RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

The Evaluation of Cascade Testing for Familial Hypercholesterolemia

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Received 26 May 2011; Accepted 6 October 2011

Familial hypercholesterolemia (FH) is an autosomal dominant disorder with a high risk of coronary heart disease at a young age that can be reduced by cholesterol-lowering drugs. Computer simulation was used to estimate the screening performance of three strategies of cascade testing for FH (a process of searching for relatives with FH once an individual is diagnosed with FH): (i) testing parents, siblings, and children (1st degree relatives) of an FH index case, (ii) testing (i) and testing 1st degree relatives of subsequently identified relatives with FH, and (iii) testing (ii) and also testing aunts, uncles, nephews, nieces, grandparents, and first cousins (2nd or 3rd degree relatives) when 1st degree relatives of an individual with FH are not available. For cascade testing to achieve detection rates of 80%, (i) 25%, (ii) 11%, and (iii) 8% of FH index cases who are unrelated need to be identified. To identify these unrelated FH index cases, (i) 45% (ii) 23%, and (iii) 17% of all individuals with FH need to be identified independently of cascade testing. Cascade testing is not a suitable method of population screening for FH, because a separate method of systematically identifying new FH index cases is required to achieve a reasonable level of FH detection in the population. Such an alternative systematic method of identifying new cases could itself be the method of population screening.

Key words: cascade testing; familial hypercholesterolemia; screening

How to Cite this Article:
Morris JK, Wald DS, Wald NJ. 2012. The evaluation of cascade testing for familial hypercholesterolemia.
Am J Med Genet Part A 158A:78–84.

INTRODUCTION

Familial Hypercholesterolemia (FH) is an autosomal dominant disorder causing high mortality from coronary heart disease [CHD] (about a 100-fold excess risk under age 40 [Simon Broome Register, 1991]). Treatment to lower serum cholesterol is effective in preventing CHD events, so identifying individuals with FH is important [Simon Broome Register, 1999]. FH affects about 2 per 1,000 people [Goldstein and Brown, 1995], so about 110,000 individuals with FH would be expected in the UK, but only about 15% of these have been identified [Wierzbicki and Ratcliffe, 2008]. The goal of FH screening is to identify all or nearly all individuals with FH in the population so that treatment can be started early enough to prevent a CHD event.

Cascade testing, a process of testing relatives once an affected individual (index case) is known and continuing this process every time a new affected relative is found, has been proposed as a means of identifying individuals with FH [Marks et al., 2002]. Parents, siblings, and offspring of an individual with FH have a one in two chance of being affected. The extent to which cascade testing can be used as a method of screening for FH is uncertain.

The performance of cascade testing as a method of screening depends on having identified independently of cascade testing a sufficient number of individuals with FH who are unrelated (FH index cases)—otherwise cascade testing will be self-limiting within a small number of families.

In this article we use data on family size in England and Wales to estimate the required number of unrelated FH index cases necessary to achieve an 80% detection rate, based on three cascade testing strategies of increasing complexity:

(i) limiting the screening to testing parents, siblings, and children (1st degree relatives) of each FH index case,
(ii) also testing parents, siblings, and children (1st degree relatives) of newly identified relatives with FH,
(iii) also testing aunts, uncles, nephews, nieces, grandparents, or first cousins (2nd and 3rd degree relatives) when any 1st degree relatives are not available for testing.

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Published online 2 December 2011 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/ajmg.a.34368

We then consider whether an alternative method for screening for FH may be preferred.

