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Cascade carrier testing after a child is diagnosed with cystic fibrosis through newborn screening: investigating why most relatives do not have testing

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Purpose: Newborn screening for cystic fibrosis is increasingly available, but cascade testing following the diagnosis in a child has received little attention. We previously reported low levels of cascade testing over time, and this study investigated motivators as well as barriers to testing.

Methods: Parents were interviewed about communicating the genetic information and also asked to recruit their relatives to receive a specifically developed questionnaire.

Results: Thirty parents were interviewed and addresses of 284 relatives were provided; completed questionnaires were received from 225 (79%). A relative's relationship to the child, as well as knowledge, is associated with having had carrier testing. Relatives' reasons for testing included curiosity and wanting information for other relatives and for reproductive planning. Reasons for not testing were perceived irrelevance, lacking awareness, and viewing it as something to do in the future. Parents communicated the genetic information to relatives in various ways, which contributed to whether relatives accessed carrier testing.

Conclusion: Newborn screening programs should provide support to parents to aid communication of genetic information to relatives. (Ir)relevance of testing is often linked to life stage; ongoing support and communication may allow relatives to learn of their risk and then seek testing, if they wish, at a time perceived to be most relevant to them.

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INTRODUCTION

Newborn screening (NBS) for cystic fibrosis (CF) has increasingly been adopted by many countries worldwide, including Australia and New Zealand (since 1981), the United Kingdom (2007), a number of other countries and regions in Europe, and the United States.[1–3] The birth prevalence of CF is ~1 in 3,500 for northern European populations,[4] with a carrier frequency of 1 in 25, making it the most common severe recessive condition in children. In the state of Victoria, Australia, CF has been part of NBS since 1989, using immunoreactive trypsinogen as the screening analyte, and from 1991, using CF transmembrane conductance regulator gene mutation analysis for elevated immunoreactive trypsinogen results.[5]

A supplement edition of *Genetics in Medicine* (December 2010) highlighted the need for establishing systems for short- and longer-term follow-up of children who receive positive screening results from NBS. Long-term follow-up of children diagnosed with CF is generally achievable due to their ongoing treatment and management.[6] One important area that has been poorly studied is the impact of family cascade testing following a child's diagnosis of CF through NBS. "Cascade testing" is the term often used to describe genetic testing of relatives of a person diagnosed with a genetic condition or identified as a genetic carrier. The "cascade" refers to the process of testing an individual for the familial mutation(s) and then, in the event of a positive result, descendants are tested; descendants of an individual who receives a negative result are not tested. The diagnosis of a child with CF inherently means relatives are at increased risk of being CF carriers (e.g., aunts and uncles of a child with CF have a 50% risk). Carrier relatives may have their partners tested. When both partners are identified to be carriers, knowledge of carrier status provides relatives with information that may be used to make reproductive decisions, which might include having no (more) children, prenatal diagnosis, preimplantation genetic diagnosis, using donor gametes, and adoption.

We have previously investigated cascade carrier testing of relatives of children diagnosed with CF through NBS in Victoria, Australia. Parents are counseled regarding the familial implications at the time of their child's diagnosis and are provided with a letter to give to relatives to assist them with communicating the genetic information.[7] Even though carrier testing was free of charge to relatives who wished to receive testing, only 11.8% of relatives accessed carrier testing.[8]

The aim of this study was to explore the reasons why relatives access or do not access carrier testing following a child's diagnosis of CF by NBS.

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MATERIALS AND METHODS

This study was approved by the Human Research Ethics Committee (HREC 27121C) of the Royal Children's Hospital, Melbourne.

Recruitment of parents and relatives

Details of recruitment are described elsewhere.[8] Briefly, parents of children with CF were approached at the Royal Children's Hospital CF clinic. Participating parents were interviewed by telephone, and a family pedigree was constructed. Using the pedigree, relatives eligible to complete the questionnaire were identified. These included relatives ≥18 years of age with a carrier risk of ≥1/8 (i.e., parents, siblings, first cousins, aunts and uncles, grandparents, great aunts and uncles, and first cousins once removed). Parents sought verbal consent from their relatives to pass on relatives' address details to the researchers.

