HHS Public Access

Author manuscript

Circ Genom Precis Med. Author manuscript; available in PMC 2023 January 25.

Published in final edited form as:

Circ Genom Precis Med. 2019 November ; 12(11): e002723. doi:10.1161/CIRCGEN.119.002723.

New Case Detection by Cascade Testing in Familial Hypercholesterolemia:

A Systematic Review of the Literature

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Abstract

BACKGROUND: The prevalence of familial hypercholesterolemia is 1 in 250, but <10% of patients are diagnosed. Cascade testing enables early detection of cases through systematic family tracing. Establishment of familial hypercholesterolemia cascade testing programs in the US could be informed by approaches used elsewhere.

METHODS: We conducted a systematic review of published studies in the English language of cascade testing for familial hypercholesterolemia, which reported the number of index cases and number of relatives tested and specified methods of contacting relatives and testing modalities methods utilized. For each study, we calculated yield (proportion of relatives who test positive) and new cases per index case, to facilitate comparison.

RESULTS: We identified 10 studies from the literature that met inclusion criteria; the mean number of probands and relatives per study was 242 and 826, respectively. The average yield was 44.76% with a range of 30% to 60.5%, and the mean new cases per index case was 1.65 with a range of 0.22 to 8.0. New cases per index case tended to be greater in studies that used direct contact versus indirect contact (2.06 versus 0.86), tested beyond first-degree relatives versus only first-degree relatives (3.65 versus 0.80), used active sample collection versus collection at clinic (4.11 versus 1.06), and utilized genetic testing versus biochemical testing (2.47 versus 0.42).

CONCLUSIONS: New case detection in familial hypercholesterolemia cascade testing programs tended to be higher with direct contact of relatives, testing beyond first-degree relatives, in-home–based sample collection, and genetic testing. These findings should be helpful for establishing cascade testing programs in the United States.

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Disclosures

None.

The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCGEN.119.002723.

Keywords

cholesterol; humans; hyperlipoproteinemia type II; prevalence; systematic review

Familial hypercholesterolemia (FH) is an autosomal dominant disorder that results in lifelong elevation of serum cholesterol levels and is associated with significantly increased risk of coronary heart disease.[1,2] The prevalence of FH is 1 in 250, making it the most common serious genetic disorder.[3,4] It is estimated that there are ≈1.3 million patients with FH in the United States of whom <10% have been identified despite established clinical scoring systems including the Dutch Lipid Clinic Network Diagnostic Criteria,[5] Simon Broome Diagnostic Criteria,[6] and the Making Early Diagnosis to Prevent Early Death diagnostic criteria.[7]

The molecular basis for autosomal dominant FH is the presence of pathogenic/likely pathogenic (P/LP) variants in *LDLR*, *APOB*, or *PCSK9*. P/LP variants in *LDLR* account for 85% to 90% of cases of autosomal dominant FH.[8] P/LP *APOB* variants account for 5% to 10% of FH cases in northern European populations but a lower proportion in other populations.[8] *PCSK9* P/LP variants are the least common monogenic cause of FH, implicated in <5% of cases.[8] A rare autosomal recessive form of FH is attributed to the reduced expression of LDLRAP1.[9] The genetic basis of FH also includes elevations in lipoprotein (a) and polygenic influences[10] and potentially monogenic causes that have yet to be identified.

Cascade testing, by early detection and treatment of family members, can reduce mortality and morbidity from FH. Based on the SAFEHEART Registry (Spanish Familial Hypercholesterolemia Cohort) data, over 10 years, the detection of 9000 new FH cases could prevent 847 coronary events including 203 coronary deaths.[11] Cascade testing is considered an effective method for identifying new cases of FH by a process of systematic family tracing and is recommended by UK National Institute for Health and Clinical Excellence.[12] A number of countries have assessed the efficacy of cascade testing for FH including the United Kingdom,[13–15] the Netherlands,[16] Australia,[17] Latvia,[18] South Africa,[19] and Brazil.[20] These studies vary in methodology making comparison difficult. Some studies utilized genetic testing, some relied on lipid testing and clinical criteria, and others used both. Additionally, the studies differed in data collection, participant interaction, and the degree of relatedness with family members who were tested subsequently.