METHODS

Number of Relatives With FH Identified Per FH Index Case

We estimated the average number of relatives with FH for an FH index case using a computer program to construct a hypothetical sample of 100,000 "extended families" based on the distribution of family sizes for women in England and Wales from 1905 to 2009. An "extended family" was defined as five generations of descendants of an individual born in 1905. The frequency distribution of the number of children in a family was determined from the Office for National Statistics data for generations born in 1980 (the parents of the present generation of children), 1955 (the grand parents), 1930 (the great-grandparents), and 1905 (the great great grandparents) [Smallwood, 2002; ONS, 2007]. The family size for the great great grandparents born in 1905 was assumed to have the same distribution as those born in 1920, as this is the earliest year for which these data are available [ONS, 2007]. The family size for the parents born in 1980 was taken as the distribution of family sizes in England and Wales in 2009 and 20% of females and males were assumed to be childless. For each extended family we determined the number of children the parents born in 1905 would have using Monte Carlo simulation. Conceptually this is equivalent to spinning a multicolored roulette wheel for the parents such that the proportion of reds on the wheel is exactly the same as the proportion of childless people (i.e., those married and without children as well as those not married and without children) in 1905, the proportion of yellows is exactly the same as the proportion of people having one child, the proportion of greens having two children, etc. If the wheel turns up red, the couple is deemed childless; if yellow they have one child, and so on. The process was then repeated for the four subsequent generations.

One individual in each couple of the oldest generation was taken to have FH, with a 1 in 500 the probability of the spouse being affected. All spouses were taken to be unrelated to anybody else in the same extended family (i.e., there were no cousin marriages). In the extended family the probability of children being affected with FH was 50% if one parent was affected, 75% if both were affected, and 0% if neither were affected. For the spouse, the probability of being affected was 1 in 500 (prevalence of FH in the population). Monte Carlo simulation was again used with these probabilities to allocate individuals as affected or unaffected.

To estimate the performance of cascade testing we assumed that all offspring of each mother had the same father, there was no non-paternity and that all relatives born after 1930 were alive, contactable, and agreed to be tested. We also assumed that there was 100% phenotypic expression of all FH mutations, all FH mutations were known and were always inherited. These assumptions estimate the "best-case" for cascade testing; in practice the screening performance will be less effective.

It was assumed that all relatives born in or before 1930 were not available to be tested, as they had died or were too old. This means that, under the three cascade strategies proposed above, the identification of an individual with FH in one extended family will not lead to the detection of individuals with FH in other extended families. For all individuals with FH to be detected through cascade testing, one individual with FH in each extended family would need to be detected independently.

Detection Rate

The detection rate is the number of individuals with FH who are detected by cascade testing, plus the number of individuals with FH who are already known as a proportion of all individuals with FH in the population. It was calculated from the proportion of FH index cases multiplied by the average numbers of relatives with FH identified per FH index case. For example, if each FH index case has nine relatives with FH and 5% of individuals with FH are already known then an additional $9 \times 5\% = 45\%$ will be identified (provided none of the known cases are related), resulting in a detection rate of $45\% + 5\% = 50\%$.

False Positive Rate

The false positive rate is the proportion of unaffected individuals who are related to an affected individual, such that they would be approached for testing in a cascade-testing programme.

Proportion of Cases Required at the Start for Cascade Testing to Achieve a Specified Detection Rate

Index cases need to be unrelated to each other in order to identify new FH cases outside the already identified families. If an index case is related to another index case then both cases will identify each other and the same relatives with FH. To extend cascade testing to new families a completely different method of identifying unrelated FH cases is needed. We randomly sampled individuals with FH from the whole simulated population of individuals with FH to determine what proportion of the sampled individuals were unrelated in order to estimate the proportions of individuals with FH that would need to be identified independently of cascade testing to ensure enough unrelated individuals with FH for the cascade to achieve specified detection rates.

RESULTS

Figure 1 illustrates the three cascade testing strategies with a six-generation pedigree of a family with FH and with two children per family in each generation. The shaded area indicates relatives (both affected and unaffected) who would not be available for testing (as they have died or are too old). The straight arrows indicate testing of parents, siblings and offspring and the curved arrow indicates the testing of a first cousin in strategy (iii). The figure illustrates how cascade testing under these three strategies cannot detect any relatives with FH outside the extended family (that is, relatives not descended from a common ancestor in the 5th generation).