Interviews with parents

The phone interviews explored parents' experiences of communicating the genetic information about CF with relatives. The semistructured interview included open-ended questions about the first-time genetics was discussed by health professionals; parents' recollection of that discussion; their thoughts at the time; their views about which relatives they thought would be interested in knowing the information; their experience talking to relatives; how their relatives responded; how this experience could have been made easier; and what parents thought might be the benefits and barriers to CF carrier testing. The interviews were audio-recorded, transcribed verbatim, and de-identified, and pseudonyms were assigned.

Questionnaire development

We developed a questionnaire to explore relatives' knowledge, attitudes, and factors that influenced decisions about carrier testing, and included closed and open-ended responses (**Supplementary Data** online). The questionnaire was developed in three stages:[9] drafting the initial bank of items; validating the content by expert review using a modified Delphi technique;[10] and testing the questionnaire. The expert review panel comprised genetics education researchers, genetics screening researchers (for CF and other conditions), experts in questionnaire design, genetic counselors, clinical geneticists, respiratory physicians, and CF clinic staff. The resulting questionnaire was tested with eight volunteers from the Cystic Fibrosis Victoria Association who were relatives of people with CF (but who were ineligible for the study sample because their relative with CF was not born in 2000–2004), and modifications were made in response to their feedback.

Data analysis

Transcripts of interviews and open-ended questionnaire responses were analyzed using conventional and summative content analysis, respectively;[11] co-coding was performed independently by B.J.M. and M.A.A. NVivo software (QSR International, Melbourne, Australia) was used for storage of transcripts and management of the coding process. All quantitative analyses were performed using Stata software (Stata Statistical Software, Release 10.1, StataCorp, College Station, TX). Continuous variables were summarized using means and SDs, or medians and interquartile ranges, and categorical variables were summarized using percentages. Knowledge scores and attitude scores were compared between the tested and not-tested groups using *t*-tests. Logistic regression was used to examine the relationship between test status (outcome) and the following variables (potential predictors): respondent's gender; respondent's relationship to the child with CF; whether or not the respondent already has children; the respondent's reproductive plans; knowledge score; and attitude score. Both unadjusted and adjusted (multivariable) logistic regression models were fitted. Rescaled versions of the two variables "knowledge" and "attitude" were created for use in the logistic regression modeling so that the reported odds ratios corresponded to a one SD unit increase in each of these variables.

Table 1 Characteristics of the 30 parents interviewed

Characteristic	Number of parents interviewed
Number of children	
1	10
2	14
3	4
>3	2
Number of children with CF	
1	29
>1	1[a]
Child with CF is last born/only child	
Yes	20
No, other child(ren) born later	10
Age range of parents (years)	22–46

CF, cystic fibrosis.

[a]The second child with CF was older than the child with CF in this study, and was diagnosed as a result of the younger child's diagnosis.

RESULTS

Description of participants

Parents of 30 children with CF, who were recruited through the Royal Children's Hospital CF clinic,[8] were interviewed (**Table 1**); of them, 24 provided addresses for themselves and their relatives. Of the six parents who did not recruit relatives, five parents could not be re-contacted after the initial interview to obtain relatives' addresses, and one parent reported all relatives to be disinterested in participation. From the 284 addresses provided, 225 (79%) questionnaires were completed and returned by parents and relatives. A description of the characteristics of the questionnaire respondents is provided in **Table 2**, including testing status.

Uptake of, knowledge about, and attitude to CF carrier testing

Eighty-three (37%) respondents stated that they had had carrier testing since their relative's diagnosis with CF through NBS.

