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How do index patients participating in genetic screening programmes for familial hypercholesterolemia (FH) interpret their DNA results? A UK-based qualitative interview study

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Abstract

Objectives: To explore patients' interpretations of their DNA results for familial hypercholesterolemia (FH).

Methods: In-depth interviews were conducted with patients from two lipid clinics in Scotland, who were offered genetic testing as part of a nationwide cascade screening service.

Results: Patients were receptive to taking part in genetic screening and most expected a positive result. Receiving a molecular diagnosis of FH could provide reassurance to patients that diet and lifestyle factors were not the primary causes of their condition. Patients who received inconclusive results tended to interpret this as meaning that their high cholesterol was not genetic, which could induce feelings of uncertainty and self-blame. With the exception of newly diagnosed patients, for whom a positive result could provide a useful rationale for initiating statins, most perceived DNA screening to be of little relevance to their own medication use or their own approaches to lifestyle management.

Conclusions: Genetic screening for FH is highly acceptable to lipid clinic patients, and positive DNA results are unlikely to have deleterious psychosocial consequences. Patients may not, however, always interpret inconclusive DNA results correctly.

Practice implications: Health professionals need to ensure FH index patients are prepared to receive, and fully understand, inconclusive DNA results.

Keywords: familial hypercholesterolemia; genetic testing; patient perceptions; inconclusive DNA results

1. Introduction

Heterozygous Familial Hypercholesterolemia (FH) is an autosomal dominant genetic disorder that causes elevated serum cholesterol levels and affects around one in every 500 people¹. If untreated, FH leads to a greater than 50% risk of cardiovascular disease (CVD) in men by the age of 50 and at least 30% in women by the age of 60 [1, 2]. The increased risk of CVD can be significantly reduced with statin therapy [3, 4]. According to current clinical guidelines in the UK, for example, a reduction in low density lipoprotein cholesterol levels of 50 per cent or greater represents an achievable target for most FH patients, following the initiation of statin therapy [1]. However, whilst effective treatments exist and are widely available, research suggests that the majority of patients with FH are undiagnosed [5, 6]. One registry based study in the south of England, for example, found that only a quarter of the cases of FH that were predicted in the general population were diagnosed routinely, and most remain undiagnosed until middle age [5].

The under-diagnosis of FH, combined with its treatability, has made early detection and prophylactic intervention key priorities in preventing premature death amongst the population [7]. Nationwide screening initiatives for FH are already in operation in the Netherlands [8], Norway [9], and Spain [10] and have recently been launched in Scotland [11] and Wales [12] in the UK, with limited service provision in England [13]. The use of DNA testing methods is central to these screening programmes, as the identification of a known mutation in index patients greatly improves the chances of obtaining a definitive diagnosis amongst relatives [14]. Hence, evidence suggests

that genetic cascade screening initiatives are cost effective [15] and may lead to significant reductions in mortality from CVD [16].

Despite the widespread use of genetic testing in these programmes, little attention has been paid to how patients interpret their DNA results. One early study suggested that receiving a positive DNA result may increase feelings of fatalism and may result in a decrease in motivation to engage in risk reducing behaviours [17]. Other studies have indicated that genetic screening for FH is highly acceptable to patients [18] and that receiving a positive DNA result can result in patients becoming more aware of the risks of CVD [19] and increasing their utilisation of medication [19] or viewing medication as more effective, and dietary control as less effective, in managing their condition [20]. These studies, however, are either based on qualitative interviews with patients, and thus explore perceptions of childhood genetic testing [17], or they have employed survey methods [18, 19, 20], which necessarily limit participants' abilities to describe their perceptions and experiences in detail and raise issues they consider to be important. Furthermore, there is a dearth of literature that explores how index patients interpret inconclusive results (as negative DNA test results do not rule out the presence of FH amongst index patients). Given that mutation detection rates amongst index patients with definite/possible FH have been less than 50% in some European screening initiatives [21, 22], there is a need to explore how patients interpret inconclusive DNA results and the impact which their understandings may have on their perceptions of risk and their commitments towards adopting and maintaining self-management behaviours; for example, taking medication and following a healthy lifestyle.

