Collecting genetic information in primary care: evaluating a new family history tool

Nadeem Qureshi, Jane Bethea, Bernadette Modell, Paul Brennan, Alexia Papageorgiou, Sandy Raeburn, Rhydian Hapgood and Michael Modell


Background. The family history is a time-honoured method for identifying genetic predisposition. In specialist practice the standard approach is to draw up a family tree based on a genetic pedigree interview, but this is too time-consuming and focused on single gene disorders to be applicable in primary care.

Objectives. To assess the ability of a brief self-administered Family History Questionnaire (FHQ), given to patients when they register with a GP, to identify genetic risk.

Methods. A comparative study. Informants completed an FHQ at registration, and later participated in a genetic pedigree interview. Two clinical geneticists independently scored results obtained with each instrument. Discrepancies were agreed by consensus. The genetic risks identified by the two instruments were compared.

Results. 326 new registrants completed the FHQ, and 121 also completed the genetic interview. 24% of FHQs and 36% of genetic interviews resulted in a score ‘higher than population risk’. There was 77% agreement in the scores obtained with the two instruments, with a moderate kappa of 0.52. (95% CI 0.40–0.64). There was 90% agreement in the scores for a family history of premature coronary heart disease (Kappa 0.67; 95% CI 0.49 to 0.85). The instruments were equally effective in identifying ethnicity-related risk of common recessive disorders.

Conclusions. The FHQ identified most informants with genetic risks that are appropriately addressed in primary care—those with a family history of premature coronary heart disease, those warranting specialist referral, and those who might appropriately be offered carrier testing. However, it was less effective in identifying those with a possible Mendelian disorder for whom more information was required.

Keywords. Clinical genetics, family history, family practice, questionnaire.

Introduction

It has long been recognised that family background must be taken into account in assessing patients’ health problems. At present, in the holistic context of general practice, the family history is more often used to obtain a short-hand view of family dynamics than for straightforward ‘medical’ reasons. Growing understanding of the role of genetic factors in health and disease is now leading to the inclusion of a family history in primary care guidelines for the prevention of common disorders, including cardiovascular disease and cancer. However, there is as yet no standard method for obtaining genetic
information in primary care. Current practice ranges from asking a simple question about illnesses in the family when a patient is first seen, to drawing a quick family tree.

Clearly, more standardised approaches for identifying familial genetic risk need to be developed. The optimal specialist approach, the genetic pedigree interview, is far too time-consuming for use in routine general practice. A simple structured format is needed to gather enough information on first degree relatives, grandparents and relevant second degree relatives to allow a preliminary assessment of genetic risk and also be suitable for review in a 10-minute consultation. Existing validated family history questionnaires are still too long and complex for this purpose.

There are three main reasons for collecting genetic family history information in primary care. Firstly, a positive family history is an important risk factor for common disorders, including premature cardiovascular disease, colorectal and breast cancer. The family history is most likely to forecast future disease if several family members have been affected, the relationship with the affected relative(s) is close, and the disease occurs at a younger than expected age (early onset is generally considered to be before the age of 55 or 60 years). Secondly, the family history may identify people at increased risk of sex-linked or dominant single-gene disorders (e.g. some forms of muscular dystrophy, familial hypercholesterolaemia, or familial cancers), who may benefit from specialist assessment. Thirdly, knowledge of ethnic background and kinship pattern (e.g. preference for consanguineous marriage) helps in identifying carriers of recessive disorders (e.g. haemoglobin disorders, or Tay-Sachs Disease) who may benefit from counselling about reproductive risk.

In secondary care, the commonest approach to genetic family history taking is disease-specific. A broader, generic approach using family history questionnaires and structured interviews has been evaluated in that setting. The objectives of this study were to develop a standardised self administered family history questionnaire (FHQ) that could be used in general practice to identify patients at possible increased genetic risk, and to compare information on genetic risk of single gene disorders, cancer, and coronary heart disease obtained using the FHQ, with information obtained by taking a detailed pedigree.

Methods

Prior to commencing the study, ethical approval was obtained from the relevant Local Research Ethics Committees.

Development of the family history questionnaire (FHQ)

Content and face validity of the FHQ was determined through several processes. In line with the method outlined by Jackson and Furnham, content validity was assessed through focus groups with GPs and practice nurses, and discussion with a panel of Clinical Geneticists. Face validity was determined through discussion with health service researchers with expertise in questionnaire design, and also through piloting the questionnaire in 3 general practices. Patients who had completed the questionnaire during the piloting phase, were interviewed to explore issues such as ease of completion and their understanding of the terms used and instructions provided. The collection of ethnicity data was adapted from another study.