Table 2 Characteristics of respondents to questionnaire

Characteristic, N^a = 225	*n* (%)	Tested, *n* = 83	Not tested, n^b = 142
Gender			
Male	90 (40.0)	26 (31.3)	64 (45.1)
Female	135 (60)	57 (68.7)	78 (54.9)
Relationship to child with cystic fibrosis			
Parent	45 (20.0)	24 (28.9)	21 (14.8)
Sibling	2 (0.9)	0 (0.0)	2 (1.4)
Aunt/uncle	55 (24.4)	29 (35.0)	26 (18.3)
Grandparent	52 (23.1)	18 (21.7)	34 (23.9)
First cousin	16 (7.1)	4 (4.8)	12 (8.5)
Great aunt/uncle	25 (11.1)	5 (6.0)	20 (14.1)
First cousin once removed	30 (13.3)	3 (3.6)	27 (19.0)
Highest level of education			
Year 11 or below	55 (24.9)	18 (21.7)	37 (26.8)
Year 12 or equivalent	40 (18.1)	16 (19.3)	24 (17.4)
Trade/apprenticeship	24 (10.9)	4 (4.8)	20 (14.5)
Tertiary certificate/diploma	38 (17.2)	15 (18.1)	23 (16.7)
University qualification	58 (26.2)	27 (32.5)	31 (22.4)
Other	6 (2.7)	3 (3.6)	3 (2.2)
Marital status, *n* (%)			
Never married	26 (11.7)	4 (4.9)	22 (15.6)
Married	150 (67.3)	61 (74.4)	89 (63.1)
De facto (living with partner)	20 (9.0)	9 (11.0)	11 (7.8)
Separated but not divorced	3 (1.4)	1 (1.2)	2 (1.4)
Divorced	14 (6.3)	5 (6.1)	9 (6.4)
Widowed	10 (4.5)	2 (2.4)	8 (5.7)
Have children already, *n* (%)			
Yes	186 (82.7)	75 (90.4)	111 (78.2)
No	39 (17.3)	8 (9.6)	31 (21.8)
Plan to have (more) children, *n* (%)			
Yes	33 (14.7)	10 (12.1)	23 (16.2)
No	174 (77.3)	64 (77.1)	110 (77.5)
Currently pregnant	4 (1.8)	3 (3.6)	1 (0.7)
Do not know	14 (6.2)	6 (7.2)	8 (5.6)

[a]Not all respondents completed "level of education" and "marital status," therefore *n* = 221 and *n* = 223, respectively for those variables. The median (interquartile ranges) age was 43 (35–62) years, with a range of 18–83 years. [b]For the variables "highest level of education" and "marital status" in the "not tested" columns, *n* = 138 and *n* = 141, respectively, because not all respondents completed these items.

Table 3 Logistic regression of variables associated with having had carrier testing

Variable	n_{tested} = 83 (%)	Unadjusted analysis OR (95% CI), *N* = 225	Adjusted analysis OR (95% CI), *N* = 225
Gender of relative			
Female	*n* = 57 (42)	1.8 (1.1–3.1)	2.0 (0.9–4.3)
Male	*n* = 26 (29)	Reference group	Reference group
		P = 0.02	*P* = 0.07
Category of relationship			
Parent	*n* = 24 (55)	Reference group	Reference group
Aunt/uncle	*n* =29 (53)	0.9 (0.4–2.3)	1.4 (0.5–4.2)
Grandparent	*n* =18 (35)	0.4 (0.2–1.1)	0.6 (0.2–1.5)
Other	*n* = 12 (16)	0.1 (0.0–0.3)	0.2 (0.1–0.7)
		P < 0.001	*P* = 0.01
Have children already			
Yes	*n* = 75 (40)	2.6 (1.5–4.5)	2.9 (0.9–8.7)
No	*n* = 8 (21)	Reference group	Reference group
		P < 0.001	*P* = 0.06
Planning to have (more) children			
Yes	*n* = 10 (30)	Reference group	Reference group
No	*n* = 64 (37)	1.3 (0.5–3.2)	0.4 (0.1–1.7)
Currently pregnant	*n* = 3 (75)	5.7 (1.0–33.0)	2.5 (0.0–123.6)
Do not know	*n* = 6 (43)	1.6 (0.5–5.4)	0.9 (0.1–7.1)
		P = 0.1	*P* = 0.4
Knowledge score		2.7 (1.8–4.2)	2.0 (1.1–3.8)
		P < 0.001	*P* = 0.03
Attitude score		1.5 (1.2–2.0)	1.3 (0.9–1.8)
		P = 0.003	*P* = 0.1