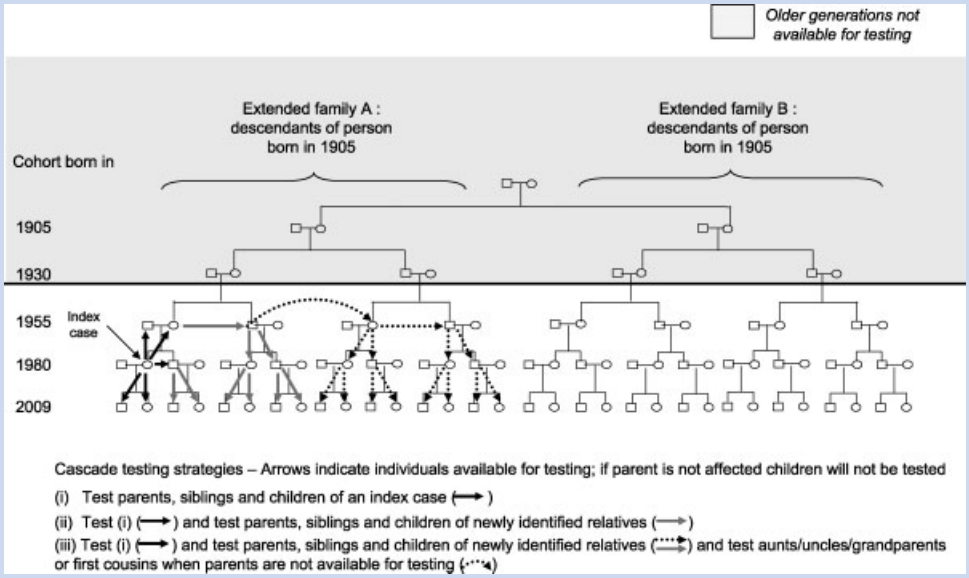

FIG. 1. Cascade testing strategies among two extended families.

In Figure 1 for strategy (i) there are two parents (at least one of whom must have FH) and three other first-degree relatives (with a probability of having FH of 0.5). Therefore one would expect on average, to detect 2.5 relatives with FH per index case and to test 2.5 unaffected relatives per index case for strategy (i). If 20% of individuals with FH (who are all unrelated) are known at the start, the detection rate would be $20\% + 20\% \times 2.5 = 70\%$. As the prevalence of FH is 1 in 500 and the probability of a 1st degree relative being affected is 0.5, $(20\% \times 2.5)/500 = 0.1\%$ of unaffected people would be relatives of individuals with FH and would have been tested (the false positive rate). The proportion of individuals with FH required to be identified such that there are 20% of FH index cases who are all unrelated cannot be simply calculated, but can be estimated using Monte Carlo simulation (see Methods section).

Tables I, II, and III show the expected screening performance for the different screening strategies given the population structure in England and Wales and the best case scenario. For the three strategies, the average expected number of relatives with FH identified per FH

TABLE I. Screening Performance of Cascade-Testing Strategy (i): Testing First Degree Relatives of an Index Case: Number of Relatives With FH Identified Per Index Case = 2.4

Proportion of FH cases identified independently of cascade testing (%) (A)	Proportion of FH cases from (A) that are unrelated, i.e., do not have an affected grandparent in common (%)	Detection rate (proportion of individuals with FH identified) (%)	False positive rate (proportion of individuals without FH being contacted through cascade testing) (%)
5	4.6	15	0.0
10	8.4	29	0.0
15	11.8	40	0.1
20	14.4	49	0.1
25	16.8	57	0.1
30	18.7	64	0.1
35	20.5	70	0.1
40	21.9	74	0.1
45	23.1	78	0.1
50	24.2	82	0.1
55	24.9	85	0.1
60	25.8	88	0.1
65	26.2	89	0.1
70	26.9	91	0.1
75	27.3	93	0.1
80	27.8	94	0.1

TABLE II. Screening Performance of Cascade Testing Strategy (ii): Testing First-Degree Relatives of an Index Case and all Subsequently Identified Cases: Number of Relatives With FH Per Index Case = 6.1