The FHQ collects data in a tabulated form. It includes five short sections. The first two collect ethnic information and relevant past medical history, the third collects information about close relatives (mother, father, siblings, children and grandparents) and two optional sections collect relevant information on more distant relatives. Information on age of onset of the diseases reported is requested, as this helps to quantify genetic risk. The FHQ is accompanied by a prompt sheet listing the commonest genetic conditions in the community, and conditions with evidence for familial predisposition for which management guidelines have been developed.

Procedure

General Practices in the two research networks were informed about the project. Thirteen practices situated in districts ranging from economically deprived multi-ethnic areas of North London to the more affluent rural parts of Nottinghamshire agreed to collaborate. There were 10 urban and 3 rural practices, and practice profiles varied from 1 to 8.3 whole time equivalent (WTE) doctors, 0.75 to 3.5 WTE practice nurses, and 1600 to 17 400 registered patients.

Researchers were appointed in the two localities and trained by the research team and clinical genetic nurse specialists. Training included taking a pedigree using the standard approach of the Mid-Trent clinical genetics service.

Patient recruitment took place in the practices at staggered intervals over 15 months between October 1999 and December 2003. Practices decided their own
recruitment methods, most choosing to recruit new registrants 1 to 2 days per week over 3 to 4 months. New
patients aged 18 to 65 were invited to participate by a receptionist or practice nurse, when they registered
with the practice. Recruitment was preceded by full written consent. New patients were handed a pack
including the introductory information usually given by the practice, plus an information sheet and consent
form, and a copy of the FHQ. They were asked to bring the completed FHQ to the registration health con-
sultation, when the practice nurse quickly checked that it had been completed correctly, but did not assess
the content. Each practice was initially supplied with a pack of 50 FHQs. Three practices were sent another
50 FHQs during the study. Thus 800 FHQs were distributed among the 13 practices, though not all of them
were handed out. All patients who completed an FHQ were contacted by letter with the offer of a
structured pedigree interview at home, at the practice, or by telephone. The majority of interviews were
conducted by telephone.

The completed FHQs, and the pedigrees obtained by interview were anonymised, and triaged for
significant findings to be acted upon immediately by the patient’s GP. They were then sent to the clinical
geneticists for scoring using the system in Box 1. Initially the FHQs were scored by SR and the pedigrees
were scored by PB. All FHQs and pedigrees with scores other than N (no significant findings) were re-scored
independently by both geneticists, as was a random 50% sample of the FHQs and pedigrees that had been
scored N. The final scores were then agreed through consensus meetings.

The two instruments were also compared for a family history of coronary heart disease and cancer occurring
before 60 years of age, taking into account closeness of

- **R** = clear evidence of a Mendelian (single gene) disorder or
- **L** = possible Mendelian (single gene) disorder, or possibly
- **P** = evidence to support familial clustering of a polygenic
- **N** = no evidence to support an inherited predisposition to ill

<table>
<thead>
<tr>
<th>Box 1 Classification score used by geneticists to assess each instrument</th>
</tr>
</thead>
<tbody>
<tr>
<td>R = clear evidence of a Mendelian (single gene) disorder or significant cancer family history warranting specialist referral (i.e. moderate or high clinical risk).</td>
</tr>
<tr>
<td>L = possible Mendelian (single gene) disorder, or possibly significant cancer family history: more information required.</td>
</tr>
<tr>
<td>P = evidence to support familial clustering of a polygenic disorder, perhaps warranting attention.</td>
</tr>
<tr>
<td>N = no evidence to support an inherited predisposition to ill health.</td>
</tr>
</tbody>
</table>

The criteria for a significant family history are given in Table 5. Based on previous studies and consensus among the research team, ‘coronary heart disease’ was agreed to include the terms: heart attack, myocardial infarction, angina, and bypass operation.20

The proportion of informants scored as at definite or possible increased genetic risk was 24% using data collected with the FHQ, compared with 36% using data collected with the pedigree interview. The main difference was in the greater proportion scored as L (possible risk of a single gene disorder: more information required) on the basis of the pedigree interview (18% versus 9%). Table 3 shows the single gene disorders missed by the two approaches.

