Lay perspectives on receiving different types of genomic secondary findings: a qualitative vignette study

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Abstract

Genome-wide sequencing may generate secondary findings (SFs). It is recommended that validated, clinically actionable SFs are reported back to patients/research participants. To explore publics' perspectives on the best ways to do this, we performed a vignette study among Finnish adults. Our aim was to explore how lay people react to different types of hypothetical genomic SFs. Participants received a hypothetical letter revealing a SF predisposing to a severe but actionable disease - cardiovascular disease (familial hypercholesterolemia, long QT syndrome) or cancer (Lynch syndrome, Li–Fraumeni syndrome). Participants (N=29) wrote down their initial reactions, and discussed (N=23) these in focus groups. Data were analyzed using inductive thematic analysis.

Reactions to hypothetical SFs varied according to perceived severity and familiarity of the diseases. SFs for cancer were perceived as more threatening than for cardiovascular diseases, but less distressing than risk for psychiatric or neurological disorders, which participants spontaneously brought up. Illness severity in terms of lived experience, availability of treatment, stigma, and individual's responsibility to control risk were perceived to vary across these disease types. In addition to clinical validity and utility, SF reporting practices need to take into account potential familiarity and lay illness representations of different diseases. Illness representations may influence willingness to receive SFs, and individuals' reactions to this information.

Key words: whole genome sequencing; incidental findings; secondary findings; familial hypercholesterolemia; long QT syndrome; Lynch syndrome; Li–Fraumeni syndrome; public perspective; illness representations; qualitative vignette study

Introduction

Prior to genetic testing for a specific hereditary disease, the traditional practice is to provide patients with thorough genetic counselling, which includes information about the disease risk and its implications. The aim of this practice is to aid individuals to make an informed autonomous decision about whether or not to proceed with testing (Riley et al., 2012). Reduced costs of genomic sequencing facilitate the analysis of large segments of the genome. As a result, genome-wide sequencing can generate various types of secondary findings (SFs) in addition to those sought in the original clinical investigation or research question. There has been intense discussion (Appelbaum et al., 2014; Berg, Khoury, & Evans, 2011; Bunnik, Schermer, & Janssens, 2012) about how to obtain informed consent to receive genetic SFs, since it is impractical to provide extensive counselling on dozens of possible disease risks.

Professional discussion concerning SFs in clinical sequencing focuses on single variants that indicate elevated disease risks. Professionals have suggested different ways to categorize SFs, in order to allow patients/research participants to decide, which types of SFs they wish to receive (Appelbaum et al., 2014). Current suggestions differentiate SFs based on their clinical validity and utility (Berg et al., 2011), i.e. the severity of disease risks indicated, and the efficiency of available preventative methods. The American College of Medical Genetics and Genomics (ACMG) recommends (Kalia et al., 2016) that when clinical whole genome/exome sequencing is undertaken, the genome should be screened for pathogenic mutations in 59 genes for which preventive methods are available. This list includes single variants causing increased risk for certain types of cancer or heart diseases. ACMG recommends that if such mutations are detected, the patient should be informed about health risks that are linked to them (Kalia et al., 2016).

Earlier research suggests that, when initially asked, majority of research participants wish to receive most types of genomic results, including those related to ancestry, pharmacogenetics, cardiovascular diseases, cancers, depression, Alzheimer's disease, Huntington's disease, and carrier status (Wynn, Martinez, Duong, et al., 2017). Most research participants state they wish to receive SFs (Jamal et al., 2017; Murphy et al., 2008) particularly if they are actionable – i.e. the diseases are treatable or preventable. However, actionability may mean different things to different stakeholders and cover not only availability of treatment and prevention, but also the possibility to plan one's lifestyle or reproductive choices (Mackley, Fletcher, Parker, Watkins, & Ormondroyd, 2016).

For example Jamal et al. (2017) interviewed 49 patient-participants of a clinical whole genome sequencing research study, and concluded that current classifications of the types of genomic results that are used in consent processes 'may not be aligned with how individuals are conceptualizing the information they could potentially learn from WGS' (p. 86). The study participants perceived the distinctions between preventable/not preventable and treatable/not treatable diseases as counterintuitive and hard to distinguish. Also, their perceptions of what constituted the most upsetting types of results varied. For example, risk for non-actionable Alzheimer's disease was not too distressing for those who had reassuring previous experience of the illness, or those who expected treatment methods to be developed in the future.