In the logistic regression, correlation of respondents' outcomes within family groups was allowed for because these cannot be considered independent. The ORs were estimated using the method of marginal modeling using generalized estimating equations with information sandwich ("robust") estimates of SE specifying an exchangeable correlation structure. Applying this method widens the CIs for the estimated ORs so that they reflect the true precision of the estimates. To account for the fact that relatives of different children had variable times within which to access carrier testing, Cox proportional hazards models (using random effects to allow for clustering with families) were fitted in a sensitivity analysis to analyze time from diagnosis until testing. Because the hazards ratios were essentially the same as the ORs, we report only the results from the logistic regressions here.

CI, confidence interval; OR, odds ratio.

The mean (SD) number of items in the knowledge section of the questionnaire that were answered correctly was 9.6 (2.2) out of a possible 12 items. Overall, respondents were knowledgeable about CF; the mean knowledge score was 10.6 points for the tested respondents and 9.0 points for the not-tested respondents, with a mean difference of 1.6 points (95% confidence interval: 1.0 to 2.2; $P \leq 0.001$).

Attitude to carrier testing was measured using five word-pair items, each on a 5-point Likert scale from 0 to 4 (the midpoint of the attitude score represents neutral attitudes, higher scores indicate positive attitudes, and lower scores indicate negative attitudes).[12] The median attitude score for the 225 respondents was 16 (interquartile range: 13–18) points out of a possible 20 points. The mean (SD) attitude scores of those who were tested and not tested were 15.8 (4.0) and 14.0 (5.1), respectively, with a mean difference of 1.8 points (95% confidence interval: 0.6–3.2; $P = 0.005$). Therefore, being tested was associated with greater positive attitudes. Both groups (tested and not tested), however, displayed positive attitudes.

Logistic regression modeling: variable associated with CF carrier testing

The adjusted logistic regression results (Table 3) show that those who are outside the immediate family are less likely to have been tested and those with higher knowledge scores were more likely to have been tested; for each SD unit increase in knowledge score, the odds of testing were doubled.

Table 4 Relatives' reasons for having had or not having had CF carrier testing

Categories of responses	Aunt/uncle	Grandparent	Sibling	First cousin	Great aunt/ uncle	First cousin once removed	Total
Reasons for having had carrier testing							
"Wanted to know"	8	11		3	3	2	27
"I wanted to pass this information on"	6	7		1	2	1	17
"I was pregnant"	9						9
"I was about to try for children…ensure our babies would be clear of the disease"	7			1			8
"Be of assistance for research"	3			1			4
"I am donating to IVF"				1			1
Total							66
Reasons for not having had carrier testing							
"I had already had my children"	10	11			9	5	35
"Never really thought about it"	5	9		1	8	11	34
"No need yet"	5	1	2	7		8	23
"Never been asked"	4	4			3	5	16
"Haven't got around to it"	3	2		1		1	7
Barriers to obtaining testing: "expensive," "it seemed very inaccessible"	1	1		3			5
"My mum had the test and she is not a carrier"		2				2	4
Already know: obligate carrier[a]		2					2
"My family said I would blame myself"		2					2
Total							128
No response	3	3		2	2	1	11

n = 180, the 45 parents who completed the questionnaire were excluded from this analysis because they are obligate carriers. The open-ended responses in the questionnaire were brief and were grouped by similarity of responses for content analysis. The number of times each category of response was given is reported. Some relatives' responses were coded into one category; others gave responses that were coded into more than one category.

CF, cystic fibrosis; IVF, in vitro fertilization.

