

# Exploring the impact of DNA testing for familial hypercholesterolaemia

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In August 2008 the National Institute for Health and Clinical Excellence published evidence-based recommendations for the diagnosis and management of familial hypercholesterolaemia (FH) (De Mott et al, 2008). This guidance made the key recommendation that DNA testing should be offered to individuals with a clinical diagnosis of FH to increase the certainty of their diagnosis and to aid diagnosis among their relatives.

FH is a common genetic disorder of lipid metabolism affecting approximately 1 in 500 people in most populations (Austin et al, 2004). FH leads to high levels of low-density lipoprotein (LDL) cholesterol and this causes increased risk of premature coronary heart disease (CHD), such that roughly half of the men with FH, if untreated will have developed clinically evident CHD by the age of 55 years, and roughly one third of women by the age of 60 years (De Mott et al, 2008: 28).

FH is mainly caused by mutations to a single gene on chromosome 19 for the LDL receptor, but can also result from mutations in two other genes, coding for apolipoprotein B (part of the LDL molecule) (Myant, 1993), or an enzyme that degrades the LDL receptor (Abifadel et al, 2003). Due to its autosomal dominant inheritance pattern each child of an affected parent runs a 50% risk of inheriting the gene for FH.

With an estimated prevalence of 1 in 500 approximately 110 000 people in the UK are thought to have FH, although at least 75% of this group remain undiagnosed (Neil et al, 2000). Preventive treatment with HMG-CoA reductase inhibitors (statins), in combination with a healthy lifestyle, is effective in delaying or preventing the onset of CHD (Civeira, 2004). Effective primary prevention however requires early diagnosis. In the UK diagnosis of FH is based on criteria developed by the Simon Broome Register Group (1991) which includes LDL-cholesterol level, plus clinically detected stigmata (external signs of cholesterol deposits such as xanthelasma and xanthomata) and a family history of either early CHD or elevated lipid levels. However, approximately 15% of the FH population have normal or slightly elevated levels of cholesterol (Agard et al, 2004). An unequivocal diagnosis can also be made by a DNA-based test.

The low rate of diagnosis, high familial risk and effectiveness of early diagnosis and treatment make cascade

screening, where relatives are screened for the condition, a cost-effective strategy for the identification of FH (Marks et al, 2002; Marks et al, 2003).

Currently in the UK most patients with a clinical diagnosis of FH are not offered DNA testing. The reasons why have not been formally identified but are likely to include lack of funding for these tests, lack of availability of DNA testing and concerns regarding the acceptability of such testing by patients and their families. The main aim of this study was to address the latter by gaining insight into the personal experiences of patients and their relatives undergoing DNA testing for FH.

## Aims

The main aim of this study was to gain an insight into the personal experiences of patients and their relatives undergoing DNA testing for FH:

## ABSTRACT

Familial hypercholesterolaemia (FH) is a genetic disorder with a prevalence of 1 in 500, approximately 110 000 people are estimated to be affected in the UK. The majority remain undiagnosed. Effective preventive treatment is available to reduce cholesterol. Untreated FH leads to premature CHD and death. The main aims of the study were to explore how patients and their families receive, make sense of and transmit genetic information and the impact that this dynamic process has on their perception of risk.

Semi-structured interviews were conducted with 7 patients with a clinical diagnosis of FH and a mutation positive result. A further 7 interviews were conducted with members of their families who had also undergone genetic testing. The interview transcripts were thematically analysed.

The findings suggest that genetic risk information help patients to make sense of their condition and acts as a stimulus to cascade testing. The process of family communication and the emotional responses to genetic risk information were complex.

## KEY WORDS

♦ Familial hypercholesterolaemia ♦ Cascade screening ♦ DNA testing/genetic testing ♦ Coronary heart disease ♦ Family

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- ♦ To explore how they made sense of the genetic risk information
- ♦ To explore how this genetic risk information is communicated through the family.
- ♦ To explore the impact of this dynamic process on perceptions of risk.

