Evaluation of Methods of Identifying Carriers of Haemophilia

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Introduction

In South Africa, the identification of carriers of haemophilia has largely been unsuccessful. This could perhaps be attributed to the use of an indirect method of carrier tracing, i.e. the issuing of letters to probands* to pass on to their female relatives.

Undoubtedly, identification of carrier status has important implications in terms of determining who in the family may be affected, timely antenatal diagnosis, and improved provision of informed obstetric care to those male foetuses at risk of haemophilia [1]. Therefore, no effort should be spared in tracing and testing at-risk relatives of people with haemophilia (PWH) to manage the potential sequelae.

The objective of this study was to review the available literature on carrier tracing in an attempt to ascertain the most appropriate and effective method for identification of haemophilia carriers in the South African context.

Method

A general internet literature search was done using MEDLINE and Google Scholar, and the key words "methods" AND "carrier identification" AND "haemophilia".

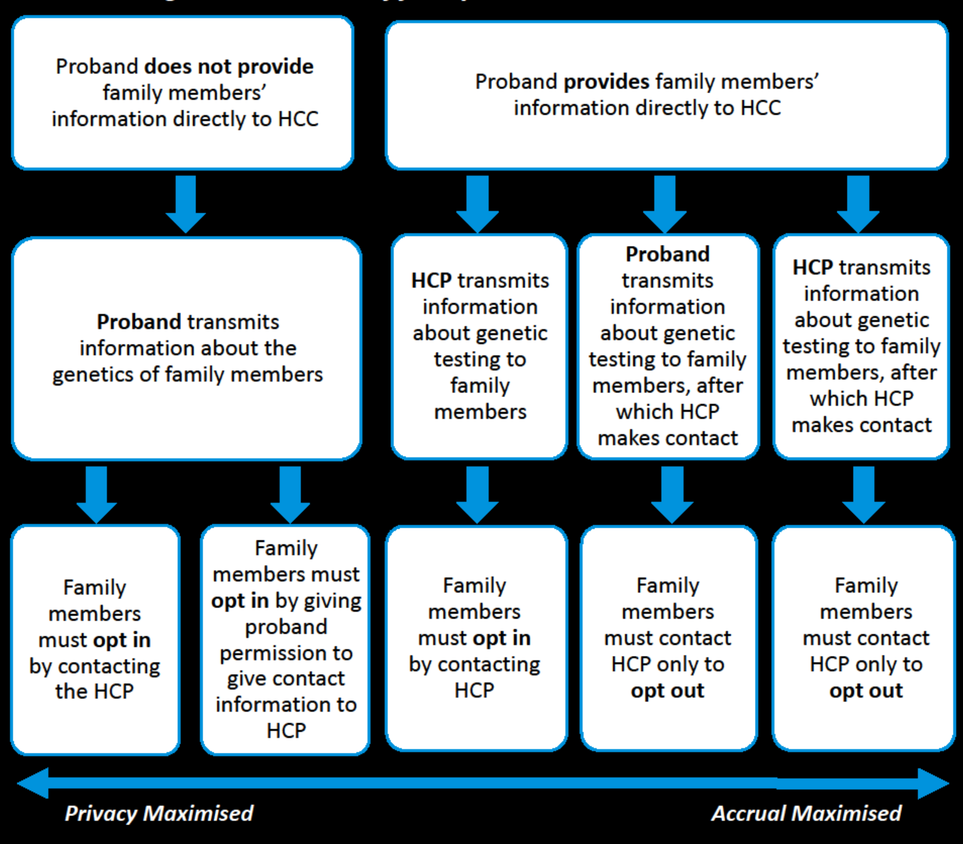
The search generated 17 articles of interest to the reviewers, which were subsequently analysed and summarised in terms of relevance.

Findings

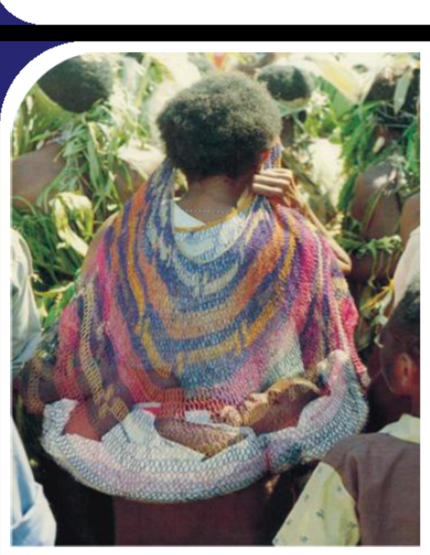
A review of the literature revealed that several approaches may be utilised to identify carriers. Indeed, Beskow *et al* in a review of family-based recruitment strategies for familial genetic research, revealed a number of possible approaches along a continuum, with direct investigator contact maximising access to potential participants and family-based recruitment (via a proband) maximising privacy[2]. *(Figure 1)*

The advantages and disadvantages of the different approaches were tabulated and analysed. *(Table 1)*

Figure 1: Overview of family-based recruitment methods[2]



Discussion



A review of the literature suggests that the nature and distance of the relationship between family members leads to different patterns and probabilities of communication, with the tendency of probands not to pass on information to relatives outside the immediate family, who may not personally be known to them[8].