[a]Two grandparents selected "No, because I know I must be a carrier." They did not provide any further comment.

Open-ended responses: relatives' reasons for having or not having CF carrier testing

A total of 169 relatives provided a response in the open-ended section of the questionnaire to describe the main reason why they had or had not had CF carrier testing; 11 did not provide a response (**Table 4**).

Interviews with parents: exploring communication of genetic information to relatives

The interviews with parents were coded into themes covering the time when information about carrier testing was first introduced to parents and the subsequent journey of communication with relatives that was undertaken. Example quotes are provided in **Table 5** to illustrate these themes.

1. *Shock of diagnosis limits parents' recollection of information given at that time*: Parents described how the impact of the diagnosis meant that their memory of this time was "cloudy" or a "blur" (**Table 5**, quotes 1 and 2).
2. *Communication to relatives focused on seeking support after the diagnosis*: The diagnosis and the information provided to parents have three aspects: the health information as it relates to their child; the genetic implications for themselves for subsequent pregnancies; and implications for their relatives. Parents described talking to their relatives and often integrating the genetic information into the discussion about the diagnosis and health implications (**Table 5**, quotes 3 and 4). There did not seem to be a demarcation of these concepts. The initial reason for talking to relatives was clearly for familial support based on the diagnosis rather than to provide genetic information (**Table 5**, quote 5).
3. *Relatives' stage of life*: Parents identified that the genetic information would be most relevant to relatives who were pregnant or known to be considering pregnancy in the not too distant future, and the impetus to tell other relatives was diminished (**Table 5**, quote 6).
4. *The process of family communication of genetic information*: Parents felt that the task of telling relatives the genetic information began with them, but could be shared based on existing social relationships (**Table 5**, quotes 7 and 8). There were some relatives with whom parents did not have a close relationship, but the parents knew how to contact them. Parents expressed reluctance to initiate contact on the basis of sharing the diagnosis and informing of the genetic implications as they felt this would be coming "out of the blue," and not appropriate (**Table 5**, quote 9). Parents also discussed the potential for

Table 5 Interviews with parents: influences of the communication of genetic information to relatives

Theme	Example quote
Parents have limited recall of information given at diagnosis: shock of diagnosis	1. "… We went up to visit [the genetic counselor] and we were up there for… I can't tell you what was said in there, it was very cloudy back then for us. All I know is that we did go up and speak to her." (Alison) 2. "He was diagnosed with it and a lot of things were going through your mind, just everything was sort of a blur so everything that we were told just didn't sink in." (Olivia)
Communication to relatives focused on seeking support after the diagnosis: talking about genetics is a "secondary thing"	3. "…When I was told what it was, and that it is a genetic condition, once I told family members that [my child] had CF, it was sort of part of the explanation anyway." (Ainslie) 4. "It was all in that one hit sort of thing." (Anthony) 5. "We were engaged in our own little world a bit, taking on all the immediate information about how to manage the condition … Dealing with the things you are talking about [the genetic information], it was really a secondary thing." (Gabrielle)
Salience of information: consideration of relatives' stage of life	6. "No one was pregnant in my family so there was no real need for concern." (Ainslie)
Process of family communication of genetic information: sharing the role of communicator, relying on existing social ties, avoiding feelings of guilt or blame	7. "We told the immediate families and if they wanted to go into it further then it was up to our parents to tell their brothers and sisters what is in the family if they wanted to. We just told immediate family at the time. Then who they told afterwards it was up to them." (Anthony) 8. "I think they are just at the stage where they just don't want to know … hopefully when their kids are in the teenage years … maybe that is when maybe mum needs to broach it again just so that they know to get tested." (Michelle) 9. "I don't think I would just ring them [my cousins] up and say, "you should have carrier testing for CF." I think I would feel a bit, "we are not that close," to ring them out of the blue." (Deborah) 10. "B.J.M.: And your parents, have you talked to them about it? Kate: No, well they didn't get the testing done, there was no point getting testing done to find out which side it was on because then there is somewhere to point the finger of blame. B.J.M.: Is that something that they both feel really strongly about? Kate: I haven't discussed their feelings with them, that was a decision that we made ourselves and realistically, if they were to go and get the testing done, I don't want to know which side it came from. B.J.M.: Why is that? Kate: I don't want there to be that element of blame in my own mind, yeah that is probably the main reason."
Relatives' limited understanding and interest in the genetic information: unrealistic image of CF, genetics concepts are difficult, "it won't happen to them"	11. "They don't see [my child] as much because they are in [a different town] compared to my relatives down here so I think they were in shock that it had all happened and when they see him and he looks fine, and it is a bit harder for them to comprehend … it is just like, "oh he just looks so well it is hard to believe isn't it" more than, because [my child] has never been skinny or, you know, anything like that and he has always been able to run around and keep up with all the kids, so yeah, it, they know it is there and they look after him and everything, but they say "oh it is hard to believe that he has this problem." " (Esther) 12. "I don't think [my sister who was pregnant] realizes the whole genetic thing and I just didn't want to get into the whole thing with her because explaining something to someone who just doesn't get it and maybe is not going to get it. So I thought "oh well, just wait and see when the baby is born," and he is fine." (Deborah) 13. "We told the family what we had to do when the kids were diagnosed but, I don't know, it wasn't…it fell on deaf ears; they don't believe it will happen to them, or that they would be interested in finding out. They say, "oh well it won't happen to them" even though it happened to us and there is no family history of CF in either side of the family." (Lois)