## Research design

A qualitative methodology was employed, in the form of semi-structured interviews with participants. This approach was chosen for several reasons. Qualitative research aims to provide an indepth and interpreted understanding of the social world of participants, by learning about their social circumstances, their experiences, perspectives and histories (Snape and Spencer, 2004). Previous research in this area has tended to use a deductive approach developing hypotheses based on informed conjecture. Once a theory has been elucidated this forms a strong basis for future quantitative research

## Sample

MREC approval was granted for a study comparing DNA testing for FH with traditional diagnostic methods; Implications for cascade testing. Ethical approval for this study was granted through an amendment to this main study by the South East Wales Research committee (Panel C).

Patients from the lipid clinic at a teaching hospital in Wales who had been identified as having a genetic mutation for FH and their relatives who had undergone genetic testing were invited to participate in the research.

Potential participants were identified using stringent criteria—i.e. all probands had received a formal diagnosis of 'definite FH' using the Simon Broome Criteria before undergoing genetic testing (Table 1).

## Data collection

Face-to-face semi-structured interviews were conducted with 7 patients in whom a clinical diagnosis of FH had been made and who had undergone DNA testing to confirm this diagnosis and received a mutation-positive result. A further 7 interviews were conducted with members of their families who had undergone cascade DNA testing, to follow the flow of this genetic risk information.

The interviews lasted approximately 1 hour, and these were audiotaped with the permission of the participant and later transcribed. The interviews were initiated by inviting participants to talk about their own personal experience of having FH in their family. Prompts were used to encourage the participants to continue and probes were used to encourage elaboration when participants touched on domains that were of particular interest to the researcher.

The domains addressed by the interview schedule included: personal experience of FH; reactions to genetic test result; meaning of genetic test, controlling FH; communication of results through the family and service delivery. The interview schedule was developed through clinical experience and extensive review of the literature.

## Data analysis

The semi-structured qualitative interviews were analysed using a grounded theory approach (Glaser and Strauss 1967). Several tools of the grounded theory approach as described by McAllister (2001) were used through the analytical process. This approach was chosen for analysis as it has built in processes that ensure both reliability and validity.

## Results

All of the participants gave detailed descriptions of their experiences of having the condition in their family and undergoing genetic testing. Although each person's story was unique, some common themes emerged through the data. Even though the process of undergoing genetic testing was different for the probands as opposed to their relatives several of the themes were common to both groups.

All participants names have been anonymized with the use of pseudonyms.

## Motivations for DNA testing

When talking about their motivations for undergoing genetic testing most of the probands (those initially diagnosed) and their relatives gave their primary reason as

**Table 1.**  
**Guidelines for the diagnosis of familial hypercholesterolaemia (FH) patients**

Diagnostic criteria	Simon Broome criteria
Definite FH	Total cholesterol above 7.5 mmol/litre and LDL-cholesterol above 4.9 mmol/litre (6.7 mmol/litre together with an LDL-cholesterol concentration above 4.0 mmol for children) Plus Tendon xanthomas in patient or 1st or 2nd-degree relative Or DNA-based evidence of an LDL receptor mutation or familial defective apo B-100
Possible FH	Total cholesterol above 7.5 mmol/litre and LDL-cholesterol above 4.9 mmol/litre Plus Family history of myocardial infarction below age 50 in 2nd-degree relative, below age 60 in 1st-degree relative. Or Family history of raised cholesterol levels, above 7.5mmol/litre in adult 1st or 2nd-degree relative; above 6.7 mmol/litre in child or sibling under 16
LDL = low-density lipoprotein Steering Group of the Simon Broom Register Group, 1991	

being not for themselves but for other family members more specifically future generations.

**How important it really is—not to me, to the next generations that's coming along. I mean it's not going to do me much good. But it's going to do others good. I've a grandson three year old so if—if he's got it, it'll help him. (Rita, female proband, age 54, mutation positive)**

## Reaction to DNA testing

An array of emotional reactions on receipt of their genetic test results were described that ranged from excitement through indifference to sadness and regret.