Further, Table 4 shows that there was 76.9% agreement for the scores between the FHQ and pedigree interview for individual respondents. The level of agreement, using the Cohen Kappa calculation, was moderate at 0.52 (95% CI = 0.40 to 0.64).22

Considering the number of relatives recorded in each instrument, 18 pedigree interviews (15%) recorded more first degree relatives than the FHQ, and 62 pedigree interviews (51%) recorded more second degree relatives that the FHQ. The difference in the number of secondary relatives recorded reached statistical significance (FHQ median 4, interquartile

### Results

Three hundred and twenty-six participants completed the FHQ prior to the ‘new registration’ check, and 121 (37%) also completed the pedigree interview. There was no statistical difference in age, sex or ethnic background between patients who only completed the FHQ, and patients who were also interviewed (Table 1). Thirty five (42%) of those respondents who provided the information had a University or higher education level.

Table 2 summarises the scores obtained using data collected by the FHQ and the pedigree interview. The proportion of informants scored as at definite or possible increased genetic risk was 24% using data collected with the FHQ, compared with 36% using data collected with the pedigree interview. The main difference was in the greater proportion scored as L (possible risk of a single gene disorder: more information required) on the basis of the pedigree interview (18% versus 9%). Table 3 shows the single gene disorders missed by the two approaches.

Further, Table 4 shows that there was 76.9% agreement for the scores between the FHQ and pedigree interview for individual respondents. The level of agreement, using the Cohen Kappa calculation, was moderate at 0.52 (95% CI = 0.40 to 0.64).22

Considering the number of relatives recorded in each instrument, 18 pedigree interviews (15%) recorded more first degree relatives than the FHQ, and 62 pedigree interviews (51%) recorded more second degree relatives that the FHQ. The difference in the number of secondary relatives recorded reached statistical significance (FHQ median 4, interquartile...
range 5–19; Interview median 16, interquartile range 9–19; $P = 0.04$).

Table 5 shows risk assessment for coronary heart disease and familial cancer using the two instruments. Based on a family history of CHD in first degree relatives with or without premature disease in second degree relatives, results using the two instruments were concordant for 109/121 informants (90%). Both instruments identified 16 informants as at increased risk of CHD, six were identified only by the FHQ and six only by the interview. The level of agreement fell slightly to 88% (107 of 121 informants) when significant family history was extended to include premature coronary heart disease only in second degree relatives.

The FHQs and pedigree interviews identifying a family history of breast/ovary and colorectal cancer were also reviewed against current primary care guidelines. Two of the three informants identified by the pedigree interview as at increased risk of breast/ovarian cancer were also noted on the FHQ. Four of the five informants identified by the pedigree interview with a first or second degree relative reported to have premature breast cancer were also noted by the FHQ. Both instruments identified two informants at increased risk of colorectal cancer. Table 5 also shows that the interview identified significantly more distant relatives diagnosed with cancer before the age of 60.

The ethnic origin of 15/121 informants (12%) conferred an increased risk of carrying a common recessive condition for which carrier testing is standard practice: 12 were at increased reproductive risk of haemoglobin disorders, and 3 (of Jewish ancestry) were at increased risk of Tay Sachs disease. All 15 were detected by both instruments. However, this ethnicity-based genetic risk was not taken into account by the geneticists.

### Discussion

Taking a full genetic family history is a sensitive and time-consuming clinical process, and no short-cut will be able to elicit equivalent information. However, simpler instruments are needed to improve the current very uneven approach to detecting genetic risk in primary care. The FHQ is not a substitute for a full pedigree but was designed as a time-efficient method of collecting relevant family history information (including ethnicity data) in primary care.

#### Results of the comparison

One hundred and twenty one patients completed both the FHQ and the standardised pedigree interview. Overall, there was a 77% agreement in scores between the two instruments, with a moderate kappa of 0.52. However, there were differences in concordance for the different categories (Box 1). The FHQ identified most people who needed specialist referral (category R). Seven informants gave a family history of a single gene disorder or cancer: of these, the pedigree interview identified six and the FHQ identified five. The FHQ was less effective in identifying those with a possible single gene disorder or familial cancer risk, for whom ‘more information was required’. Particularly relevant from a primary care perspective, when broad definitions of familial coronary heart disease risk were applied, both instruments identified similar numbers of at-risk informants (Table 5).