Understanding how index patients interpret their genetic results is of paramount importance to the effective development of cascade screening initiatives, especially for programmes which depend on index patients coming forward and subsequently communicating their results correctly and effectively to family members [23, 24]. Hence, this qualitative study aimed to explore, in-depth, interpretations of DNA results amongst index patients who participated in a genetic cascade screening initiative for FH in Scotland. As Scotland is one of the first regions within the UK to develop a nationwide system of FH DNA cascade screening, which is mediated by patients, we were presented with a timely and important opportunity to draw upon their experiences in order to help inform future policy and practice decision-making.

2. Methods

2.1 The setting

In-depth interviews were conducted with patients who participated in the FH genetic cascade screening service. In Scotland, patients referred by general practices to specialist lipid clinics with a clinical diagnosis of possible or definite FH are normally asked, during their consultations, to provide blood samples for the purposes of genetic testing. If a gene change is identified, patients are then referred to a genetics clinic [11]. At the genetics clinic, a detailed family pedigree is drawn and patients' at-risk relatives are identified. Family members are then contacted by patients using tailored information packs provided by staff at the genetics clinic. If a gene mutation is not identified, patients receive a letter from the clinic informing them that their DNA results were inconclusive and recommending that family members access cholesterol screening. Hence, participants with inconclusive DNA results (i.e. no gene mutation was identified) were not usually invited to attend clinical genetics.

2.2. Sampling and recruitment

Index patients were recruited from two lipid clinics within the Lothian region of Scotland between May and December 2010 using an opt-in procedure. One hundred and fourteen patients with DNA results, as well as the one patient who was listed as having formally declined genetic testing (total n=115) were identified by clinic staff and contacted by letter and/or face to face. Each patient received an information sheet outlining the study, an expression of interest form and a stamped addressed envelope. Patients who wished to opt-in to the study were asked to complete the expression of interest form and return it to the research team. Of the 115 patients contacted, 43 opted-in to the study. Of these, one participant was excluded as they were below 18 years of age; four patients were unavailable for interview. The remaining 38 patients were interviewed; all of whom had undergone genetic testing and had received their DNA test results (Table 1).

2.3 Data collection and analysis

In order to inform the patient topic guides, NJ and NH observed 37 routine patient consultations, and NJ interviewed eight health professionals, at the lipid and genetics clinics during the study period. The patient interviews were conducted by a non-clinical researcher (NJ) between June and December 2010 at a time and location most suitable for participants. With the exception of one interview that was conducted online, using instant messaging, and took over 4 hours, interviews ranged from 48 to 116 min. Patient topic guides included a series of open-ended questions designed to encourage participants to talk, at-length and in-depth, about their experiences of genetic testing and to raise issues that may have been unanticipated by the research

team. Substantive areas included: personal and familial disease histories, perceptions and experiences of genetic testing; obtaining and interpreting DNA results and the impact of genetic testing on health behaviours. The amount of time which had passed between patients receiving their DNA results and being interviewed for the study ranged from approximately one month to over one year.

Interviews were digitally recorded, transcribed and analysed using an inductive thematic approach [25]. This involves concurrent data collection and analysis. Interview transcripts were systematically and repeatedly compared in order to identify cross-cutting themes and highlight common experiences. Themes which emerged in early interviews were explored in-depth in subsequent interviews. During data collection, transcripts were reviewed regularly and independently by NJ, NH and JL who met to identify common themes and discuss areas of agreement and divergence. A coding framework was developed to capture data relating to the primary research aims as well as emergent themes. Data collection ceased at the point where no new themes were identified. NVivo 8 (QSR International, Victoria, Australia), a qualitative data indexing package, was used to manage the data.

Ethical approval for the study was obtained in January 2010 from the South East Scotland Ethics Committee (ref: 09/S1102/66).

3. Results

3.1 The routine nature of genetic testing

As previously mentioned, blood samples used for DNA analysis were taken alongside blood samples for routine biochemical analysis. In one of the lipid clinics, it was

observed that blood samples were taken prior to patients seeing the doctor and were sent for DNA analysis once the patient had been informed about the genetic test (and given consent for their blood to be used for this purpose) during their consultation with the doctor. Our observations also highlighted that doctors did not discuss FH genetic testing at-length during these sessions but often did highlight the benefits of genetic testing in helping to identify affected family members.