**It was like an adventure. You know, it was marvelous really interesting and breathtaking. This sounds a bit dramatic but it's was all that Thank God and Good God, I didn't know that and that's me on paper—that's what makes me, you know, all very excited. I'd like to frame it! ... It was like giving us a birthday present. (Georgina, female proband, age 71 years, mutation positive)**

On reflecting back on their experiences, many of the participants expressed sadness and regret for the relatives that had died of a condition when it is so easily detectable and treatable now.

**I felt sad for my grandmother—these eight grandchildren and she was sitting there watching them die around her. In fact she was actually told that the family must be cursed and she died, you know, not knowing. (Mary, female proband, age 61 years, mutation positive)**

## Meaning of genetic test result

Several probands described how having a name for the condition, and the actual 'knowing' of the underlying genetic cause of it, provided a sense of resolution and a way of making sense of what had happened to family members in the past

**It puts closure, living with it whatever names you want to put on it, you feel better. And that's basically it ... But the actual knowing, it's very interesting, it's fascinating, but it actually settles your mind quite a lot. (Raymond, male proband, age 50 years, mutation positive)**

Several of the probands spoke of how having the DNA result made the condition that had previously been invisible and intangible into something real and visible. They described how the silent, hidden nature of the disease meant that they did not feel unwell until they had established CHD. They had no sense of the progression of the disease and it was often not apparent or diagnosed until it was too late and a member of the family had died. The

availability of the genetic diagnosis meant that the condition could now be detected at an early stage, and that premature CHD and sudden death could be prevented. In a sense they knew better what they were dealing with and they had an early warning that they could act on.

**It makes it something real because it isn't always an illness that you feel, you can't see it. You can see a broken leg. But you haven't got anything you can see—haven't anything that's any different, and then when they show you it, that's wrong, now I know what's wrong. In my mind you can fix on that. (Raymond, male proband, age 50 years, mutation positive)**

Both probands and their relatives found that having genetic information about the condition provided them with hope for the future, both in terms of preventative treatment and surveillance of the condition. Additionally there was a belief in the potential for gene therapy.

**Because you read a lot, like, of particularly cancers, they're always writing about cancers in the papers. And they're saying if they can isolate the gene that causes the cancer they may know how to treat it or they can find ways of treating it and destroy that line. And I suppose this will be the same won't it? (Glyn, male proband, age 68 years, mutation positive)**

## Family communication

All of the probands and relatives described how positive they felt about discussing their results with other family members, reporting an open style of communication. All probands had informed their first-degree relatives but only a couple of the female probands had gone to the wider family.

**I suppose we've talked about it more since this has happened. Yes because a couple of them I didn't even know whether they were being treated or not. So yes they have come forward and told me their stories. So yes, in a way I suppose it has made it more open. (Mary, female proband, age 61 years, mutation positive)**

A couple of the probands even spoke of the process of genetic testing actually facilitating the communication process not only with family members but also with friends and other interested parties because it provided them with a name and a genetic explanation for their health problems.

**I can tell people what's wrong with me. I can explain what it is, whereas before, I've got FH. Oh yeah? What's that then? What's FH? I've not heard of FH. And you tell people things like that and it's like what, did you catch it abroad? It's something nobody knows. But when you start talking—every-**

one watches crime channels, everyone knows what DNA is, and when you start talking about it and say this one's wrong and that one's wrong, yeah, yeah, I understand. It makes it easier to explain to people that don't know. (Raymond, male proband, age 50 years, mutation positive)

However, several of the probands spoke of family members who were not interested in having genetic testing because they had a fatalistic attitude towards the condition and their mortality.

There were difficulties experienced with communication, especially when there were difficult family dynamics that had to be negotiated. This was the case when, for example there had been a sudden death of a relative and there were differing perspectives on the reasons for that death. The FH specialist nurse was reported to take a supportive role in these delicate negotiations amongst family members.

The patients were offered the opportunity by the FH specialist nurse of different methods of communicating this risk information to their family, either through family contact or direct contact through the clinic with their permission. Both methods of contact were used and usually a mixture of the two, whereby the FH nurse was used for further explanation, clarification or legitimization of the genetic risk information.