The inclusion of a question on ethnicity as an integral part of the family history is particularly relevant for
primary care, as both instruments identified 15 people in ethnic groups at increased risk of carrying a recessive disorder for which carrier screening in primary care is recommended. The fact that these individuals were not scored as L (possible risk of single gene disorder) by the clinical geneticists illustrates the difference in perspective between primary care and specialist genetics services.

We conclude that although the FHQ will not identify all patients at increased familial risk, it is capable of detecting many genetic risks of particular relevance to general practice and is an advance on the present haphazard methods of collecting this information.

**Strengths and limitations of the study**

Previous studies of FHQs in a primary care setting have not assessed the quality of the information recorded against an accepted standard. Currently there is no standard systematic method of identifying familial risk at the registration consultation in general practice. The ideal method of validating the information a patient provides about relatives might be to collect medical details directly from the relatives or from their medical records, but this is impractical, both ethically and logistically. Therefore the FHQ was compared with current best specialist practice: the clinical genetic pedigree interview. We did not see the pedigree interview as a gold standard for primary care, especially as the objectives of collecting genetic information in primary care and specialist practice are significantly different. However, it does permit the performance of the FHQ to be compared with optimal current practice.

The participation rate was low. From discussions with the practices’ reception staff it was evident that the ethical requirements for detailed pre-consent information, the consequent bulk of the documentation, and the two-staged data collection procedure ensured that only the most enthusiastic new registrants joined the study and completed the process. In a previous study that did not include this detailed consent procedure, and when the FHQ was used as part of routine practice, over 70% of new registrants complete the questionnaire. The completion rate is likely to be higher when the FHQ is completed by established patients, for example as part of an opportunistic health check.

Because the respondents were self-selected, it is possible that they were more likely to have a familial risk than the general population. This was taken into account in the sample size calculation. However the respondents had higher education levels than the general population. Approaches need to be developed to engage patients with lower literacy levels.

**Improving the FHQ**

The FHQ requires further modification and validation to improve its practical use. Subsequent to this study it has been adapted to allocate relatives to the maternal or paternal side, as this facilitates pedigree drawing and interpretation of the data using guidelines. The FHQ missed a number of people shown by the pedigree interview to be at possible increased genetic risk, a limitation that has also been noted with other approaches to gathering family histories. The fact that the FHQ was completed before the pedigree interview may have contributed to this difference, because patients had time to ruminate over their family history between the two stages of the study. This may also partly explain why the interview identified a larger number of more distant relatives, and yielded more

---

**TABLE 3** Mendelian (single gene) disorders identified by the geneticists in each instrument

<table>
<thead>
<tr>
<th>Type of condition</th>
<th>Familial risk information identified by BOTH instruments (scores in brackets)</th>
<th>Familial risk information MISSED by FHQ (scores in brackets)</th>
<th>Familial risk information MISSED by Pedigree interview (scores in brackets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite or Possible</td>
<td>Myotonic Dystrophy (R &amp; L)</td>
<td>Haemophilia (L)</td>
<td>Kerataconus (L)</td>
</tr>
<tr>
<td>Single gene disorders</td>
<td>Macular degeneration (L)</td>
<td>Childhood Liver disease (L)</td>
<td>Raised cholesterol (L)</td>
</tr>
<tr>
<td></td>
<td>Sickle cell trait (R)</td>
<td></td>
<td>Porphyria (R)</td>
</tr>
</tbody>
</table>

See Box 1 for the definitions of L and R categories.

**TABLE 4** Agreed scores for each instrument

<table>
<thead>
<tr>
<th>Pedigree Interview</th>
<th>FHQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>73</td>
</tr>
<tr>
<td>P</td>
<td>6</td>
</tr>
<tr>
<td>L</td>
<td>12</td>
</tr>
<tr>
<td>R</td>
<td>1</td>
</tr>
</tbody>
</table>

Kappa = 0.52; 95% CI for kappa = 0.40 to 0.64; % agreement of scores = 76.9% (95% CI = 69.3–84.4% ).

See Box 1 for the definitions of N, P, L and R categories.
details about age of onset of cancer in these relatives. This suggests that the accuracy of the FHQ might be enhanced by encouraging patients to discuss family illnesses with other relatives before completing it, and by highlighting the importance of recording the age of onset of illnesses. Further research could explore how information about genetic risks, identified from the FHQ, is disseminated through the extended family.