Proportion of FH cases identified independently of cascade testing (%) (A)	Proportion of FH cases from (A) that are unrelated, i.e., do not have an affected great grandparent in common (%)	Detection rate (proportion of individuals with FH identified) (%)	False positive rate (proportion of individuals without FH being contacted through cascade testing) (%)
5	4.2	30	0.1
10	7.1	51	0.1
15	9.2	65	0.1
20	10.7	76	0.1
25	11.7	83	0.1
30	12.4	88	0.2
35	12.9	92	0.2
40	13.3	95	0.2
45	13.5	96	0.2
50	13.8	98	0.2
55	13.8	98	0.2
60	13.9	99	0.2
65	14.0	99	0.2
70	14.0	100	0.2
75	14.1	100	0.2

index case were (i) 2.4 (95% CI: 2.2–2.6), (ii) 6.1 (95% CI: 5.9–6.3), and (iii) 8.6 (95% CI: 8.2–8.9). In order for cascade testing to achieve detection rates of 80% for example, (i) 25% [80%/(1 + 2.4)], (ii) 11% [80%/(1 + 6.1)], and (iii) 8% [80%/(1 + 8.6)] of FH index cases (who are all unrelated) need to be identified. The three strategies would involve between 0.1% and 0.6% of unaffected people in the whole population being approached and tested on account of being related to an individual known to have FH (0.1% to 0.6% false positive rates). For strategies (i) and (ii), as first degree relatives have a one in two chance of having FH, 50% of relatives tested in the

TABLE III. Screening Performance of Cascade Testing Strategy (iii): Testing 1st Degree Relatives of an Index Case and Newly Identified Cases and 2nd and 3rd Degree Relatives if Parents or Siblings are Unavailable: Number of Relatives With FH Per Index Case = 8.6

Proportion of FH cases identified independently of cascade testing (%) (A)	Proportion of FH cases from (A) that are unrelated i.e., do not have an affected great-great grandparent in common (%)	Detection rate (proportion of individuals with FH identified) (%)	False positive rate (proportion of individuals without FH being contacted through cascade testing) (%)
2.5	2.2	21	0.1
5.0	4.0	38	0.2
7.5	5.4	52	0.3
10.0	6.4	62	0.4
12.5	7.3	70	0.4
15.0	8.0	77	0.5
17.5	8.5	82	0.5
20.0	8.9	86	0.5
22.5	9.2	88	0.6
25.0	9.5	91	0.6
27.5	9.7	93	0.6
30.0	9.8	94	0.6
32.5	10.0	96	0.6
35.0	10.1	97	0.6
37.5	10.1	97	0.6
40.0	10.2	98	0.6

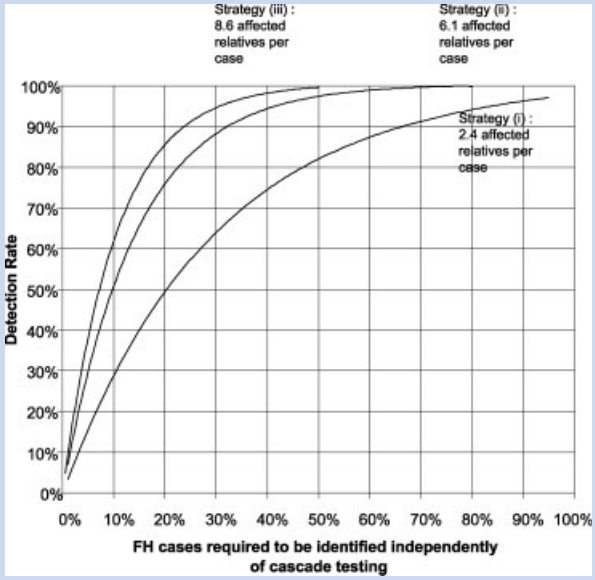

FIG. 2. Detection rate of different cascade testing strategies according to the proportion of FH cases identified independently of cascade testing.

extended families will be false positives. This will be greater for strategy (iii), which tests more distant relatives. To identify the necessary proportion of unrelated FH index cases to achieve a detection rate of 80%, a random sample of (i) 47%, (ii) 23%, and (iii) 17% of individuals with FH identified independently of cascade testing is required (see Tables I, II, and III).