In this context, all participants described the decision to undertake genetic testing as straightforward and uncomplicated. None reported that they had needed time to consider their decision or that they had held any substantial concerns or reservations prior to giving their consent. In contrast, participants frequently described genetic testing for FH as involving little more than providing doctors with “a wee bit of blood after all” [FH20], which was “completely innocuous” [FH12]. Hence, participants often appeared to have “noticed no difference” [FH07] between their participation in genetic screening and their regular visits to the lipid clinic. As FH02 explains:

“It (genetic testing) didn’t involve anything; it didn’t involve an extra visit, it didn’t involve an extra examination or anything like that. It was simply a question of a bit more blood got taken out, but that’s no problem.” [FH02]

3.2 Aiding the wider family

The majority of participants reported that their prior dealings with health professionals, their experiences of following a balanced diet, and of having family members with high cholesterol or a family history of CVD had already led them to conclude that their condition was inherited. Hence, as the majority already believed

that a tendency towards high cholesterol ran in their family, genetic testing tended not to be seen, especially by more experienced lipid clinic patients, as offering any new insights or personal benefit.

“It never really bothered me because I’ve always known, or thought, that there’s been a family connection anyway, you know. So I suppose I was expecting the results.” [FH13]

Whilst this was the case, several participants highlighted the potential benefits to other family members. Children, siblings, nieces and nephews were often seen as the main beneficiaries of DNA results, especially when screening could help identify the condition in family members at an early stage and thus prevent the onset of problems later on in life.

“I thought it (the genetic test) was a good thing because of my daughter and her family; that’s what I was thinking about. She’s also a diabetic, which exacerbates the whole thing, so it was important to know and to advise her care going forward.” [FH31]

Participants overwhelmingly reported positive experiences of managing their cholesterol levels over time and with medication, which lead them to believe hypercholesterolemia was an eminently manageable condition. Hence, the potential to receive a positive diagnosis either for themselves or their family members did not appear to induce feelings of anxiety or dread amongst participants. This, some participants emphasised, was in contrast to the prospect of genetic testing for other

conditions, such as Huntington's disease, where effective treatment is not currently available. Indeed, genetic testing for FH was only viewed as potentially anxiety provoking if the presence of a more serious disorder could be highlighted. As FH18 emphasised, "It would be much more worrying to me if somebody says, 'Oh, by the way, you've got familial hypercholesterolemia and you're going to have Alzheimer's.'"

3.3 Receiving a positive result: providing affirmation and offering reassurance

As participants often expected genetic testing to confirm an inherited susceptibility to high cholesterol, receiving a positive DNA result appeared to have had little impact on how they viewed their condition. As FH04 explained, "I mean, to some extent you just say, yeah, I knew that already." Only one participant gave any indication that receiving a positive result could have a detrimental psychological impact.

"When it come back genetic I went to him (doctor), "Oh God! That's all I need!" (laughs)." [FH03]

Most participants, especially those who had discovered their high cholesterol relatively recently, appeared to view a positive DNA result as reassuring. This was because receiving a positive result allowed them to rule out, definitively, diet and lifestyle factors as being the primary cause of their elevated cholesterol, thus absolving them of any potential blame for their condition. This did not mean, however, that participants who received a positive DNA result viewed diet and lifestyle control as being any less important following genetic testing. In fact, some

participants reported that receiving a positive result had helped reaffirm their commitment to living a healthy lifestyle.

“I knew that everything I was doing I was doing for the right reasons, you know. It made me grow stronger, to look after myself better.” [FH25]

3.4 Surprise, uncertainty and the inconclusive DNA result

Participants, who had received inconclusive DNA results, often reported being surprised by the outcome of their genetic testing as this was at odds with what they had expected, based on their family histories. As FH17 explained:

“I remember being surprised because I had naturally assumed it would be genetic, with my mother’s high cholesterol, you know, my natural assumption was I’m expecting this.”

Of the 15 participants who received inconclusive DNA results, nine appeared - at least upon receiving their results letters from the lipid clinic - to have interpreted this as meaning that the cause of their high cholesterol was not genetic. Participants who interpreted their results as negative described feeling how they may have done something wrong to have high cholesterol.

