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ORIGINAL ARTICLE

Timing and context: important considerations in the return of genetic results to research participants

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Abstract General consensus exists that clinically significant germline genetic research results should be fed back to research participants. A body of literature is emerging about Australian research participants' experiences of feedback of genetic research results and factors that influence a participant's actions after receiving such information. This exploratory qualitative study conducted interviews with 11 participants from the International Sarcoma Kindred Study, four probands and seven of their relatives. They had been informed by letter of the availability of clinically significant germline *TP53* mutations identified through research. We examined the participants' views about the feedback of these genetic test results. Thematic (inductive) analysis was used to analyse the data. A number of factors influenced participants' responses following notification. This included participants' understanding of the notification letter and their perception of the relevance of the information for them and/or their family. Most notably, timing of the letter in the context of an individual's current life experiences was important. Timing and context are novel factors identified that may impact on research participants' understanding or their ability to access clinically significant research results. We outline strategies for disseminating results to research participants and their next of kin that may reduce their uncertainty around the receipt of research results.

Keywords Results disclosure · Feedback · Genetics · Sarcoma · Li-Fraumeni · Research results

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Introduction

New genomic technologies mean increasing numbers of clinically significant genetic results are being generated through research studies. It is widely accepted that researchers have a responsibility to notify research participants of clinically significant results arising as a consequence of their research participation (Knoppers et al. 2013; Gerdes and Terry 2014; Quaid et al. 2004). A broad ethical framework underpinning return of research results is emerging. It is recognized that a duty to 'maximize benefit and minimize harm' should remain an overarching aim (Bredenoord et al. 2011b). Priority has been placed on disclosure of results with clinical utility and a recommendation results be returned with the involvement of a trained genetic specialist and careful explanation in a way participants can understand (Bollinger et al. 2012; Gerdes and Terry 2014). More debatable is whether research results must also be 'actionable' for return i.e. there should be associated

therapeutic or preventative strategies which may alter health outcomes (Knoppers et al. 2013).

Studies suggest research participants are interested in receiving individual research results believing researchers have an obligation to return them (Bollinger et al. 2012). Participants also want 'actionable' and accurate genetic research results returned (Murphy et al. 2008; Young et al. 2013). The term 'actionable' can have a different meaning to researchers and research participants. For example, researchers may consider interpretation and clinical utility to be an important, or defining, aspect of actionability. Participants may have a different view and also regard personal utility as being part of actionability. This includes feeling a sense of control and helping to plan for the future (Young et al. 2013; Kopits et al. 2011).

Despite general 'consensus' about returning clinically significant genetic research results and participants wanting to receive results, few concrete guidelines exist to guide researchers in providing the information. Similarly, little is known about participants' experiences of actually receiving this type of information.

Participants are often notified by letter that genetic information is available. Studies suggest rates of uptake of clinic appointments/genetic testing following receipt of such letters are variable (Meiser 2005; Lerman et al. 1999; Lerman et al. 1996; Meijers-Heijboer et al. 2000; Wakefield et al. 2011; Wakefield et al. 2013; Hallowell et al. 2013; Keogh et al. 2014). In most clinic/research populations, uptake of genetic counselling and testing is consistent at ~50 % for germline mutations associated with breast, ovarian and colorectal cancers (Meiser et al. 2013; Lerman et al. 1996; Lerman et al. 1999; Botkin et al. 2003). Where public knowledge of cancer predisposition genes is less well known, uptake is lower (Bishop et al. 2002; Hayward 2003). An Australian study found 21 % of research participants underwent clinical genetic testing when notified of a *CDKN2A* mutation associated with melanoma in the family (Kasparian et al. 2009). Lack of awareness of genetic risk and low uptake of research results may similarly be observed in families with a genetic predisposition to sarcoma. Sarcoma is a rare cancer and thus, there may be low general knowledge of heritable factors. There is also an absence of proven risk reduction strategies for those at risk of sarcoma, such as *TP53* mutation carriers (Box 1) (Ruijs et al. 2010; Birch et al. 2001; McBride et al. 2014; Garber et al. 1991).