CF, cystic fibrosis.

carrier testing to result in apportioning blame and evoking feelings of guilt. Parents, therefore, did not want some relatives to access testing and chose not to pass on the information. Although parents wanted to avoid relatives (usually the grandparents) feeling guilt or blame, quote 10 provided in **Table 5** demonstrates that parents may have wanted to avoid these feelings themselves toward their own parents.

5. *Relatives' limited interest in and understanding of the genetic information*: Parents expressed some frustration that their relatives did not perceive CF to be a serious, life-shortening condition, because they did not have frequent contact with the affected child, and therefore believed that their relatives judged testing to be unnecessary (**Table 5**, quote 11). Although parents were satisfied with their own understanding of the genetic cause and inheritance of CF, they felt that these were difficult concepts for their relatives to understand (**Table 5**, quote 12). As such, communication was challenging. Parents felt that relatives believed it will not "happen to them" (**Table 5**, quote 13).

DISCUSSION

This study has identified factors that contribute to whether relatives access cascade carrier testing after a child is diagnosed with CF through NBS. The quantitative data have shown that a relative's relationship to the child with CF, as well as the relative's knowledge about CF, is associated with having had carrier testing. Qualitative data from the questionnaire identified

relatives' main reasons for having had testing to be curiosity, a desire to provide information for other relatives, and for reproductive planning purposes. Relatives' main reasons for not having had carrier testing were a perception of irrelevance due to completed families, lacking awareness of the possibility, viewing it as something to do in the future, and waiting for someone to ask them to have testing. Interviews with parents highlighted the role they play in communicating the genetic information to relatives and how information is not always disseminated equally to relatives, which may contribute to whether relatives access carrier testing.

Cascade testing following NBS is an important area to address because the diagnosis of a child has implications for other relatives. Our clinical practice is an approach in which parents are counseled about familial implications at the time of diagnosis, and provided with a resource to give to relatives, but this results in a small proportion of relatives accessing testing.[8] Overall, the respondents to the questionnaire had positive attitudes toward carrier testing, yet nearly two-thirds had not had testing. If relatives are aware of their risk and make a conscious decision to not be tested, then relatively low uptake rates such as this are not of concern; however, this study has shown that misinformation (or lack of information) about salience and availability of testing for relatives means that many relatives are in fact unaware of their risk and have not actually made a decision about testing.