Obviously professionals and lay people approach the issue of SFs, as well as genetics in general, from different perspectives. Rehmann-Sutter & Mahr (2016) explain that 'for medical professionals, the genome is primarily a source of health information that can be used for diagnoses and disease risk assessment', whereas a lay person understands genetic information from the perspective of their personal life, identity and social relations (Rehmann-Sutter & Mahr, 2016). Hence, professional and lay perspectives on meaningful ways to categorize and report SFs related to different types of

illnesses may differ to some extent (Graves et al., 2015; Jackson, Goldsmith, O'Connor, & Skirton, 2012; Townsend et al., 2012). Professionals' knowledge of various mutations and their implications provides them a different set of tools to approach the issue of SFs, compared to lay people who may instead use their experience of various types of illnesses as a background for what types of findings genome-wide sequencing might reveal.

Lay representations of different illnesses (Leventhal, Meyer, & Nerenz, 1980) and the extent to which they influence individuals' desire to receive SFs need to be taken into account in genetic counselling (Shiloh, 2006). To provide people with meaningful disease categories and support decision making, lay people's views of different illnesses need to be examined and taken into account when formulating SF reporting practices. In this paper, our aim was to explore how lay people react to different types of hypothetical genomic SFs. We used four exemplar vignette letters reporting risks for Mendelian cancer syndromes or cardiovascular conditions.

Methods

We conducted a qualitative vignette study that included an online writing task and focus group discussions (Barbour, 2008). We recruited Finnish adults to participate via an announcement in the Helsinki area Metro newspaper (Figure 1) (see also Vornanen et al., 2018).

Procedures

An online survey was sent to 32 interested volunteers and filled in by 29 participants. The online survey contained a sociodemographic questionnaire, and a writing task accompanied by a vignette letter. Each participant was randomly assigned to read one of four versions of the vignette letter, declaring that in their earlier hypothetical clinical WGS a SF was identified, suggesting

susceptibility to familial hypercholesterolemia (FH), long QT syndrome (LQTS), Lynch syndrome (LS), or Li–Fraumeni syndrome (LFS) (Table I) (Vornanen et al., 2018). Participants were asked to imagine themselves receiving that letter in real life, and to write down their initial reactions to it. These four diseases were chosen since the ACMG recommends reporting back mutations in genes linked to these conditions (Kalia et al., 2016), and we had previous experience of disclosing SFs linked to LQTS (Haukkala et al., 2013) and of inviting LS families to attend genetic testing via letter (Aktan-Collan et al., 2007). To include cardiovascular diseases and cancers with varied treatment and surveillance possibilities, we chose medically treatable FH, and LFS with less efficient preventive possibilities (Schneider, Zelley, Nichols, & Garber, 1993) compared to LS.

The vignette letters (Table I) resembled letters that were sent to research participants to reveal LQTS findings in an earlier study (Haukkala et al., 2013) and to contact untested Lynch syndrome family members to uptake genetic test (Aktan-Collan et al., 2007). In those studies, the letters aimed to communicate general information about the disease, so that more detailed information could be provided in a following counseling session face to face or over the phone. We adopted a similar approach in the current study, since this kind of procedure has reasonable costs and is a likely manner of reporting SFs in the Finnish context. Before use, the vignettes were tested and discussed by a student sample.

The structure of the four vignettes was parallel, but some differences were in the level of detail describing the diseases in question (see Table I). When contacting people about their genetic risk via letter, the dilemma is to communicate that the risk concerns a serious health problem, but at the same time not to cause excessive distress. This is why information on the cancer syndromes and LQTS was presented at a relatively general level; no risk percentages or worst case scenarios were described. The vignette reporting FH contained somewhat more detailed information, to highlight

that the finding concerns a more serious condition compared to somewhat elevated cholesterol level, which is a common problem. A brief slide show (described in next paragraph) provided participants with more information on the conditions during the focus group discussions.

Within a week after completing the writing task, participants (N=23) attended focus group discussions led and moderated by MV and KA-C. During each session (duration 94–125, mean 114 min), two versions of the vignette letter were discussed; one revealing a cancer related SF and the other revealing a cardiovascular related SF (Table 2). Each participant had read one of the two while completing the earlier writing task. The focus group guide (Appendix) included prompts on the following topics: first reactions to letter, perceptions of disease and risk, searching for information, family, recommendations for implementation, and consent. However, discussions were not strictly structured: participants spontaneously brought up their perspectives on these topics, and they were encouraged to discuss the topic of SFs and different diseases freely.