In the United States, a nationwide cascade testing program is yet to be established, likely because of several reasons—the US healthcare system comprises many providers and payers across a large geographic region.[21] The Health Insurance Portability and Accountability Act prohibits direct notification of at-risk relatives by healthcare providers unless prior authorization has been obtained from probands.[22] We conducted a systematic review of the literature to compare diagnostic yield and new case detection between published studies of cascade testing and to describe these values in the context of individual study methodology. Our goal was to generate comparative data from FH cascade testing studies to inform establishment of cascade testing programs in the United States.[21]

METHODS

Institutional review board approval was not required for this study per local institutional guidelines. All supporting data used in the study along with a detailed study methodology are available in the Data Supplement. These data, methods used in the analysis, and materials used to conduct the research are available to any researcher for purposes of reproducing the results or replicating the procedures of this study. A flowchart depicting selection of FH cascade testing studies for this systematic review (based on preferred reporting items for systematic reviews and meta-analyses for protocols) is depicted in the Figure. The research studies are listed in the Data Supplement.

RESULTS

Study Characteristics

Ten studies were examined as part of this review, with the earliest published in 2001 and the most recent in 2018 (Table 1). Countries represented United Kingdom,[13–15] the Netherlands,[16] Australia,[17] Latvia,[18] South Africa,[19] and Brazil[20]; no studies from the United States were available. The total number of index cases per study ranged from 21 to 733 with a mean of 242 and a median of 232. Family members included in the cascade were selected from either first-degree relatives (FDRs) or both FDRs and second-degree relatives (SDRs) and third-degree relatives (TDRs). The number of relatives in each study population ranged from 64[23] to 5442.[16] The mean diagnostic yield was 44.76% with a range of 30% to 60.50%.

CONTACTING RELATIVES

The design of each contact protocol met local privacy and confidentially requirements. The method of contact was either direct or indirect, with indirect being more common (Table 2). Indirect contact involved the index case being provided with a letter to distribute to family members; in some cases, this letter was labeled specifically for the attention of individual family members who were considered at risk. Direct contact involved the mailing of letters by study staff to at-risk family members with the consent of the index case. The letter to relatives typically outlined that a family member had been diagnosed with FH and that they may be at risk, as well as explaining the benefits of screening and how to enroll in the study. In the study by Marks et al,[15] the diagnosis of FH was initially withheld in an attempt to minimize any undue stress on the contacted relative; however, at-risk family members were informed of the potential risks and the nature of the disease if they did not respond. Nine of the 10 studies provided information on family member contact with 4 being indirect, 4 direct, and 1 being a combination of direct and indirect. The mean new cases per index case (NCIC) with direct contact was 2.06 and with indirect contact was 0.86.

Degrees of Relatedness of Proband With Tested Family Members

Each study set out the degree of relatedness to which the cascade would progress either explicitly or implicitly (Table 2). Seven of the studies were limited to FDRs. In the 2001 study by Vergotine et al,[19] testing was described as confined to close relatives, which was inferred as referring to FDRs. One study included both FDRs and SDRs,[23] whereas 2 studies

included FDRs, SDRs, and TDRs.[16,17] The mean NCIC for studies that advanced beyond FDRs was 3.65 versus 0.80 for studies that tested FDRs only.

COLLECTION OF SAMPLES FROM RELATIVES

The method of collection of samples ranged from passive approaches including attending a primary care clinic or an associated study clinic to the more proactive strategy of in-home testing by study staff (Table 3). The most common approach was an invitation to relatives either by the proband or directly by the study team to attend a primary care clinic or a study-associated clinic, which was typically located in an academic center associated with the study investigators.[13,14,17,18,20,23] These clinic visits included blood draws and in some cases outpatient assessment including physical exam and the completion of a study questionnaire. In 2 studies, relatives were given the option of either visiting a centralized clinic or their primary care clinic.[13,14] The most active approach was taken by Umans-Eckenhausen et al[16] in the Netherlands with relatives visited in their home by specialist nursing staff who performed blood draws and collected family and personal history. In the United Kingdom, Marks et al[15] offered both primary care clinic–based testing and in-home blood draws by a nurse. Muir et al,[24] in New Zealand, included in their mail-out packets a laboratory requisition form, allowing participants to attend a local health center for blood draw. The mean NCIC with home-based testing (considered active) versus clinic-based testing was 4.11 versus 1.06.

MODE OF TESTING: BIOCHEMICAL VERSUS GENETIC

Testing of relatives was either primarily genetic (n=6 studies) or biochemical (n=4 studies). The study by Umans-Eckenhausen et al was unique in that it used a combination of biochemical and *LDLR* testing but for the purpose of this review was considered to represent a genetic testing study. Of the studies utilizing genetic testing, 2 studies tested only *LDLR*, 1 study tested *LDLR* and *APOB*, and 3 studies tested *LDLR*, *APOB*, and *PCSK9* (Table 2). The diagnostic yield for each individual study is summarized in Table 2. The mean yield in biochemical and genetic testing cohorts was similar at 45% and 44%, respectively. The mean NCIC (Table 2) for genetic testing–based studies was 2.47 (range, 0.89–8.0; SD, 2.8), whereas the mean NCIC for nongenetic-based studies was 0.42 (range, 0.22–0.70; SD, 0.21). Even when excluding the prodigious study from the Netherlands that had an NCIC of 8,[16] the mean for studies using genetic testing was higher than for biochemical studies at 1.37.