Varekamp and Sorenson *et al* showed that kin, especially parents (mothers) and sisters were the most important source of information for potential carriers[3,6]. Sorenson and Reid argued that the fact that these discussions clearly followed gender-lines may be anticipated with an X-linked genetic disease[6,7]. Indeed, in many studies, it was recognised that women often play the role of "kin keepers', particularly in taking responsibility for their family's health, and this may extend to genetic issues[8], where women may be regarded as "genetic housekeepers"[1,7].

The literature review revealed that there also may be cultural and ethnic differences in attitudes towards the autonomy and confidentiality of genetic information[8]. In South Africa, where cultural taboos, linguistic challenges and education levels may prohibit open discussion surrounding issues of heredity, and hence identification of carriers, Solomon found that there was a critical need for socio-culturally tailored language-specific education for families with haemophilia[9].

Reid found that the level of education influenced the uptake of services by at-risk relatives, with those responding to a professional rather than a proband, being more likely to be educated to a higher level [1]. Ranta *et al* found that, in a relatively well-educated study population, the attitudes towards research on haemophilia and carrier testing were positive, the hereditary nature of haemophilia, and understanding of the implications of not disseminating relevant genetic information was well known[10].

Table 1: Methods of approach

	DIRECT	INDIRECT	HYBRID/ INTERMEDIATE
Description	Letters to carriers either from Haemophilia Comprehensive Care Centres (HCCC) or patient organisations	HCCC may approach proband to provide information to at-risk relatives to recruit them for carrier testing	Proband provides at-risk relatives contact information after advising relative, with follow-up by HCCC. [1,4]
Advantages	• Maximises access to carriers/ uptake of service[1,2,5]. • Increased accuracy of information[5] • Relieves burden from proband [2,5] • Exercising of ethical "duty to warn"[5]	• Maximises privacy • Probands have a good knowledge of personality traits and family dynamics[2,5] • Potential for psychological harm through unsolicited contact is minimised[5]	• High response rate[3], especially with opt-out option[2.] • Limited or no perception of invasion of privacy[6] • Lower potential for psychological harm through unsolicited contact • Confidentiality is protected • Balanced approach[2]
Disadvantages	• Perceptions of invasion of privacy [5] • Psychological harm to relatives [5,7] • Right "not to know" violated[5] • Actual harm to relatives[5] • Detrimental impact on family dynamics [5,7] • Breach of confidentiality[5] • Potential for undue influence[5]	• Perceived burden by proband • Perceived undue pressure by at-risk relatives [2,5] • Inaccurate information is conveyed by proband • Eligible relatives not actually contacted [1,2] • Perceptions of invasion of privacy • Right "not to know" violated	• When cascade approach** utilised, success or failure of recruiting one family member can affect participation of others • Response rates may be lower if proband sole source of information[5.]

Conclusion

Based on the findings of our research, it appears that for successful carrier tracing, an appropriate balance is provided by an intermediate or hybrid approach in which informed consent is sought from the proband, who is then provided with standardised written material regarding genetic counseling and testing availability, to distribute to at-risk female relatives. This should be followed by an opt-out approach[11].

In order to optimise this hybrid approach, we propose that reminders be sent to probands, since it has been found that response rates may be low in the absence of reminders[12,13]. In addition, we propose that reassurance of probands that relatives may actually welcome the information and the opportunity to have their carrier status assessed, will motivate probands to disseminate information accurately.

Recommendations

- Genetic counseling and carrier testing information should be directed via women, instead of a proband[3].
- Communication with relatives must be sensitive to family dynamics, language, level of education and socio-cultural context[1,8, 9,10].
- An intermediate/hybrid model of carrier tracing is well-suited to a resource-constrained setting.
- Carrier testing services should be readily available at HCCC and every opportunity should be taken to discuss carrier testing at the point of care[15].
- Timing of testing should be age appropriate with due consideration of the "best interests" of the potential carrier, and informed consent[7, 11].
- A multi-disciplinary team approach should be employed as this is beneficial in terms of improvement of quality of care[16].
- Support groups/self-help groups should be established to empower carriers[14], including availability of services to guide reproductive choice [10].
- Family genetic records and a Haemophilia Genetic Register should be established and maintained at each HCCC[11].
- The pedigree should be established and updated at least annually to try to confirm family relationships and add new family members[11].

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* Proband is the first affected family member who seeks medical attention for a genetic disorder.

** Cascade approach begins with eldest generation and approaches relatives in successive generations in a step-wise fashion

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