Box 1: Implications of germline *TP53* mutations for sarcoma patients

- Potentially 1 in every 30 sarcoma patients carries a germline *TP53* mutation regardless of family history (Mitchell et al. 2013)
- Germline *TP53* mutation are associated with the Li-Fraumeni Syndrome (LFS)
- LFS is a rare cancer syndrome characterized by the high risk of cancer at multiple body sites from early childhood through adulthood (Nichols et al. 2001)
- 50 % of *TP53* mutation carriers identified by family history will develop cancer by the time they are 30 years old (Lustbader et al. 1992)
- The most frequent cancers associated with LFS are sarcoma (soft tissue and osteosarcoma), breast cancer, leukaemia, adrenal cortical carcinomas and brain tumours (Petitjean et al. 2007)
- The cancer risk of relatives of sarcoma patients is difficult to quantify as family history is not always a perfect guide
- If a germline *TP53* mutation is identified in a person with cancer, there is high probability of a second malignancy with 57 % chance within 30 years after diagnosis (Hisada et al. 1998; Hwang et al. 2003; Varley et al. 1997)
- *TP53* mutation carriers face unique psychosocial challenges given their predisposition for developing several types of cancer. For example, unlike women with germline *BRCA1/2* mutations, *TP53* mutation carriers may receive little reassurance knowing their carrier status as there is currently only preliminary evidence for effective prevention and/or early detection of *TP53*-related cancers other than early breast screening or breast cancer preventive surgery in female carriers (Villani et al. 2011; Masciari et al. 2008; McBride et al. 2014)
- Ionizing radiation increases cancer risks synergistically although the exact magnitude of risk is unknown (Kleinerman 2009; Heymann et al. 2010)

Identification of cancer risk alleles will be important for people with sarcoma for future surveillance measures and reproductive decisions

Barriers to accessing genetic testing and counselling have been identified in clinical and research populations. Barriers include: concern about the nature of the result, inconvenience of travelling to a genetic clinic, fear about obtaining life insurance, young age at the time of notification and a lower cancer burden in the family (Lerman et al. 1996; Barlow-Stewart et al. 2009; Warner et al. 2005; Biesecker et al. 2000; Godard et al. 2007; Geer et al. 2001; Lobb et al. 2009). A perception of 'genetic responsibility' has been found to be a significant factor in whether individuals opt to have genetic testing in both clinical and research populations, with those having a greater sense of responsibility and having children more likely to undergo testing (Dancyger et al. 2010; Geer et al. 2001; Etchegary et al. 2009; Hallowell et al. 2003; Hallowell 1999). Other barriers observed in Australian research populations include: a lack of understanding of the notification letter, unmet information and support needs, systemic barriers making access to clinical genetics services difficult and a time delay between giving research consent until genetic information becomes available (Wakefield et al. 2011; Wakefield et al. 2013; Crook et al. 2014).

One other possible barrier less well explored is the timing of notification of results in relation to life context. Participants and/or their relatives enrolled in research studies may be notified of the availability of genetic information years after enrolling in the research study. Timing has been examined from the perspective of the communication of research results to parents or individuals

several years after the death of their child or relative (who was a research participant) (Ormondroyd et al. 2007; Sexton and Metcalfe 2008; Sexton et al. 2008). Returning results had some positive effects such as relief from feeling guilty over the cause of death for their child or highlighting the need for surveillance for other family members. Negative impacts included: contradictions to former beliefs about inheritance, uncertainty about how to communicate genetic information within the family and scepticism about the result itself (Sexton and Metcalfe 2008; Ormondroyd et al. 2007). Timing in the context of life experiences, past and current, on an individual's response to the disclosure of results is a key issue requiring further investigation.

While there is consensus that genetic research results should be returned to participants, in Australia, rates of uptake of clinical genetic counselling and testing following notification of clinically significant results is variable. This qualitative exploration of research participants and their family members' experiences of receiving a notification letter from the International Sarcoma Kindred Study (ISKS) was undertaken to add to the understanding of factors influencing uptake of germline genetic information generated through research.

Box 2: The International Sarcoma Kindred Study

The ISKS is a population-based cohort study. Since 2009, 728 individuals with sarcoma have been enrolled. As well, 765 relatives (of whom 285 are affected with cancer) and 270 unrelated age-matched controls have been recruited. Biospecimens, clinical and epidemiological data have been collected. A primary aim of ISKS has been to ascertain the prevalence of germline *TP53* mutations in a cohort of patients with sarcoma. Ninety percent (1570/1747) of participants indicated that they would like to be notified of any clinically significant research results. Participants are notified when a germline *TP53* mutation is detected in their family.