In the midst of the discussion, KA-C provided a brief slide show (13 slides) about the two diseases under discussion, and answered participants' questions. KA-C is a psychotherapist and a medical doctor, who has been working as a physician, specializing in clinical genetics. She has several years of experience in counseling and providing genetic information to people. She provided the study participants with the type of information about the different diseases that they would receive in a brief genetic counseling session. The slide show contained more detailed information on the diseases: mode of inheritance, prevalence, magnitude of risk, typical age of onset, symptoms, and preventive methods. Participants were informed about special features related to the syndromes e.g. high penetrance, early age of onset, multiple tumors occurring among those affected, and childhood manifestations.

Data analysis

Written reactions to receiving the letter and transcribed focus group discussions were analyzed using inductive thematic analysis (Braun & Clarke, 2006) to answer the following question: In which ways does type of disease matter when receiving genetic SFs? In our earlier study (Vornanen et al., 2018) we reported the focus groups' perspectives on receiving SFs in general. For the current analysis, we included the written accounts and those parts of the focus group discussions, which concerned particular diseases and their meanings. MV coded the data and grouped codes into larger themes (Braun & Clarke, 2006); KA-C agreed with the interpretation. Overall thematic structure was further elaborated and agreed by MV, KA-C, and NH. To ensure anonymity of the written accounts, we will not link individual participants' written accounts (referred by participant numbers P1–P29) with their comments in focus groups (A–D, A1 refers to the first speaker of focus group A).

Results

Participants were primarily female, middle-aged (between 20−64 years, mean 49), and with diverse educational backgrounds (Table III). The sample was diverse in professions, including e.g. entrepreneur, teacher, artist, salesperson, welder, accountant, and archeologist. Three participants reported working in healthcare professions (nurses, personal assistant). Reasons for not participating focus groups after completing the writing task (N=6) were not systematically collected, but included difficulties to find a baby sitter and being ill at the time of the focus group discussion. The average age of these six participants was 44 years (range: 30–61).

Perspectives on receiving SFs tended to vary according to different diseases. Vignette letters (Table I) reporting genetic risk for cancer were perceived as more threatening compared with letters

reporting risks for cardiovascular conditions. Earlier experiences and understandings of the disease described in the letter could either amplify or alleviate emotional reactions to it.

First reactions in written accounts: interplay of familiarity and perceived severity

Individuals' descriptions of their first reactions to receiving the hypothetical letter about SFs varied from neutral or grateful to terrified, angry, or regretting giving consent to receive this information. Individual's familiarity with the disease described in the letter together with perceptions of its severity and treatability, shaped their initial reactions to receiving information about SFs. In their written accounts (2–333 words, 1–26 sentences), each participant commented on only one disease (FH, LQTS, LS or LFS) that had been described in the hypothetical letter they received. Some differences between the reactions to the four diseases were identified.

Familial hypercholesterolemia: First reactions to receiving the FH letter were the most neutral. Participants described being calm or slightly worried, and commented that they would contact health care personnel for further examinations, as suggested in the letter: 'I would act according to the recommendations in the letter' (P20). One participant (P17) briefly described being 'disappointed' on learning that leading a healthy lifestyle was not enough to prevent hypercholesterolemia. Written reactions to FH tended to be short, including the very briefest one containing only two Finnish words: 'I would go for laboratory examinations' (P21).

Long QT syndrome: Compared to FH, the letter for LQTS evoked more questions from recipients about the nature of the disease. Participants wondered what this disease means for one's life, and said they were keen to search for more information online, or contact more knowledgeable friends/relatives or healthcare professionals: 'I would be frightened at first and wonder what this information really means for my own and my possible child's life' (P23). Some participants said

192 they would be grateful, content or relieved, while others expressed shock and anger at (potentially)
193 receiving this type of information via letter: ‘A letter is a shockingly rude way of informing one
194 about a serious illness’ (P27).

195 *Lynch syndrome*: First reactions to the LS letter were two-fold. Initial shock was processed through
196 focusing on the preventive methods mentioned in the letter: ‘Sure the information would be
197 overwhelming for a moment (--) I would find out about the treatment/prevention possibilities as
198 much as I can and start trying those’ (P1). Coincidentally, one of the participants who had received
199 the LS letter had a family history of colorectal cancer. Her written reaction highlights the fact that
200 preventive measures mentioned in the letter may pale into insignificance in the light of one’s
201 personal experiences: ‘I’m terrified (--) I will call the hospital immediately for further instructions (-
202 -) I don’t want the same destiny (--) I would die slowly too’ (P4).