DISCUSSION

FH poses a significant public health burden by increasing the risk of early-onset coronary heart disease, including myocardial infarction and sudden cardiac death.[25] Yet, awareness of FH in the United States continues to be poor, recommended screening approaches are limited by several barriers, and the uptake and yield of current methods of cascade testing is low.[26] Given this reality, there is a need for cascade testing programs in the United States to enable early detection and treatment and thereby help reduce the morbidity and mortality from FH. In this systematic review, we compared diagnostic yield and NCIC in 10 previous

FH cascade testing studies in the context of each study's methodology. Based on our review, the number of new cases detected in a FH cascade testing program was higher with direct contact of relatives, inclusion of more distant (second and third degree) relatives, in-home sample collection, and the use of genetic testing.

The 2 studies with the highest NCIC pursued only direct participant contact.[7,21] Direct contact may relieve probands of the burden and anxiety of contacting relatives and overcome barriers related to proband communication with relatives.[15,27] Probands are generally welcoming of assistance from the healthcare team to contact relatives,[28] and relatives are more likely to follow recommendations from healthcare providers.[29] Direct contact may be particularly effective for more distant (second or third degree) relatives.[30,31]

The Dutch study by Umans-Eckenhausen et al and the Australian study by Bell et al[17] both tested beyond FDRs to include SDRs and TDRs, whereas the Brazilian study by Alver et al[23] included SDRs. Overall, the average NCIC for studies that advanced beyond FDRs was 3.65 versus 0.80 for studies that did not test beyond FDRs. It is logical that studies that include SDRs and TDRs would have a higher NCIC given the increased number of tested individuals. Thus, to maximize new case detection, a cascade testing program should extend to SDRs and TDRs.

Utilizing in-home testing directed by dedicated nursing staff is likely to have had an impact on the studies' success. The Dutch study by Umans-Eckenhausen et al—a clear outlier in terms of NCIC—can be considered the most active in its design, utilized home-based testing and extending the cascade through SDR and TDR. Such an approach could impose a significant cost and logistical burden in the United States. However, approaches used by genetic testing companies might reduce such burden—saliva kits to obtain DNA can be mailed to relatives, and some companies also offer in-home blood draws.

Four of the studies used LDL (low-density lipoprotein) cholesterol measurement and either Dutch Lipid Clinic Network or SBR criteria to diagnose FH in relatives. A limitation of this approach is that LDL cholesterol levels of members with and without an FH variant can overlap.[32] Measuring lipid levels of family members of an FH patient in the absence of genetic testing could potentially miss up to 20% of new FH cases.[16] Also, detailed family history and additional FH clinical criteria at the time of case ascertainment may not be easily available. An advantage of genetic testing is that it provides unambiguous diagnosis in relatives of a proband with a defined P/LP variant. Nonetheless, biochemical testing is inexpensive, convenient and potentially the only feasible method in low-resource setting and when FH is ascertained in the proband based on clinical criteria.

At the time of writing this systematic review, no FH cascade testing studies in the US setting have been published. A majority of family members do not under-go cascade testing once a proband sends out letters recommending such testing.[27] The proportion is likely to increase with direct contact but remains low.[27] In an ongoing study of cascade testing in the United States, where personnel obtained consent from a proband to contact relatives, the NCIC was low; 0.8 cases were identified per proband (unpublished data).[33] These data indicate a need to develop and implement the best practices for cascade testing in different settings in the

United States[34] and increase awareness and knowledge of FH among healthcare providers, probands, and their relatives, to promote cascade testing.

The findings of this systematic review can inform the establishment of future FH cascade testing programs in the United States. The cost-effectiveness and feasibility of measures such as direct contact of relatives, home visits by staff, extension of cascade testing beyond close relatives, and use of genetic testing need further study. Overall, higher case detection is likely to have positive impact on cost and practical implementation of a screening program.