“I suppose I thought that this test would actually prove that I had this problem because I had a genetic link and then it was kosher that ... the NHS was taking me into clinics once a year and giving me all this medication, that it was ok because I had this genetic difficulty. But that moment (receiving the results)

was the bit where, well maybe they're doing all this for me and I'm causing it." [FH16]

Although the majority of participants with inconclusive DNA results reported encouraging family members to have their cholesterol checked, which is what they were advised to do by their health professionals, interpreting DNA results as negative *could* lead to the belief that other family members may not be at increased risk of CVD.

"I know that the link isn't there so in terms of my nieces and nephews it doesn't affect them, although I'm still saying to them 'take care'" [FH33]

3.5 Starting on statins, and staying on statins

For a minority of newly diagnosed participants, who reported undertaking genetic testing at the point where medication had recently been recommended, receiving a positive DNA result could promote receptiveness towards taking statins. This seemed to be related to their belief that, while individuals had a personal responsibility to reduce dietary cholesterol by improving lifestyles, 'nothing can be done' [FH19] about genetic causes of high cholesterol and hence drug treatment is essential. Indeed, one participant specifically reported that, had she not received a positive DNA result, she might have been less amenable to starting on statins.

"I knew that once you start statins you're on them for the rest of your life and before I started them I knew that there could be some side effects so I

wouldn't have gone for them unless I thought there was a good reason to do so and the genetic test then gave me that reason." [FH42]

In contrast, participants who reported undertaking genetic testing years after initiating drug treatment frequently suggested that their results had little, if any, impact on their behaviour. This was because participants often viewed genetic testing and personal risk-management as separate spheres of activity, where the results of the former did not affect the latter. As FH01, for example, stated, "I have high cholesterol for whatever reason and my only concern is to lower it." Hence, for these participants, an inconclusive or "negative" result was not seen as a reason for stopping or otherwise reducing their use of cholesterol-lowering medications, nor was a positive result seen as a reason for being less conscious of diet and lifestyle.

"[Just] because I take a tablet doesn't mean to say that I'm going to automatically eat all the wrong things because, I think, even although it's a, you've got a genetic thing, if you're going to be eating all the wrong things as well ... you're gonna make that drug work harder or you're gonna have to increase your dosage or whatever." [FH24]

4. Discussion and conclusion

4.1 Discussion

Participants were overwhelmingly receptive to the idea of taking part in genetic screening for FH. Whilst the majority did not see any direct personal benefits to obtaining a molecular diagnosis, the potential for genetic testing to benefit other family members was often highlighted. Positive experiences of managing high

cholesterol, coupled with the routine nature of the testing procedure, contributed to patients viewing FH genetic testing as unexceptional and non-threatening. Based on their family histories and their experiences of managing their diets and lifestyles, participants often expected a positive result. Receiving a positive result provided reassurance that diet and lifestyle were not the primary causes of participants' condition, yet this did not appear to lead to participants believing that their behaviour was not important. Being provided with a positive DNA result could promote receptiveness towards cholesterol-lowering medications amongst those new to drug treatment. Participants who received inconclusive genetic results often interpreted this as meaning that they, and other family members, did not have a genetic predisposition to high cholesterol. This could lead them to question why they had high cholesterol, and to feel that they might have failed to manage their lifestyles appropriately.

Studies have shown that the prospect of genetic testing for conditions where effective treatments and management strategies exist may induce fewer feelings of anxiety and concern compared with testing for less treatable conditions [26]. Our study supports these findings. In line with previous qualitative research [27, 28] FH was overwhelmingly experienced by participants as a manageable, non-stigmatising condition. Hence, participants neither reported needing time to consider their decision to test for a condition which they already believed they had, nor that they were concerned about the prospect or implications of receiving a positive result. Whilst experience of cholesterol as eminently manageable was a key factor promoting willingness to undergo genetic testing, our study also highlights that the context of testing is also important. A number of blood samples are routinely taken in the lipid

clinic. Thus, genetic testing was, for the majority, incorporated within the taken-for-granted flow of their clinic consultations. This may well have contributed to the perception of the test as ‘genetically unexceptional’ [29]. Indeed, in support of this suggestion, research has shown that practices in which people engage in frequently are often perceived as being less risky compared with those which are considered to be out of the ordinary [30]. Following this, patients’ perceptions of FH genetic testing as routine and unexceptional may have implications for how well they understand the testing protocol and their subsequent DNA results. This is because, in the perception of routine/mundane events, patients are likely to adopt less elaborate and detailed considerations of the situation at hand, than might otherwise been the case when responding to more exceptional circumstances [30, 31].