In this sample, a third (59/180) of nonparent relatives reported having had carrier testing since the diagnosis of their relative with CF through NBS. Aunts and uncles of the child with CF in this study who were tested associated testing with reproductive plans; their reasons for testing included "I was pregnant" and "I was about to try for children." A recent study describes reproductive decision making for CF carrier couples with and without an affected child; once relatives learn that they are carriers and if their partner is also a carrier, there are significant impacts both emotionally and practically for future (and existing) pregnancies.[13]

Aside from reproductive planning, another reason for carrier testing is to clarify carrier status to pass information on to other relatives. This may particularly apply to grandparents of a child diagnosed with CF through NBS, and to great aunts/uncles who are in a similar stage of life to grandparents. In Australia, grandparents are offered testing to narrow the scope of testing in the family through risk clarification. In a study in the United Kingdom, testing grandparents was specifically discouraged due to the potential for either evoking feelings of guilt and blame, or the discovery of nonpaternity.[14] Similarly, a study in the United States excluded testing of grandparents.[15] Despite the restrictions in those two studies, both report receiving requests to test grandparents who were interested. Limiting testing to relatives of reproductive age because of the possibility of raising feelings of guilt in the grandparents[14] has been challenged in our study. The interviews revealed that parents of the child with CF sometimes discouraged their own parents (the grandparents of the child) from being tested, not because they were concerned that the grandparents would blame themselves, but because they did not want to blame their parents for passing the mutation on to them and subsequently onto their child (**Table 5**, quote 10). Although potential harms exist, testing older generations removes the need for many in subsequent generations to be tested.[16] Another benefit may be taking on a role in communicating the genetic information within the family.[17] In our study, parents described how their own parents took on the task of talking to the more distant branches of the family tree.

The main reasons stated by relatives for not being tested were related to their stage of life (**Table 4**); some had completed their families, whereas others had "never really thought about it." In a US study, relatives planning a pregnancy were more likely to have testing than those who were not when offered carrier testing.[15] That study describes a research setting in which an "active" approach was taken to offer carrier testing to relatives, which has been shown to increase testing uptake[15,18,19] compared with a more passive research approach[20] or uptake in a clinical setting.[8] Translation of active approaches into the clinical setting is unlikely to be possible, primarily due to the extra resources required. A research project may employ a specific person to facilitate the process for families, or attempt to remove barriers by taking testing to the family rather than requiring relatives to take action and contact a clinical service for an appointment. In addition, active approaches that make direct contact from the clinical service to warn relatives of their genetic risk may not always be possible due to privacy or similar legislation. For example, in Victoria, Australia, it is not possible for a state clinical service to directly contact a relative to pass on relevant information unless the person who was tested has consented to their details being provided to the relative (L. Skene, personal communication). A person who wants genetic information from a relative about their risk of having a child with CF has to contact their relative who has been tested to seek consent for the service to pass on genetics information to them, or ask the service to seek the relative's consent. Therefore, this still relies on parents making contact with their relatives to seek consent to pass on contact details. As described in our study, some parents were reluctant to contact relatives with whom they have little or no contact.

An alternative to taking an active approach with relatives is to take a more active approach with parents. In our setting, the discussion of familial implications happens at the same time the parents are receiving further information about the diagnosis and the management of CF after NBS. Although this approach is successful to some extent,[8] this protocol does not work for all families, or indeed all members of a family. There may be benefit in offering parents a second genetic counseling session, after a period of time allowing for the parents to adjust to the diagnosis, in which issues related to carrier testing (both for parents' subsequent pregnancies and cascade testing for relatives) can be revisited. This should not replace discussion at the time of diagnosis because talking about the genetic implications with parents immediately is necessary to provide parents and their relatives the opportunity to learn the information quickly, and

make a decision about carrier testing, especially with regard to future pregnancies for the parents. For these reasons, talking about cascade testing should remain part of the genetic counseling provided to parents at the time of diagnosis through NBS, but could be supplemented with further specific contact in the future.