Limitations

It is important to note that none of the included studies were completed in the United States, and as result, they did not have to conform to Health Insurance Portability and Accountability Act. The included European studies were completed before the implementation of the European General Data Protection and Regulation (2018), which is broadly comparable to Health Insurance Portability and Accountability Act but arguably more restrictive to large-scale medical research. Moreover, nearly all of the prior studies were based in jurisdictions with established single-payer healthcare models, which negated concerns related to effects on providers, payers, and participants. The number of available studies was small, which limited our ability to establish statistical significance in the association of NCIC with degrees of relatives tested, sample collection, testing, or contact methods. We did not include studies using reverse cascade testing such as the one reported by Wald et al[12] because the methodology was fundamentally different from conventional cascade testing studies. Such wider screening, however, may be a useful complementary strategy by identifying new FH cases which can feed into a cascade testing program.

Conclusions

Cascade testing is considered a cost-effective method for detecting new cases of FH.[11,35] Active approaches including direct relative contact and in-home visits had a higher new case detection rate than passive participant engagement. Studies that include SDRs and TDRs are likely to detect more cases of FH than those limited to FDRs only, and genetic-based testing appeared more successful than biochemical screening. Based on our systematic review of the literature, the ideal FH cascade screening program would involve direct contact of relatives, progress beyond FDRs through a family tree, utilize in-home sample collection, and would use genetic testing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Sources of Funding

This study was supported by National Human Genome Research Institute-supported Electronic Medical Records and Genomics Network (U01HG006379) and National Heart, Lung, and Blood Institute grant K24 HL137010 (Dr Kullo).

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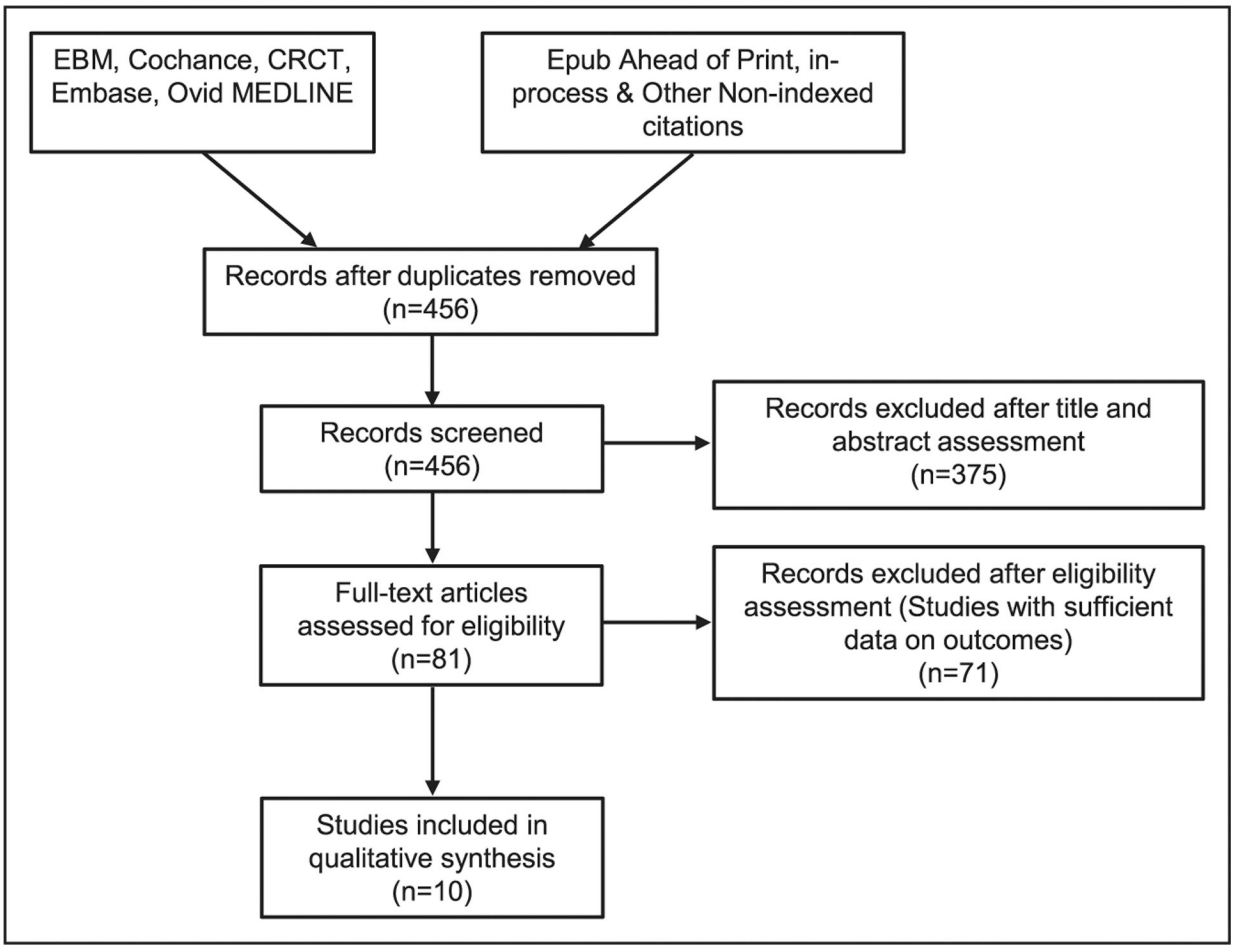

Figure.