### Who is at risk?

Despite feeling moral absolution from their own lifestyle choices through their genetic test results, these same individuals surveyed their family members and targeted those who they perceived to be at greatest risk of having the condition. The relatives they saw as being at greatest risk were those who were overweight and smoked, lifestyle risks that are commonly associated with high cholesterol levels. They concentrated their efforts on encouraging those family members to seek genetic testing and to identify their risk.

**It will sound, make me sound like a snob but mainly the people that died suddenly were all working class—had dodgy jobs, dodgy social habits, smoked too much, drank too much. It seemed to be a lifestyle thing and you just think FH you know they are hard working but they are fairly chavvy and they probably eat shit food live in dirty houses all those things that as you grow up you think oh that's not going to happen to me. You know that it's not class aware. I think that's the problem that people don't realise I think a lot of people think it is lifestyle. (Paul, male relative, age 42 years, mutation negative)**

Other relatives that were perceived and identified as most at risk were those that resembled affected members of the family in both physical characteristics and personality traits.

**She walks like him. You know she'll undoubtedly end up swearing like him or there will be some little character trait that she'll have that I'll go your father used to do that and if anyone's got it she's got it. (Paul, male relative, age 42 years, mutation negative)**

### Discussion

The probands and relatives gave similar reasons for undergoing genetic testing, with the most common theme being a sense of moral responsibility towards other family members. They referred to past generations, their own and future generations but the emphasis was on future generations. They also emphasized the possibility of preventative treatment and monitoring for themselves and for other family members. These findings are supported by previous research in the field (Lynch et al, 1997; Hughes et al, 2002; Gaff et al, 2005)

This perceived moral responsibility seemed to be driven by anxiety about whether other family members had inherited FH and could subsequently develop CHD, and an altruistic desire to protect relatives from avoidable harm. This concern and anxiety about relatives developing CHD has been highlighted in previous research studies (Hollman et al, 2002; Hollman et al 2003).

There was also a belief in the future potential of gene therapy, which seemed to be fed by media representations of genetic technology. Interestingly only three of the participants mentioned concerns about undergoing genetic testing and these were all made in hindsight. The concerns raised were regarding the future use of their DNA sample. Apparently, most respondents let the benefits of testing prevail over the limitations. However, it is not possible to say whether the participants in this study had been given the opportunity to fully consider the potential risks and limitations of undergoing genetic testing. As a point of practice patients should be given the opportunity of an indepth discussion of the limitations and risks as well as benefits of testing as part of the pre-test counselling to ensure that they are facilitated in making an informed choice. The discussion should include fears and misconceptions surrounding DNA, and more specifically, the future uses of the individual's own DNA as well as social and economic issues such as insurance.

The probands in this study expressed an array of emotions on receipt of their genetic test results that ranged from excitement through indifference to sadness and regret. These emotions focused on the new genetic knowledge they had received about their condition. Some expressed excitement at the gift of knowledge about their condition, although also sadness and regret that the previous generations of their families did not have this knowledge.

Indifference was expressed by some as the genetic information was merely confirmation of what they already knew. Every proband in this study had already been diagnosed as having FH on clinical grounds and been managing the condition for many years.



Furthermore, no adverse psychological reactions on receipt of their genetic test results were reported. This was to be expected as previous research has not observed any clinically relevant adverse reactions to undergoing genetic testing for this condition (van Maarle et al, 2001; van Maarle et al, 2003a; van Maarle et al, 2003b; Marteau et al, 2004). Indeed, no empirical evidence has been found to support negative psychological effects of genetic screening in other disorders (Broadstock et al, 2000).

This knowledge of the genetic nature of the condition may have even enhanced their sense of wellbeing, with a main theme reported by the probands being a sense of resolution and closure. This, they reported, was because it provided a way of explaining what had happened in the past, a knowledge that made living with the condition easier in the present and gave hope for the future.

Another common theme among both probands and relatives was a sense of moral absolution, where they described how a genetic explanation for their health problems provided a sense of moral absolution from the lifestyle causes commonly associated with high cholesterol.