203 *Li–Fraumeni syndrome*: The letter for LFS tended to evoke lengthier and more emotional written
204 responses. One participant (P10) wrote that they regretted having consented to receiving SFs, others
205 said they wished for personal contact, more information, or retesting. Many participants indicated
206 that they would be fearful about the implications for their family members’ health. ‘Maybe I
207 shouldn’t have signed the consent for contact. First feeling is despair, in particular if I have children
208 at this point, I mean worry for children’ (P10).

209 In summary, past experiences and other knowledge/beliefs about these diseases and their treatment
210 were important in shaping first interpretations of and reactions to the letter. This was evident not
211 only in the written accounts, as indicated above, but also in the focus group discussions. For
212 example, one focus group participant (C3) said she would possibly not contact genetics clinic after
213 receiving information about LS because she thought the letter was vague concerning the

magnitude of risk and the effectiveness of surveillance, and because her previous experience of having a colonoscopy (not cancer related) had been devastating.

'Cancer as a word is worse straight away'…

Focus group discussions further illuminated reasons behind the differences in reactions to the different vignettes. Each focus group had two vignette letters to discuss – one with a cancer related SF and the other with a cardiovascular related SF. Discussions revealed that participants perceived high cholesterol as commonplace and hence, the FH letter not so threatening.

> *B2: my heart would've probably been racing more if I had read this cancer thing. In my opinion everybody has cholesterol, and it's not fatal straight away, so I think these [letters] are on a completely different level*

LQTS also tended to be perceived less threatening than cancer.

> *D1: I somehow, indeed, well I didn't take very seriously that disease [LQTS] (laughs) I just read it and like 'so what'. So if I had received this cancer letter [LFS] I might have responded differently. Cancer as a word is worse straight away, it takes you aback in itself.*

In general, the word 'cancer' evoked emotional reactions that were related to vivid experiences of cancer in the family or close friends. Cancer tended to be treated as a general disease category, despite the fact that participants acknowledged different implications of different types of cancer.

> *C4: [the word cancer] evokes such a strong association, so that it links to all your own [people with cancer] who you know, even if these [Lynch syndrome associated cancers] are, these are not the same diseases*

In sum, earlier experiences of and impressions of disease severity and treatability strongly influenced reactions to and elaborations of the SF. Next we demonstrate that even though cancer was perceived as severe, genetic information on actionable cancer risk was still perceived as less distressing than certain other types of risk information.

…but cancer is not the worst possible

The original aim of this study was to find out whether the four chosen diseases evoked different reactions from participants, due to their different treatment/prevention possibilities. When allowed to discuss the topic freely in the focus groups, however, it turned out that participants regarded the four diseases described in these scenarios as similar in many ways. Despite the fact that cancer was perceived as more distressing than cardiac diseases (LQTS and FH), susceptibility to cancer was still considered less threatening than genetic risk for non-treatable or psychiatric disorders. As A4 and A3 discussed in focus group A:

> *A4: those [Lynch syndrome] screening examinations are not pleasant, that's how it is, I don't know, heart problems [LQTS] are easier [compared to cancer] since there's only ECG, but what I thought was (pause) those are in a way (pause) so called easy illnesses and they already have cures, surveillance. How about if they found out you have some illness for which there's no cure invented yet*
>
> *A3: Yeah, or a very high likelihood of having some mental, mental problems. If something like that was found it would probably be quite a lot harder to read about it perhaps than if there is this type of physical illness.*

Three out of the four focus groups spontaneously commented that receiving genetic risk information about psychiatric illnesses (e.g. bipolar disorder, schizophrenia), incurable neurological disorders (e.g. Alzheimer's disease), alcoholism, or intellectual disability of children would be more

257 distressing than receiving SFs about somatic diseases. Most participants made no straightforward
258 statements that they either would or would not like to know risks that they found hardest to come to
259 terms with. However, they outlined several reasons why they found risk information on common
260 somatic diseases less threatening than other types of disease risks. Psychiatric and somatic diseases
261 were, in general, perceived to differ in their 1) severity in terms of lived experience of disease, 2)
262 treatability and access to treatment, 3) level of stigma, and 4) individual's responsibility for
263 managing the risk.

264 Severity in terms of lived experience and access to treatment

265 Participants commented that knowing one's risk for psychiatric diseases or Alzheimer's disease
266 would be frightening since those diseases would be extremely hard to live with for the individual
267 and their family.