Figure 2 shows the detection rate according to the proportion of individuals with FH required to be identified independently of cascade testing. To achieve high detection rates increasingly high proportions of individuals with FH are needed to be identified independently of cascade testing. For example, in order to achieve detection rates of 90% (i) 67%, (ii) 33%, and (iii) 24% of individuals with FH need to be identified independently of cascade testing. The maximum detection rates that could be obtained given that 15% of the population could be identified independently of cascade testing would be only 40%, 65%, and 77% under the three strategies.

DISCUSSION

Our analysis is based on "best case" circumstances in which all FH mutations were known and tested for and all eligible relatives could be found and agreed to testing. In spite of this, cascade testing fails to achieve sufficient coverage to be a practical method of population screening. In reality these assumptions will not be fully satisfied, and the efficacy of the screening method would be worse. Figure 2 illustrates that in order to achieve reasonable detection rates (say over 80%), a separate systematic method of identifying individuals with FH would be necessary to identify the required number of FH index cases.

To determine the actual performance of cascade testing we used a MEDLINE search (1966–August 2009) and search terms [FH] and [cascade or test or identify] to identify studies which provided the number of relatives with FH per index case, or results from which this could be estimated [Bhatnagar et al., 2000; Umans-Eckenhausen et al., 2001; Leren et al., 2004; Wonderling et al., 2004; Marks et al., 2006; Bourbon et al., 2008; Hadfield et al., 2008, 2009]. Table IV shows the observed number of relatives with FH identified per index case for reported cascade testing studies. The only programme that comes close to being effective is the one conducted in the Netherlands, where cascade testing has been performed for over 10 years based on strategy (iii). The average number of relatives with FH detected per index case was about 8.6, a high number due mainly to high participation rates among relatives (90%), cascading only from cases with a certain FH diagnosis (proven by DNA analysis), and testing of aunts, uncles, grandparents, grandchildren, and first

TABLE IV. Results of Published Cascade Testing Programmes Giving, the Extent of Relative Tracing, the Method of Diagnosis of FH Cases, Number of Relatives With FH Identified Per Index Case and the Proportion of All Affected Individuals Required as Index Cases in Order to Identify All Remaining

				Number of		
Author	Country	Cascade testing strategy[a]	Method of diagnosis	Index patients	Relatives with FH identified[b]	Relatives with FH per index case
Umans-Eckenhausen et al. [2001], Wonderling et al. [2004]	Netherlands	(iii)	Mutation	237	2039	8.6
Leren et al. [2004]	Norway	(ii)	Mutation	188	407	2.2
Bourbon et al. [2008]	Portugal	Not given	Mutation	88	116	1.3
Hadfield et al. [2008, 2009]	UK	(i)	Clinical	931	621	0.7
Bhatnagar et al. [2000]	UK	(i)	Clinical	259	161	0.6
Marks et al. [2006]	UK	(i)	Clinical	227	98	0.4

[a]Cascade-testing strategies are (i) testing parents, siblings, and children (1st degree relatives) of an index case, (ii) testing 1st degree relatives of an index case and of subsequently identified cases, and (iii) testing (ii) and also testing aunts, uncles, grandparents, or first cousins (2nd or 3rd degree relatives) when 1st degree relatives of a case are not available.
[b]Relatives outside the area of the study were assumed to have the same response rate and the same proportion affected as those within the study area. Relatives who had already been tested were assumed to have the same proportion affected.

cousins in addition to parents, siblings, and children of known cases. Testing these more distant relatives allows the cascade to continue if a closer relative cannot be contacted or does not wish to be tested. The national cascade-testing programme in the Netherlands has identified about 80% of the estimated number of FH cases in one region (Zeeland) [STOEH, 2010]. In spite of identifying so many relatives with FH per index case, there remains a need for a method of identifying new FH index cases so that cascade testing can identify the remaining cases in this region.