The need for updating
Any family history instrument must be a dynamic and not a static tool. For example, when the information obtained was reviewed against currently available familial cancer guidelines, five informants who had reported one first or second degree relative with premature breast cancer would be pushed into a higher risk category by the subsequent identification of another close relative with premature breast cancer. This observation underlines the requirement for regular updating, which could be facilitated both by the continuity of care offered by UK general practice, and by prompts generated by electronic health records.

Conclusion
If the full potential of the primary care family history is to be realised, standardised methods of recording are needed that are realistic in the context of general practice, and can respond to advances in genetic knowledge and patient record-keeping. Our FHQ represents the beginning of the task of designing a relevant instrument.

We do not consider that the FHQ is suitable for use as a general family history screening tool. Rather, it is a means to collect relevant information from patients with concerns about their family history, or when familial risk is indicated at an opportunistic health check with the doctor or nurse. The FHQ should be used to assess possible familial risk for conditions where there are effective interventions. Five conditions that fulfill this requirement and are a significant public health burden have been identified by the Centers for Disease Control and Prevention Family History Initiative consensus group, namely coronary heart disease, stroke, diabetes mellitus, breast/ovarian cancer and colorectal cancer. Intervention will not necessarily involve specialist referral: for example, a family history of premature coronary heart disease should lead to a diligent search for other modifiable cardiovascular risk factors, and if relevant the prescription of cholesterol lowering drugs. As genetic knowledge advances, and relevant evidence-based interventions become established, the list of conditions where identifying the familial risk is important will be extended, making enquiry about the family history increasingly important for the health of patients and their families.

Acknowledgements
We are very grateful for the support provided by the North Central Thames Primary Care Research Network (NoCTeN) and Trent Focus Collaborative Research Network (CRN). We are particularly indebted to the practices for their collaboration: The Caversham Group Practice; Bounds Green Group Practice; Park End Surgery; Dr H T Bilginer and Dr J S Rohan; Ampthill Square Medical Centre and the eight practices recruited through the Trent Focus CRN. Contributors to the study: Design, data collection, analysis, interpretation and drafting article: N Qureshi, J Bethea. Design and important critically intellectual content: A Papageorgiou, JA Raeburn, R Hapgood. Statistical advice: M Griffin, S Armstrong, C Coupland. Data Collection: M Elkins. BM is a retired Wellcome Principal Research Fellow.

<table>
<thead>
<tr>
<th>Classification of a significant family history</th>
<th>n (%) fulfilling criteria in both FHQ &amp; Interview</th>
<th>n (%) fulfilling criteria only in FHQ</th>
<th>n (%) fulfilling criteria only in Interview</th>
<th>Kappa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more 1st degree relative with CHD diagnosed &lt;60 or One or more 1st degree relative with CHD diagnosed at 60yrs or older, or unknown age &amp; a 2nd degree relative with CHD diagnosed &lt;60</td>
<td>16 (13%)</td>
<td>6 (5%)</td>
<td>6 (5%)</td>
<td>0.67 (0.49 to 0.85)</td>
</tr>
<tr>
<td>Above criteria, or Two or more 2nd degree relatives with CHD diagnosed &lt;60</td>
<td>16 (13%)</td>
<td>6 (5%)</td>
<td>8 (7%)</td>
<td>0.62 (0.45 to 0.80)</td>
</tr>
<tr>
<td>ONE or more 1st degree relative with Cancer diagnosed &lt;60</td>
<td>12 (10%)</td>
<td>6 (5%)</td>
<td>3 (3%)</td>
<td>0.69 (0.49 to 0.88)</td>
</tr>
<tr>
<td>ONE or more 2nd degree (or more distant) relative with Cancer diagnosed &lt;60</td>
<td>3 (3%)</td>
<td>10 (8%)</td>
<td>14 (12%)</td>
<td>0.09 (0.00 to 0.30)</td>
</tr>
</tbody>
</table>
Declaration

Funding: NHS Research and Development levy, NoCTeN and CRN. NQ is also receiving fellowship support from the Commonwealth Fund (a private independent foundation based in New York City). The research was undertaken independent of the funding organisations and the views expressed in this publication are those of the authors and not necessarily those of the NHS executive or the Commonwealth Fund, its directors, officers, or staff.

Ethical approval: Camden and Islington Community Trust and Enfield and Haringey Research Ethics Committees; Queen’s Medical Centre Research Ethics Committee.

Conflicts of interest: none.

References