268 *A4: like schizophrenia or depression, they get to in a way churn inside the person, and you*
269 *don't get the medication fixed, or rehabilitation, so it's really one, one of the worst diseases*
270 *there is [A7 agrees]. So I think if my children got ill, I would rather have them with a physical*
271 *illness [A2: So would I], because their life is pretty horrible with those fears and delusions*

272 As the above quote illustrates, perceptions of lived experience of psychiatric disease were closely
273 linked to perceptions of treatability and access to treatment. Knowing one's genetic risk for a
274 psychiatric disorder would be distressing because the participants perceived that treatment was less
275 available for them, compared to common somatic diseases.

276 A6: *For the physical stuff we perhaps have more the feeling that there is some control of it,*
277 *since they have promised that this medicine will have this and that effect and so on (--) for the*

area of mind we are (pause) I mean at least I have the impression that we are quite, quite in baby shoes [with regard to treatment]

Participants acknowledged that medication and treatment exist for psychiatric disorders, too. As the above quote indicates, however, the effectiveness of treatment for psychiatric disorders tended to be evaluated as less predictable. In addition, participants commented that these treatments were more difficult to access:

A7: if I have a (pause) some kind of physical illness, they won't tell me that 'Well let's wait until you rot, then we will take you in for treatment' but they will start to examine [A2: Yeah] based on first symptoms to find out what it could be and as soon as possible start medication and treatment so that it will not get worse [A2: It's about attitudes] but for psychiatric illnesses it's completely the other way around

In addition to lived experience of disease and access to treatment, the burden of knowing one's risk for disease was linked to potential stigma associated with having the disease and responsibility for managing disease risk. These were seen to vary across different diseases.

Stigma and perceived responsibility to manage risk vary across diseases

Participants perceived psychiatric disorders as more stigmatizing compared to somatic diseases: '*stigma is thrown upon the whole family [when psychiatric disorder occurs*]' (A2). However, also rare somatic diseases were seen to have the potential to isolate individuals and families, since peer support and treatment could be harder to find. Even though cancer was, in general, considered as a common disease, one participant commented that LFS occurring at a young age, i.e. a less typical presentation in terms of the timing of cancer in the life course, might have the same effect:

B1: you know cancer usually affects older people, so the rarity [of LFS] (--) why it would perhaps be psychologically harder to go through something like this would be if you got cancer at a young age, and then there would in a way be no peer support, people who would share the experience, so that you could have some psychological (pause) support then

Also perceptions of responsibility for managing risk varied across diseases and influenced how FGD participants' conceptualized knowing one's genetic risk - as either a burden or a relief. Overall, the primary means of controlling somatic and psychiatric diseases were emphasized differently. Whereas treating and curing somatic diseases was described as the responsibility of the medical profession, it was implied that lay individuals have more responsibility for controlling or preventing psychiatric diseases (see A7, B1 and B3 below). Primarily this was because monitoring early symptoms of depression, schizophrenia, or alcoholism was perceived as easier compared to somatic diseases, which might not show any observable early symptoms.

A7*: I think also with mental health problems [similar to alcoholism] (--) I can pretty well analyze my own behavior after all (--) Say for example if you have depression in your family. (--) But for this type of physical illnesses, you can't, if they show no symptoms, you can't do anything [to monitor it]*

Thus, as a consequence of the 'visibility' of psychiatric symptoms or preconditions and difficulties to access treatment, individuals were seen as more responsible for preventing and coping with psychiatric illnesses compared to somatic illnesses.

B1: when you know there is a hereditary risk for depression in your family (--) then you can start to, build your life or your lifestyle, take it into account, like for example 'I have to avoid extreme stress, because stress predisposes to depression' (--) or hereditary susceptibility to

alcoholism, also then, when the person knows it, they can influence, so that it is perhaps best to stay away from using alcohol completely

In contrast, knowledge of genetic risk for hypercholesterolemia had the potential to alleviate the individual's responsibility to prevent it by healthy lifestyle. One participant described how it would be a relief to find out a genetic susceptibility after failing to lower cholesterol as a result of dietary changes.

C2: I would indeed like to know [--] because it [high cholesterol] has been in my family [--]
MV: So what would it mean to you if, if you found out it is hereditary?
C2: It would somehow make it easier [--] somehow you feel guilty always when eating cheese

Even though individuals were perceived to have some control and responsibility in preventing somatic diseases, for example, by leading a healthy lifestyle, one was not blamed for developing such diseases in the end. The following extract shows how participant B3 evaluates an individual's responsibility for preventing hypercholesterolemia or cancer. Even though she perceives the individual having some control over the development of these diseases, she does not hold them responsible for falling ill in the end.