Wierzbicki and Ratcliffe [2008] estimated that 17,000 individuals with FH have been identified in the UK. This represents about 15% of all FH cases, which is equivalent to 11.8% of unrelated FH cases. It would achieve a detection rate of 40% for strategy (i) only in the "best-case" situation in which 2.4 cases are identified per index case (see Table I). In practice however, only 0.7 cases per index case were identified in UK studies (see Table IV) which can achieve a maximum detection rate of only 20%.

The report of the National Collaborating Centre for Primary Care on the Identification and Management of FH [DeMott et al., 2008] proposes that FH index cases sufficient for cascade testing to be viable as a method of screening could be identified by searching General Practice electronic registers, to identify potential FH cases, or by searching secondary care registers of patients who have suffered a heart attack under age 50. However, a reported search of General Practice records failed to identify a sufficient number of FH index cases [Gray et al., 2008]. Two previously unidentified individuals with FH (10 were already known) in a practice population of 12,100 (with an expected number of 24 individuals with FH) were identified [Gray et al., 2008].

Our analysis is based on the distribution of family sizes for women in England and Wales from 1905 to 2009. However, the results are applicable to most developed countries with an average family size of around two children per family, such as the United States of America. The performance will be less good for those with smaller family sizes and better for those with larger family sizes.

Child–parent screening is a method that could provide the necessary coverage of the population to identify most families with FH in a population [Wald et al., 2007]. In child–parent screening, the total cholesterol levels of children aged 1–2 years are measured when they undergo routine immunization (this is the age when a cholesterol measurement best discriminates between individuals with and without FH; total cholesterol and LDL cholesterol have a similar screening performance), and if a child has a high level (greater than about 1.5 multiples of the age-specific population median) then they are "positive" (estimated detection rate of 90% for a 0.1% false positive rate) and the parents are tested. The parent with the higher cholesterol level has a 96% probability of being affected. The method tests two generations simultaneously at a time when parents and children are already visiting their general practitioner for preventive health reasons. A pilot study of this method in general practice has shown it to be feasible and acceptable (>90% of parents agreed for their children to be screened and simultaneous immunization and blood spot sampling was performed in all cases) [Wald et al., 2011].

In child–parent screening an increasing proportion of children would, over time, be born to parents who themselves were tested as children. If a national FH register of all people tested for FH were established, then the policy of testing children would progressively switch to one of interrogating the register to determine the parents' "FH status". Figure 3 gives an indication of the projected screening activity for this method over time, based on the distribution of maternal ages in 2007 and allowing for 10% of 2-year-old children not having a known or contactable parent when they are tested (for example due to non-paternity or parental separation). After about 30 years most of the screening activity would reduce to a simple enquiry regarding the parents' FH status and testing the children only when this was positive or unknown.

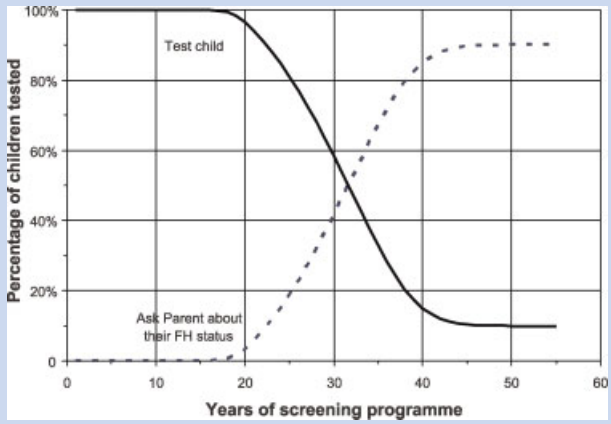

FIG. 3. Projected activity of child–parent screening over time.

Cascade testing is not a suitable method of population screening for FH, because a separate method of systematically identifying new FH index cases is required to achieve a reasonable level of FH detection in the population. Once an alternative systematic method of identifying new cases is developed, such as child–parent screening, it could itself be considered for population screening.

AUTHOR CONTRIBUTIONS

JM participated in the data collection, statistical analysis, and writing the manuscript and is guarantor. DW participated in the data collection and writing the manuscript. NW participated in writing the manuscript. JM had access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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