Between 2012 and 2013, ISKS participants in whom a *TP53* mutation had been identified, or their nominated next-of-kin if they were deceased, were notified in writing:

'…The purpose of this letter is to notify you that we have identified a genetic change in your family. This information is important and has implications for you and your family…We strongly recommend that you discuss this letter with a genetic counsellor or doctor at a family cancer clinic. This information may be important for you and your family in reducing risk of cancer…'

Direct contact details to a genetic counsellor familiar with the ISKS were provided as well as a list of contact details for Australian family cancer clinics.

Methods

Recruitment

Ethical approval for the International Sarcoma Kindred Study (ISKS) (Box 2) psychosocial sub-study was obtained from Peter MacCallum Cancer Centre's Human Research Ethics Committee. ISKS participants who received a notification letter about the availability of genetic research results (i.e. a pathogenic *TP53* mutation had been identified in the family), who were aged between 18 and 75 years and fluent in English were included in this interview study. A letter was simultaneously sent to probands and all relatives participating in the study notifying them that clinically significant germline genetic results were available. The letter also contained contact details of a genetic counsellor familiar with ISKS and information on Australian Family Cancer Clinics (FCCs). A genetic counsellor then contacted participants by telephone 2 weeks after the notification letter was posted. The genetic counsellor checked the letter had been received, asked if the participants had any questions and, if requested, facilitated appointments at a local FCC. On average, 4 weeks later (range 2–8 weeks), notified participants were then sent an invitation to participate in this psychosocial study, including an opt-out card. A researcher telephoned the participant to arrange an interview 2 weeks later if the opt-out card had not been returned. Interviews were conducted on average 10 weeks post notification (range 6–28 weeks).

Data collection and analysis

Between October 2012 and March 2014, in-depth semi-structured interviews of 30–90 min were conducted. Informed consent was obtained from all individual participants included in the study. Interviews were informed by a schedule that explored the following themes: recollection of signing the research consent form, recollection of receiving the notification letter, understanding and response to the notification letter and influences on decision-making on following up at an FCC. Interviews were recorded and transcribed verbatim. All identifying information was removed and pseudonyms used throughout. Data analysis took place during the research process. Transcripts were analysed by thematic (inductive) analysis, informed by grounded theory methodology (Rice and Ezzy 1999).

Transcripts were coded using the method of constant comparison (Strauss and Corbin 1991). The constant comparative method utilizes an inductive approach in which theory emerges from the data (Thorne 2000). This iterative process consisted of systematically identifying, comparing and coding themes within and between the interviews. Emerging themes and associations among the codes led to the development of several categories. Analytical rigour was achieved by independent review of transcripts by three members of the research team (KM, MAY, NH). This paper focuses on interviewees' reaction to the notification letter, understanding of the letter and factors influencing their decision-making about following up on the information.

Results

We identified 13 eligible participants. Two declined to participate; therefore, 11 individuals who had received ISKS notification letters (four probands, six biological relatives, one next of kin) were interviewed in this psychosocial sub-study (Table 1). The mean age was 42 years (64 % female). At the time of interview, six participants—two probands (both female) and four relatives (three females)—had attended an FCC, with five of these (one proband, four relatives) going on to have genetic testing. To our knowledge, these interviews did not prompt additional follow-up on genetic results.

Three main themes were identified: 1) *varying participant interpretation of the personal relevance of the letter*; 2) *response to the letter*; 3) *timing of the letter in individuals' lives influences uptake of genetic information*.

Theme 1: varying participant interpretation of the personal relevance of the letter

Despite the letter specifically saying a genetic change had been identified in the family (Box 2), its content was understood differently. Some participants found the letter vague and felt there was nothing definite in the information it provided.

...I didn't know what that actually meant exactly in regards to my situation in general and whoever else I'd taken into the study, so I guess I was sort of left in the dark there…the letter was sort of vague in regards to what sort of information it would, it would give me so I kind of just let it go…
(Ben 22, proband—no testing)
...the letter was vague…it didn't provide any certain information…
(Fiona 49, proband—no testing)

Some believed the letter was not personally relevant, viewing the information as general rather than specific to them, and understood they did not need to act on it.

...It just seemed pretty general to me so it didn't really say anything much just that, yeah…I think we came up with the consensus that we were just simply unsure, yeah…
(Andrew 22, proband—no testing)

Conversely, other participants understood the letter meant genetic information had been found in their family and they needed to act.