The re-contact could focus on educating parents about the implications of the diagnosis for their relatives, and working through a pedigree to identify how the information may relate to specific individuals in the family. Strategies for contacting and communicating with relatives could be discussed. Emphasis could be placed on how to accommodate the changing perceptions of (ir)relevance of carrier testing as relatives' life stages change.[21] Further research would be needed to determine the best approach to providing this additional support to families.

There have been a small number of studies in which interventions have been described and/or trialed to offer more structured support to facilitate communicating genetic information in families.[22,23] None, however, have been reported following a diagnosis through NBS; future research could address this gap. Important differences between a NBS setting and a regular clinical genetics setting might be that a child diagnosed with CF through NBS may not be symptomatic, and thus relatives may not have a realistic view of the condition, which may limit their interest in testing (quote 11, **Table 5**); or that parents are not only receiving the diagnosis, they are also adapting to life with a newborn and perhaps their ability to retain and process the information given at this time about familial implications may be reduced (quotes 1 and 2, **Table 5**).

There are some limitations to our study that may affect generalizing these findings. First, questionnaires were only sent to relatives after consent and addresses had been supplied to the study by parents. Asking parents to provide their address details for their relatives, without the consent of the relatives, is prevented under the Information Privacy Act 2000 in the state of Victoria.[24] It is possible that relatives who declined to provide their address details, or relatives not approached by parents, have different attitudes, knowledge, and/or factors that influence their decision about carrier testing as compared with relatives who participated.

The rate of testing in this sample of nonparent relatives who responded to the questionnaire is higher than we previously reported in our audit of pedigrees and laboratory testing records: 33% (59 tested from 180 responses) compared with 11.5% (82 tested from 716 eligible records). When just "close" relatives from both data sets are considered, the proportions are more similar: 31% from the audit (59 tested from 189 eligible records) as compared with 44% from the questionnaire (47 tested from 107 responses). Therefore, although there is a potential response bias from relatives who completed the questionnaire, when close relatives (representing those who are more likely to have carrier testing) are considered, this bias is somewhat reduced because the observed proportion tested is similar to the expected proportion tested.

In addition, relatives may have used a number of resources when completing the questionnaire, in particular, the knowledge component. The high knowledge scores may be the result of relatives seeking the answers from their own understanding, or they may have used other resources, such as the Internet, other relatives, or resources provided in genetic counseling. Finally, the majority of respondents were parents, aunts/uncles, or grandparents of the child with CF. The small numbers of relatives who were more distantly related to the child limited the ability to include this factor in its original form in the logistic regression. Consequently, the smaller categories were grouped together for analysis. Future research should seek to include greater numbers of relatives who are more distantly related to a child with CF because they are underrepresented in the current study.

This study has examined cascade testing following a child's diagnosis of CF through NBS. Another opportunity for cascade testing exists following the identification of carrier status through population-based carrier screening (either in a preconception or a prenatal setting). Further studies could investigate the communication of information to relatives in these settings, and measure the rate at which relatives seek testing.

In conclusion, this study is the first to investigate factors associated with the uptake of CF carrier testing among relatives of children diagnosed with CF through NBS. The study assessed standard clinical practice that included consultation with a genetic counselor soon after the diagnosis of CF through NBS. The results demonstrated that relatives outside the immediate family are less likely to have been tested and those with higher knowledge scores are more likely to have been tested than relatives who were not tested. Tested relatives stated that they simply "wanted to know" whether they were carriers, whereas those who were not tested made their decision on the basis of their perception of the (ir)relevance of the information for them, or may "never really have thought about it." The process of family communication of genetic information influences testing, as does relatives' perceptions of the salience of testing for themselves. Informing relatives about carrier testing should be considered a "process, rather than an act"[25] with varied influences, but commonly life stage is the driving force. Re-contacting parents after they have had a period of time to adjust to the diagnosis to further discuss the familial implications and the process of cascade testing should be considered as a follow-up component of NBS programs in which CF is included.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/gim

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DISCLOSURE

The authors declare no conflict of interest.

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