B3: suddenly life turns around, there comes an uninvited guest [=somatic disease] (pause) [--] we can't that well, we can't like earn a good life ourselves cause, cause verifiably people die of for example some horrible disease, even if they look so healthy and have lived so healthily, cause nothing is hundred percent certain

In sum, people's perceptions of the degree of stigma and responsibility for managing risk varied across diseases and influenced their perceptions of how burdensome receiving genetic risk information would be.

Discussion

The current study aimed to examine whether lay perspectives on receiving genetic SFs varied according to disease type. The four exemplar diseases used in this study were two cardiovascular related conditions (FH and LQTS) and two cancer syndromes (LS and LFS). Participants' first (written) reactions to receiving SFs about cancer in hypothetical letter were more distressed compared with the cardiovascular related letters. Yet, due to small number of participants (N=29) and variation in individual perspectives, such comparisons are very tentative. In focus group discussions, participants also considered cardiovascular diseases and cancers similar in many ways; they lumped them into the category of common, familiar somatic diseases. Receiving genetic risk information on common somatic diseases was, in general, perceived less threatening than potentially receiving genetic risk information related to other types of diseases; psychiatric diseases like schizophrenia, alcoholism, or Alzheimer's disease. Comparing views about somatic and psychiatric genetic risks was not part of the original study plan, but participants spontaneously emphasized this comparison during three out of four focus group discussions.

Our study participants made sense of potential SFs through their personal experiences of different diseases. Preventive methods mentioned in the vignette letters provided little reassurance in comparison to negative personal experiences of (similar) illnesses. Earlier experiences influenced these perspectives even after receiving more specific information on preventative methods related to the four exemplar diseases during the focus group slide show. In line with previous literature (Shiloh, 2006; van Oostrom et al., 2007), our results suggest that lay illness representations (Leventhal et al., 1980) of different diseases need to be taken into account when disclosing SFs. Since various diseases linked to SFs may either be familiar or unfamiliar to the recipient, personal experiences are likely to play a central role (Jamal et al., 2017; Wynn, Martinez, Bulafka, et al.,

2017). Since individual experiences vary greatly, predicting reactions to different types of SFs seems challenging.

Cancer was, in general, perceived as more threatening than cardiovascular diseases. Participants tended to intuitively process risk for cancer in quite general terms, even though they explicitly pointed out that types of cancers vary. Hence, evaluations of risks for LS and LFS differed to a lesser extent than professionals might expect, due to LFS's earlier onset and less efficient preventive possibilities (Schneider et al., 1993). However, none of the focus groups discussed these two cancer syndromes together; had this been the case these differences might have been more evident.

Similarly, none of the focus groups discussed LQTS and FH at the same time, but FH seemed a great deal more familiar compared to LQTS. Participants easily understood that FH concerns high cholesterol, which they knew to be a common problem and a risk factor for heart disease. Hence, the FH letter was perceived not very frightening, but useful and easy to understand. In contrast, it was harder for participants to make sense of what LQTS means for one's life, which led some participants to express considerably more worry than others. Despite these differences, we emphasize that no simplistic conclusions should be drawn; FH may not be less threatening to everyone, and reactions are likely to depend on varied past experiences of (similar) conditions.

Distinguishing Mendelian and polygenic risks

When conducting genome-wide sequencing it is possible to detect high risk single variants, but also to calculate polygenic risk scores for multifactorial diseases. So far, polygenic risk scores are not widely used in healthcare settings, but private companies offer direct-to-consumer testing for susceptibilities of varied multifactorial diseases (Bunnik et al., 2012).

Professionals may approach genomic results from the point of view of known variants and their implications. In contrast, lay people tend to approach genomic risk information primarily from the point of view of disease type, instead of the magnitude of risk or mode of inheritance (Bacon et al., 2015). Our study participants made sense of hypothetical SFs – related to Mendelian cancers and cardiovascular conditions – through their general understanding of cancer and heart disease. This suggests that communicating different implications of Mendelian and polygenic risks requires special care. This may be particularly important with disease types that can be either Mendelian or multifactorial (e.g. cancer and Alzheimer's disease). However, comparing perspectives on Mendelian and polygenic risks was not the original aim of our study, hence, further research in this area is needed.