…there's definitely something within the genetic makeup and yeah something that I need to be aware of and have some action I guess…
(Elise 34, family member—has had testing)
…I think I took it as we're informing you and here's your options…
(Grace 48, family member—has had testing)

Theme 2: participants' responses to the letter

Participants described mixed responses to the notification letter. Not surprisingly, where participants had a strong history of cancer in their family, they felt the research had validated their beliefs about their family history, generated useful information for their family and given them an option to act.

… I said thank god someone's found something out…. I'll be content if they tell me what the gene is or where it is or which side of the family they think it's come from, I'll be content with that…
(Cara, 74 family member—has had testing)

Others had mixed feelings, as relief was tinged with sadness with the realization of the potential impact on their wider family, including children and grandchildren.

… It was hard. I was happy that I had an answer but unhappy that I realized the kids could have it or that it may be passed on even to my granddaughter…for years it was like I didn't know why and there was no breast cancer in the family and stuff like that so like I say it was good, because I don't think of that anymore. It used to constantly be on my mind…
(Diane, 39, proband—has had testing)

In contrast, some participants appeared unconcerned about the letter, despite their own cancer and high likelihood that any genetic information identified would pertain to them. Some of these individuals were at a loss as to how to react to the letter.

…Just I don't know, I don't know how to respond to it… My parents were the people that read it first and, I don't know, like they told me that and I was just like I don't know how to respond to it and they don't know how to respond to either…
(*Andrew 22, proband—no testing)*

Others appreciated that genetic information had been identified but appeared to assign the information less significance.

...I wasn't concerned that much about it at the time because it's like I don't think I was really ready to sort of, you know sort of go into it any more than that at that time …I thought well that could happen I mean you

Table 1 Study demographics

	ISKS probands $n=4$		ISKS relatives $n=7$	
	Range	Mean	Range	Mean
Age (years)	22–49	33	34–85	51.8
Time since diagnosis (years)	1.5–4	3	–	–
Gender				
Female	2		5	
Male	2		2	
Relationship to proband				
Spouse	–		1	
Parent	–		1	
Sibling	–		3	
Aunt or uncle	–		2	
Highest level of education completed				
Year 10	–		2	
Year 12	1		1	
Vocational training	1		2	
University degree	2		2	
Marital status				
Married or living as married	1		3	
Divorced or separated	1		2	
Widowed	–		2	
Never married	2		–	
Children				
≤16 years	1		3	
>16 years	1		2	
No children	2		2	

know with anybody, it's not necessarily a bad thing or a, you know it can, like a genetic change can be just, just sort of happen anyway because it's just sort of part of evolution I suppose or yeah…
(Brooke, 57, family member—no testing)

Theme 3: timing of the letter in individuals' lives influences uptake of genetic information

Timing and life context in which the letter was received appeared to be important for both probands and some relatives. For some, life context facilitated uptake of genetic information. This was particularly the case when there were children in the family or where there was a strong family history of cancer.

…it's really hard watching so many people in your family go through it and to know that you know I have such a high risk, but I guess a lot of it too is for my kids and do as much as I can so that they don't have to be there and go through that …
(Elise 34, family member—has had testing)

The notion of high risk and desire to do something for others motivated these participants into acting. Even those estranged from their family considered the familial implications of the information.

…I thought about family as well if there was something genetic for family to know even though I'm estranged from them really. We're not close, and my kids definitely was a big motivation…
(Diane 39, proband—has had testing)

In contrast, timing and context appeared a barrier for some probands who had more pressing priorities and thus appeared unable to comprehend or deal with the contents of the letter due to their own recent diagnosis of sarcoma and subsequent treatment.

… I'm kind of just getting on with my life [since diagnosis] *and I'm pretty busy and everything I didn't want to go out of my way and break up my routine for, for this. I kind of thought I'd leave it at the time and I think I kind of thought about maybe asking a doctor when I was in Melbourne for a check-up next but I actually forgot at the time…*
(Ben 22, proband—no testing)

Indeed, some probands said their treatment took precedence over following up the information the letter.

…No, too many things going on at the time maybe should have been more concerned knowing the genetic information, but you can't know these things in advance, and had other more concerning cancer-related appointments, scans and treatment going on over in the hospital…
(Fiona 49, proband—no testing)

Timing and context also impacted on parents who were struggling with their child's diagnosis of sarcoma; they felt unable to cope with anything else at this time.

