret. However, this finding could be due to random variation as well as the composition of 2nd degree relatives compared to other degrees of relatedness. With more replications of the simulation, it is likely that testing with an age threshold of 5 would be cost-effective since the upper bound of the confidence interval ($61,880) is only marginally greater than $50,000. Therefore, cascade testing is likely cost-effective if started by age 10–15 for 2nd degree relatives. To our knowledge, prior cost-effectiveness analyses of cascade testing have not specifically looked at age thresholds for cascade genetic testing [5,6,7,8]. In countries where a form of cascade testing had been implemented and evaluated on a national or local level, the ages at which relatives underwent cascade testing varied widely. For instance, in a regional initiative in Australia, the average age of relatives who were tested was 35–37 years, with standard deviation 19-20 years [32]. In a local initiative in Brazil, the average age of relatives who were tested was 43–45 years, with standard deviation 17-18 years [33].

Though cost-effectiveness thresholds are typically based on QALYs and a threshold of $100,000 per QALY is typically used [20,21], we did not have information regarding QALYs. A QALY is equivalent to 1 year in perfect health, and if the quality of the life years gained in our simulation was at least 50% of perfect health, our results would show that testing is still cost-effective with a threshold of $100,000 per QALY. Furthermore, our analysis likely underestimates the cost-effectiveness of cascade genetic testing. Costs incurred following diagnosis of FH through cascade testing were applied for all patients diagnosed with FH in the population where cascade testing was implemented (**Table 1**). However, as previously described, there is a subset of FH patients (with or without a clinical diagnosis) that our simulation assumes is already being followed and treated in the baseline state without cascade testing. This group should not incur any additional costs above what is already accounted for in the baseline state, but we were unable to isolate and exclude these costs from our simulated population with cascade testing. Additionally, the genetic testing cost used for family members was $250 per relative, which is a conservative estimate as it may be offered free for family members of identified probands within a 90-day period. Furthermore, costs of cardiovascular events were not included in our simulation. It is likely that the cost-effectiveness of cascade testing would be even greater if the costs of cardiovascular events were included, as these costs would be lower if individuals with FH were identified earlier and treated.

In a recent systematic review of the literature [34], the yield of FH cascade testing was higher with direct contact of relatives, progressing beyond 1$^{st}$-degree relatives through a family tree, utilizing in home sample collection, and use of genetic testing. In the U.S., most of these approaches are not implemented [35,36]. Awareness of FH among health care providers is low and genetic testing for FH is not commonly utilized. Additionally, patients and family members may be concerned about the stigma associated with genetic diagnoses and the potential implications for employment and health insurance coverage. Interestingly, in a study looking at the uptake of genetic testing, even when the barriers of cost and privacy were removed, uptake of family cascade testing was low at 25% [37].

Our results are applicable when a pathogenic variant is identified. FH patients without an identifiable pathogenic variant in *LDLR, APOB*, and *PCSK9* may have a polygenic etiology [38]. The efficiency of a cascade testing program is likely lower in the setting of index cases with a polygenic rather than monogenic cause of hypercholesterolemia, as the proportion of relatives who might also have an elevated LDL-C is less than the 50% that is predicted for monogenic FH.

### 4.1. Strengths

We utilized a novel simulation of FH transmission through generations to provide contemporaneous data regarding the cost-effectiveness of cascade testing. Our study reflects contemporary practice including marked reductions in genetic testing costs due to advances in next generation sequencing technology and the availability of most statins as generic medications.

### 4.2. Limitations

Our study has several limitations. First, our simulation model did not evaluate lipid testing. However, the objective of our study was to assess the cost-effectiveness of cascade genetic testing given the increasing availability and reduced costs of genetic testing. Additionally, we calculated life years gained but did not have the information to assess quality-adjusted life years, a more patient-centered outcome as it incorporates not only quantity of years gained but also quality as well. Our study is also limited by the absence of long-term data regarding the FH population in the U.S. in terms of diagnosis, treatment, and outcomes. Though we did not have good information on the number of offspring fathered by men, we did have census information on marriage rates for men by a certain age as well as age differences between men and women that were included in the model. We assume by extension that discrepancies due to various family units will be accounted for by known numbers of offspring to women. Furthermore, we did not take into account the costs of contacting and interacting with relatives of FH probands in advance of genetic testing. Costs of identifying probands were not included as our simulation model evaluates the cost-effectiveness of cascade genetic testing of relatives after an index case has already been identified through standard care. In terms of outcomes, the risk of cardiovascular events is technically incorporated into the life expectancy data from the UK populations from which our U.S. FH treated population life expectancy data were obtained. However, costs of cardiovascular events were not included in our simulation as discussed previously. Lastly, we were unable to perform sensitivity analysis around the costs due to computational limits, but we tried to account for this by using conservative estimates for our costs.

## 5. Conclusion

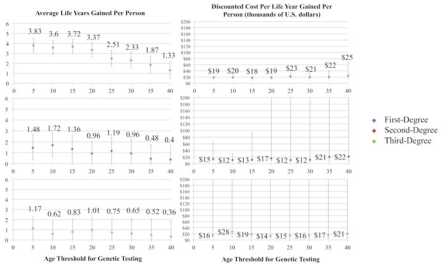
Based on a novel simulation model, we demonstrate that cascade genetic testing of relatives of individuals with FH is cost-effective if started before age 40 in 1st degree relatives and before age 15 in 2nd degree relatives. Our results support establishing FH cascade testing programs in the U.S.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at:

## Central illustration

**Central Illustration**. Life years gained per person and discounted cost per life year gained per person (thousands of U.S. dollars) when genetic testing is implemented in 1$^{st}$-degree, 2$^{nd}$-degree, and 3$^{rd}$-degree relatives of a proband with familial hypercholesterolemia. The upper bound of the confidence interval extends above the maximum value for the vertical axis scale for some results.



## Disclosures

None

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: None.

## CRediT authorship contribution statement

**Candace L. Jackson:** Investigation, Writing – original draft, Writing – review & editing, Resources, Data curation. **Todd Huschka:** Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Formal analysis, Validation, Resources, Data curation. **Bijan Borah:** Conceptualization, Methodology, Investigation, Formal analysis, Validation, Resources, Data curation. **Katherine Agre:** Conceptualization, Resources. **Magdi Zordok:** Conceptualization, Writing – original draft. **Medhat Farwati:** Conceptualization, Writing – original draft. **James Moriarty:** Conceptualization, Methodology, Investigation, Writing – review & editing, Formal analysis, Validation, Resources, Data curation. **Iftikhar J. Kullo:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Formal analysis, Validation, Resources, Data curation, Supervision, Project administration.

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## Supplementary materials

Supplementary data associated with this article can be found, in the online version, at 10.1016/j.ajpc.2021.100245.

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