Contrasting somatic and psychiatric risks

Unprompted, our study participants stated that they were more hesitant to receive genetic risk information for psychiatric disorders compared to actionable somatic diseases, in line with previous literature (Bacon et al., 2015; Bunnik et al., 2012). In an earlier Finnish survey from the 1990s, physicians and midwives were less in favor of genetic screening for schizophrenia compared to somatic diseases like cancer or FH (Toiviainen, Jallinoja, Aro, & Hemminki, 2003). Results of the current study support Bunnik et al.'s (Bunnik et al., 2012) concerns that psychiatric genomic results could potentially stigmatize, threaten personal integrity or evoke a self-fulfilling prophecy. Importantly, however, the reasons why our study participants considered psychiatric genomic results threatening were not primarily based on a fixed, essentialist distinction between psychiatric and somatic diseases. Severity of lived experience, access to efficient treatment, and level of stigma were considered to vary across diseases in general.

Not only treatability, but also access to treatment

In addition to whether treatment exists, our participants discussed whether treatment is accessible for all types of diseases. Even though tax-funded public healthcare is available in Finland, the current healthcare system includes many pitfalls and does not always function in an optimal manner. The perception that early psychiatric care is not easily available amplified participants' concerns around potentially receiving psychiatric genomic risks. On the one hand, the possibility to monitor and manage early psychiatric symptoms could increase feelings of control over the risk. On the other, without early access to treatment if needed, the same possibility might become a burdensome responsibility for the individual to cope with psychiatric symptoms on their own. Shiloh (2006) concludes that control and responsibility are inevitably linked to each other; the perception of being responsible – having control – may both burden and empower. To conclude, potential use and burden of knowing one's genetic risk depend on nuanced perspectives, including cultural meanings of stigma and how treatment for various types of diseases is organized in different contexts.

Genetic risk may stigmatize or provide relief

Finally, our results suggest that individual reactions to different types of SFs may depend on whether the SFs predict future illness or explain current symptoms. Our results suggest that those who, for instance, struggle with high cholesterol may regard genetic susceptibility to be a relief from responsibility and guilt over failing to decrease cholesterol by healthy diet. In contrast, risk for future illness, particularly psychiatric disorders, was seen to potentially stigmatize the whole family. Similarly, previous research has found that knowledge of genetic risk for obesity may be a relief for those with weight problems, but induce negative affect in those with normal weight (Meisel, Walker, & Wardle, 2012). Also among those who struggle with addictive problems (Dingel, Ostergren, Heaney, Koenig, & McCormick, 2017) and among families with psychiatric disorders

(Austin & Honer, 2005) genetic explanations may reduce experience of stigma. Hence, it seems that genetic risk information has different meanings for those who already suffer from the condition to some degree – providing explanation and relief – compared to non-symptomatic individuals who might, in contrast, experience the information as stigmatizing.

Study limitations

Our study has a number of strengths and limitations. First, the participants were self-selected and primarily middle-aged females; however, their educational and professional background was diverse. As the sample was not drawn from genetic patients or genetic research participants, the results provide some insight into perspectives of those who have limited prior experience of genetic testing. Second, it must be noted that hypothetical accounts do not always match with real situations; for example people tend to be more in favor of receiving all possible types of SFs in a hypothetical situation compared to a real situation after pre-test genetic counseling (Wynn, Martinez, Bulafka, et al., 2017). However, a strength of this design was that we were able to collect participants' immediate accounts on the hypothetical findings.

Our focus group participants provided various ideas on how the vignette letters could be improved. Some participants said the letters were perfectly considerate and informative, while others found sending such risk information via letter unacceptable, or stated that the letters were not comprehensible for everyone. Some wished for more information, others thought the level of detail was just right. Further studies need to test different types of letters to find the best practical solutions.

Choosing to discuss one cancer syndrome and one cardiovascular syndrome in each session possibly encouraged comparisons between these disease categories, whereas asking participants to

discuss, for example, two cancer syndromes in one session might reveal more nuanced evaluations of different types of cancer syndromes. However, focus group discussions provided insight into why SFs for certain diseases might be regarded as more distressing than others. Since we allowed participants to elaborate varied points of views on the topic, we identified a wide range of perspectives that were meaningful for participants, some of which we had not initially expected. Bearing this in mind, our results should be interpreted as exploratory and descriptive: further experimental and quantitative research is needed to draw conclusions on generalizability of differences in reactions to different diseases.