As noted, the majority of participants who received inconclusive DNA results appeared to interpret this as meaning that the cause of their high cholesterol was not genetic. The potential for index patients to interpret inconclusive results as meaning that a familial disorder is not inherited has been observed in studies of *BRCA1* and *BRCA2* mutation searching [32]. Given that mutation detection rates amongst index patients with possible/definite FH may be lower than 50 per cent [21, 22, 33], there is an obvious need to ensure that, in future, service providers are aware of the potential for this to happen.

Findings from previous studies also suggested that FH genetic testing may influence risk perception and risk management behaviours [17, 19]. Our study suggests that prior experiences of managing hypercholesterolemia play an important role in determining the impact of genetic results. For participants who reported undergoing

genetic testing at a point when they were deciding whether or not to initiate treatment, receiving a positive result could provide a useful rationale for starting statin therapy. This was because they overwhelmingly felt that a genetic cause of high cholesterol was beyond their sphere of control and, as such, medication was essential. Participants who were veteran patients, however, reported that the results of their genetic testing (be they positive or inconclusive) had little impact on their perceptions and behaviours. This was because their risk perceptions and self-management behaviours appeared to be guided primarily by their cholesterol levels, rather than by disease aetiology.

4.2 Study strengths and limitations

The main strength of this study is that it provides an in-depth account of index patients' experiences of genetic testing for FH, this being an important yet under-researched area. It is limited in that it was conducted within Scotland where the vast majority of participants are likely to be White British, thus restricting the extent to which the findings may be transferred to other countries and ethnic groups. It must also be noted that approximately half of the patients interviewed were from professional/ skilled non-manual backgrounds (Table 1). A similar distribution of FH patients' occupational characteristics was observed in a previous qualitative study conducted in the UK, and was attributed to the low numbers of patients from manual backgrounds attending specialist lipid clinics [34]. Indeed, census research suggests that as little as 17% of all patients with FH may be receiving care in specialist lipid clinics, which are mainly located in urban areas [6]. Finally, only patients who had consent to genetic testing and received their DNA results were interviewed. As such, we were unable to explore reasons why FH patients might decline genetic testing.

Future qualitative research could usefully explore interpretations of FH DNA results amongst patients from manual occupational backgrounds and/or from rural communities. There is also scope for further qualitative research which explores reasons why FH patients may, or may not, attend specialist lipid clinics and why they may decline to participate in genetic screening.

4.3 Conclusion

Genetic testing for FH can be easily incorporated within routine lipid consultations and is likely to require little input in the form of specialist counselling, prior to patients receiving their DNA results. Undertaking genetic testing for FH is not likely to result in deleterious psychosocial consequences, or to a decrease in medication use or lifestyle control, amongst index patients.

4.4 Practice implications

Health professionals need to be aware that index patients may interpret inconclusive DNA results as meaning that they and other family members do not have a genetic predisposition to elevated serum cholesterol levels, even if they have received a letter from their doctor informing them that the result is most likely due to current limitations in DNA screening. Index patients should be fully informed about the likelihood of receiving an inconclusive result prior to undertaking genetic testing. Health professionals must ensure that adequate information and advice is made available to patients so that they fully understand their DNA results. Health professionals should continue to emphasise to patients with inconclusive results that they and their relatives could still be at risk of developing CVD and should therefore undergo cholesterol screening and initiate drug treatment if appropriate. Patients

should also be encouraged to inform family members that they have undergone DNA testing and have received an uninformative result, so that family members who attend other clinics do not undergo DNA testing needlessly [32].

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Statement of anonymity

I confirm all patient identifiers have been removed or disguised so that the patients described are not identifiable and cannot be identified through the details of the story

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