Flowchart depicting selection of familial hypercholesterolemia cascade testing studies for this systematic review (based on preferred reporting items for systematic reviews and meta-analyses for protocols). CRCT indicates Cochrane Central Register of Controlled Trials; and EBM, evidence based medicine.

Table 1.

Study Characteristics

Study	Country	Probands, n	Detection of Index Cases	Family Members, n	Contact and Collection	Testing
Bhatnagar et al[14]	United Kingdom	259	SBR	200	Letter advising an appointment with PCP	Biochemical
Umans-Eckenhausen et al[16]	The Netherlands	237	Diagnostic protocol followed by GT	5442	Nurse home visit	*LDLR*+Biochemical
Vergotine et al[19]	South Africa	379	GT	790	…	*LDLR*
Marks et al[15]	United Kingdom	227	SBR	165	Letter with choice of home visit or an SAC visit	Biochemical
Hadfield et al[13]	United Kingdom	733	SBR	769	Letter advising an appointment with GP or to attend SAC	Biochemical
Muir et al[24]	New Zealand	76	GT	353	Letter advising to attend SAC	*LDLR, APOB*
Bell et al[17]	Australia	100	GT	366	Letter with telephone counseling and advice to attend SAC	*LDLR, APOB, PCSK9*
Jannes et al[20]	Brazil	248	GT	394	Referral to SAC	*LDLR, APOB, PCSK9*
Latkovskis et al[18]	Latvia	140	DLCN score	68	…	Biochemical
Alver et al[23]	Estonia	21	GT	64	Family member directed invite to SAC	*LDLR, APOB, PCSK9*

DLCN indicates Dutch Lipid Clinic Network; GP, general practitioner; GT, genetic testing; PCP, primary care provider; SAC, study-associated clinic; and SBR, Simon Broome Register.

Table 2.

Yield and NCIC: Contact Method, Degree of Relatedness, Sample Acquisition, and Testing Method

Study	Initial Contact Method	Relatives Tested	Site for Obtaining Sample	New Case Ascertainment	Yield, %	NCIC
Bhatnagar et al[14]	Direct	FDR	SAC or PCP	SBR criteria	60.50	0.47
Umans-Eckenhausen et al[16]	Direct	FDR, SDR, TDR	Nurse home visit	Diagnostic protocol followed by GT	37	8
Vergotine et al[19]	Unclear	FDR (close relatives)	Unclear	GT	42	0.89
Marks et al[15]	Indirect (response rate 35%)	FDR	Home visit or SAC	SBR criteria	30	0.22
Hadfield et al[13]	Direct and indirect	FDR	SAC or PCP	SBR criteria	30	0.7
Muir et al[24]	Direct (letter, laboratory form, consent)	FDR	Local laboratory	GT	45	2.09
Bell et al[17]	Indirect	FDR, SDR, TDR	SAC	GT	51.40	2
Jannes et al[20]	Direct	FDR *	SAC	GT	59.40	0.94
Latkovskis et al[18]	Indirect	FDR	SAC	DLCN score	60.30	0.29
Alver et al[23]	Indirect	FDR, SDR	SAC	GT	31	0.95

DLCN indicates Dutch Lipid Clinic Network; FDR, first-degree relative; FH, familial hypercholesterolemia; GT, genetic testing; NCIC, new cases per index case; PCP, primary care provider; SAC, study-associated clinic; SBR, Simon-Broom Registry; SDR, second-degree relative; and TDR, third-degree relative.

* Cascade testing extended to SDRs of the proband upon detection of FH in FDRs.

Table 3.

Mean Yield and NCIC Compared Between Various Study Methodologies

	Yield, %	NCIC
Direct contact	46.38	2.06
Indirect contact	43.17	0.86
Beyond FDR	39.8	3.65
FDR only	54.5	0.80
Active sample collection	33.5	4.11
Centralized collection	47.45	1.06
Genetic testing	44.3	2.47
Biochemical testing	45.2	0.42

FDR indicates first-degree relative; and NCIC, new cases per index case.