…Yeah well not at the moment, I'm not really sort of you know mentally or you know psychologically up to sort of you know running around and doing tests and sort of looking for things that yeah may have caused this…I just chose not to sort of you know do anything further … I've just sort of got enough to cope with…. you know do whatever you have to do every day without looking for more trouble…

meeting with doctors and that, no I'm not really ready for that…
(Brooke 57, family member—no testing)

Feelings of loss and grief also impacted upon the next of kin's responses to receiving the letter.

…I was still in pretty deep grief, I couldn't even spread toast, so let alone take in something like that…I suppose when you're just delivered news like that you just don't - it was like rubbing salt into the wound…like I can't actually get out of this nightmare, like it's going to keep continuing. You know, I can't rebuild my life and, you know, look after the kids…
(Angie 34, wife—deceased husband had testing)

Like Angie, Grace and Daniel were overwhelmed by their sister's multiple cancer diagnoses and her apparent unwillingness to act because of added stress. Grace and Daniel said they changed their minds over the course of time with regard to following up the letter. For Daniel, this change occurred after he was called by the local genetic counsellor.

…I became a bit upset about her situation [sister] and the discussion we had about whether we, do we really want to know because of the added stress and emotional trauma and stuff…yeah it made me a bit more hesitant to go and do anything or to go and get the results…but then as I said I spoke with the counsellor by phone and she got me to understand that it was you know worth coming in just to have a talk about it and stuff, so I agreed…
(Daniel 53, family member—has had testing)

Grace, who is based in the USA, said she changed her mind after her gynaecologist outlined possible benefits being tested for *TP53* (Box 1) for future surveillance.

…Normally I would have been fine but the timing of just having to think about anything, you know, I mean it was not a good time…I went in and I was talking to my doctor when I went in for my annual exam and he's the one when I said, you know, what do you think about this and he said well you definitely need to get tested…
(Grace 48, family member—has had testing)

Discussion

This study highlights the unique and different ways participants respond to clinically significant information fed back from a genetic research project. Some factors motivate participants to act and follow up the information contained in the notification letter whereas others hinder them in this process. Participants have varied understandings of and reactions to the letter and may make different decisions regarding attending genetic counselling and having genetic testing. This study also suggests timing and context may affect uptake rates of research-generated genetic information.

With regard to participants' understanding of the notification letter, the findings of this study are consistent with those of previous research (Wakefield et al. 2011; Hallowell et al. 2013). Some ISKS participants did not understand the information in the notification letter as having implications for themselves, while others did. Lack of understanding for some may be because the letter in this study and in the previous studies did not emphasize the clinical significance of the information (Box 2) (Wakefield et al. 2011; Hallowell et al. 2013). A unique finding of this research in this setting is that individuals may be unable to process the information in the letter when they first receive it. This may be because they are dealing with a recent diagnosis/treatment or have received a poor prognosis (probands) or because they are emotionally distressed, grieving or bereaved (relatives). Individuals in such situations may require a more supportive approach and longer term follow-up as opposed to a single notification letter.

This research thus indicates that timing and context should be taken into consideration to improve uptake of genetic counselling and testing for clinically relevant research findings. Participants overwhelmed either by their own or close relative's recent sarcoma diagnosis and treatment wanted to avoid the extra burden of further appointments and genetic testing. For some of our participants who were overwhelmed, even a telephone call by an experienced genetic counsellor did not assist them to see the significance of the letter or influence their 'readiness' to hear the information (O'Neill et al. 2006). Following receipt of a notification letter, research participants may require even more support and information. This could take a number of forms including a more targeted conversation with professionally trained genetics staff who have links to the research team (Crook et al. 2014).

At the point of interview, ~50 % of our interviewees had not initiated any form of follow-up despite there being an average of 10 weeks (range 6–28 weeks) from receipt of the notification letter. Hence, the challenge now lies in overcoming potential barriers to uptake of genetic counselling and testing in research populations. This is particularly important where there are implications for treatment and surveillance, as is the case with carriers of germline *TP53* mutations (Box 1).