The sense of moral absolution from lifestyle choices may raise concerns about whether it will affect management in terms of adherence of the individual to risk-reducing behaviours and there is a cohort of research that has addressed behavioural change following DNA diagnosis. These authors had concerns that using DNA as distinct from other biological markers would engender a sense of fatalism (Senior et al, 1999; Senior et al, 2002; Senior et al 2004; Marteau et al, 2004). However, these concerns have not been upheld (Umans-Eckerhausen et al, 2003). Marteau et al (2004) in a randomized controlled trial, concluded that finding a mutation to confirm a clinical diagnosis of FH in a previously aware population does not reduce adherence to risk-reducing behaviours.

A further common theme was how having a genetic diagnosis made the condition that had previously been invisible or intangible into something visible and real. It would seem that the concept of 'seeing it' as termed by Featherstone et al (2006) is an important means of making sense of what has happened in the past and an important strategy for surveillance in the future.

In keeping with previous research findings, although all of the participants in this study described how they felt happy and were willing to share their genetic risk information, both within their family and with extra-familial persons, in practice the majority had only alerted first-degree relatives (Agard et al, 2004; van den Nieuwenhoff, 2007). It would seem, as suggested by Wilson et al (2004), that due to the genetic nature of FH, a large proportion of the relatives were already aware of cardiovascular problems within the family, as well as the existence of effective therapeutic measures, and that these factors have encouraged disclosure.

As previously described in the literature there were certain family members who just did not want to know (van den Nieuwenhoff, 2006). It must be remembered that these

individuals may not wish to deal with the practical and emotional problems that could potentially result from being aware of a genetic condition and therefore their wishes should be respected.

There were also some instances where there was a breakdown in communication between the proband and other family members. In the present study, this dynamic was negotiated by other family members communicating the risk information and was facilitated by the FH specialist nurse providing either contact, or support and information. Several of the probands spoke of how they alerted their relatives to the availability of the genetic test but referred them to the FH specialist nurse to legitimize this information and provide an explanation.

When considering who was at greatest risk both probands and their relatives introduced personal/family theories of inheritance based on physical and personality characteristics. Richards (1995) described this phenomenon as 'personal theories of inheritance' and as a means by which family members rationalize their own genetic risk and that of other family members. In this study these 'personal theories of inheritance' seemed to exist alongside the genetic model. However, it highlights the need for a health professional to clarify who is at risk and to challenge any existing misconceptions.

All of the relatives were satisfied with the way in which they were contacted. Tonstad et al (1996) found 75% of relatives would prefer to be contacted by a health professional—all of the participants in this study indicated that they would be happy to have been contacted by a health professional directly, but this was in retrospect.

In practice a mix of the methods of contact (family and direct) were used and individualized to the family. Hughes et al (2002) suggested that the health professional should not only emphasize the importance of sharing genetic risk information but also help develop strategies that allow effective communication in the existing family dynamics.

## Conclusions

DNA diagnosis of FH can have wide ranging implications for both the individual and his/her family. Although the results of this research study are compelling it is important not to overstate the findings of such a small research study.

The results support a body of evidence that genetic testing does not have any significant adverse psychological effects and may even improve wellbeing by helping individuals to make sense of their condition. As well as improving understanding of the condition DNA testing can also act as a stimulus to family cascade testing.

This study highlights the complexity of communication patterns within families. Despite the respondents willingness to inform their relatives about genetic testing for FH, several participants encountered barriers to this process, though these hurdles were negotiated within the family with the support of a FH specialist nurse.

The role of the specialist nurse is integral to the DNA cascade testing process in legitimizing information, and

## KEY POINTS

- ♦ FH is a common genetic disorder of lipid metabolism affecting 1 in 500 people
- ♦ Roughly half of men with FH, if untreated, will have developed clinically evident CHD by the age of 55 years
- ♦ An unequivocal diagnosis can be made using a DNA-based test
- ♦ Genetic testing does not have any significant adverse psychological effects and may even improve wellbeing by helping individuals to make sense of their condition
- ♦ DNA testing can also act as a stimulus to family cascade testing

facilitating family communication.

Health professionals working within cardiology should be alert to the possible diagnosis of FH when encountering early onset CHD or a dominant family history of CHD.

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