A number of Australian population-based studies report returning results via notification letters alone (Hallowell et al. 2013; Wakefield et al. 2011; Wakefield et al. 2013; Affleck 2009). This process of one-off notification has been sub-optimal as defined by the low uptake of genetic

counselling and testing, and therefore other approaches require consideration. These include additional information and support as well as for some, long-term follow-up (Wakefield et al. 2011; Wakefield et al. 2013; Kasparian et al. 2006). Other methods to increase engagement with genetics services following notification have been proposed. One suggestion has been for participants to be better informed about possible findings during the informed consent process (Bredenoord et al. 2011a; Clayton 2008). However, this may not be practical, as care should be taken not to overload participants at the time of consent, particularly in a clinical setting. For cancer projects, in particular, this may not be effective or practicable when considering that at the time of consent, participants are often in the midst of burdensome treatment and may not take in the information or remember it. Researchers could consider a more participant-friendly recruitment method, such as introducing the project in clinic before conducting the informed consent process at another, less stressed time.

Genetic counselling models for the return of results have also been suggested, with two studies using a genetic counsellor. One study educated participants via telephone at the time of consent on the risk factors for melanoma, which include germline *CDKN2A* mutations (Christensen et al. 2011). Participants were then offered genetic counselling before deciding whether to receive their result. This may be more useful in communicating the importance of information to research participants and allow discussion of information in a supportive environment—this research project had a 70 % uptake rate. A recent international colorectal cancer research project had uptake in the USA and Canada of 72–86 % but only 56 % in Australia (Keogh et al. 2014). The difference in uptake may be explained by the fact that participants from the USA and Canada had genetic counselling throughout the research study. However, this may be an expensive approach and would necessitate the inclusion of this expense into research funding applications (Fernandez 2008; Bredenoord et al. 2011a). Furthermore, an evaluation of the potential benefits of this approach versus anticipated costs would be needed though one possible method to reduce this expense could be less frequent telephone contact combined with regular emailed newsletters.

As current life context appears to be an important influence on the follow-up of information contained in notification letters, another way to communicate results more effectively could be to involve the treating physician. Many participants in cancer genetics research studies are in the midst of ongoing active follow-up or treatment. It may be more practical for genetic health professionals to work with the patient's treating team and to communicate genetic research results at an existing oncology clinic appointment. Involvement of their treating clinician may help reinforce the importance and/or relevance of the findings to research participants while making the process of acting on the information less burdensome for them.

In terms of the timing of result disclosure, one possible solution is to use patient-centred initiatives such as web-based interactive technology, which would permit research participants to engage with full or partial information at a time of their choosing (Hallowell et al. 2013; Kaye et al. 2012; Yu et al. 2013). Social media tools such as individual participant interfaces, blogs, online experts and webcasts could allow participants to choose the form of communication most suitable to them at an appropriate time (Kaye et al. 2012). Using the same information technology interfaces that social media tools use can help participants manage information pertinent to them when it suits them the most so they are able to follow up with researchers as and when they need to, not as a one off initiative (Kaye et al. 2012). This could empower participants and engage them more fully in the research process thus encouraging more follow-up of results after notification. The efficacy of this approach however is yet to be established. Furthermore, this approach may not be a timely enough for those where there are implications for treatment and screening.

Conclusion

There are minimal data available on how research participants react to the disclosure of genetic research information and what compels them to act on it. Participants may or may not choose to act on clinically significant information due to different personal circumstances, regardless of proband or family member status. Consideration of timing and context of notification may be important in motivating participants to act on important genetic information generated by research projects. It is unlikely, however, that a standard approach can be developed that suits all research participants, thus researchers may need to be more flexible and disregard a 'one size fits all' approach. More involvement of the treating physician, genetic counsellors, use of web-based technology and more information given at recruitment are all options that may be considered. Research is needed to establish whether these different approaches work. Insights from this study may help shape a framework for the successful communication of genetic research findings.

Study limitations

As only a few people had received notification letters from ISKS at the time of this study, our research is based upon a small sample. There were varying times between receipt of the notification letter, invitation to the psychosocial study (average 4 weeks, range 2–8 weeks) and semi-structured interview (average 10 weeks, range 6–28 weeks), which raises the potential for variation in opinion and recall bias.

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Compliance with ethics guidelines

Conflict of interest Kate McBride, Nina Hallowell, Judy Kirk, Mandy Ballinger, David Thomas, Gillian Mitchell and Mary-Anne Young declare no conflict of interest.

Ethics compliance All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

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