Conclusions

In addition to clinical severity and actionability of different diseases, lay illness representations may shape reactions to, and coping with, different types of SFs in a variety of ways. Predicting reactions to SFs for different diseases is complex, due to individuals' varied experiences and knowledge of different diseases. Research and practical attention needs to be directed to communicating the difference of Mendelian and polygenic risks and their implications, since lay people may primarily make sense of risk information through their understandings of different illnesses, instead of mode of inheritance. We argue that lay illness representations need to be taken into account, if we want to find the best ways of categorizing and reporting SFs.

Conflict of interest

All authors declare that they have no conflict of interest.

Informed consent

All procedures followed were approved by University of Helsinki Ethical Review Board in the Humanities and Social and Behavioral Sciences and in accordance with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all individual participants for being included in the study.

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Figure 1. Data collection process.

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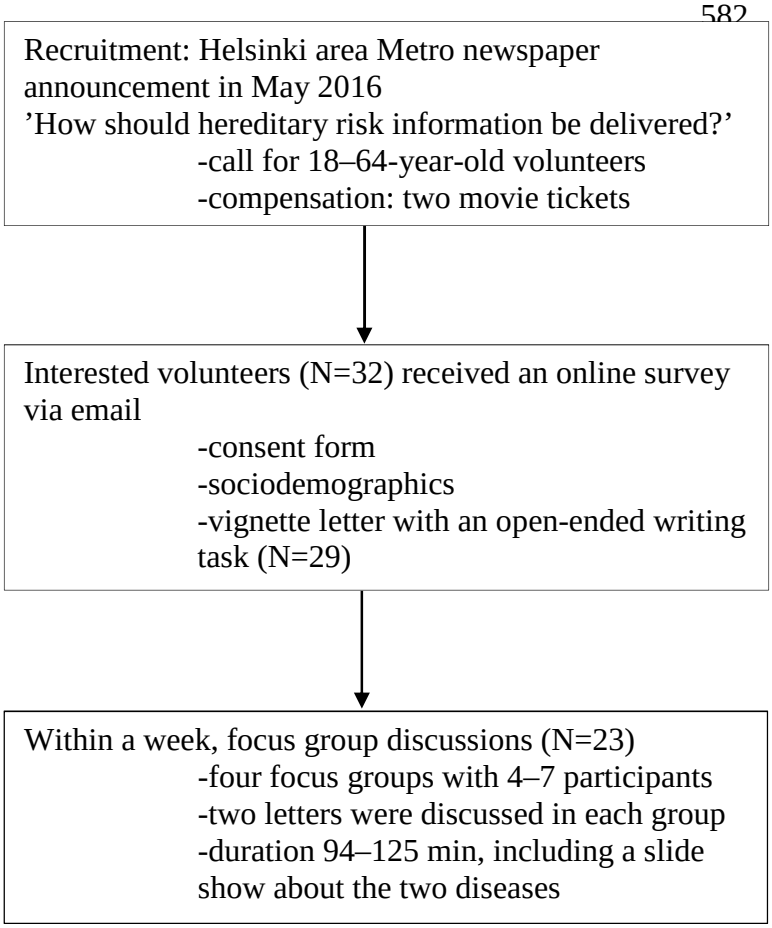
Recruitment: Helsinki area Metro newspaper announcement in May 2016
'How should hereditary risk information be delivered?'
-call for 18–64-year-old volunteers
-compensation: two movie tickets
Interested volunteers (N=32) received an online survey via email
-consent form
-sociodemographics
-vignette letter with an open-ended writing task (N=29)
Within a week, focus group discussions (N=23)
-four focus groups with 4–7 participants
-two letters were discussed in each group
-duration 94–125 min, including a slide show about the two diseases

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585 **Table I. Four vignette letters.**

Please read the following and write down what You would think and do in the situation.

[COMMON TO FOUR VERSIONS:]

Dear recipient,
You recently visited the university hospital, where your blood sample was drawn to examine a disease, and the sample was used to sequence your whole genome (genes were spelled out letter by letter). When genes are spelled out letter by letter, it is possible that also other health related genetic mutations are found.
Before giving the blood sample, you signed a consent form stating that we can contact you if we find some other health related findings during the examination.

[VERSION FAMILIAL HYPERCHOLESTEROLEMIA:]

Your recently analyzed results indicate that you may have a hereditary disease that increases cholesterol.

The condition is called familial hypercholesterolemia, which increases blood cholesterol. Among disease carriers, cholesterol level is often over 10 mmol/l, but the value may be lower too. In Finland around 10 000 people are affected by this disease. If it is not treated, it is associated with early coronary heart disease, among men usually at the age of 40–50 years, among women approximately a decade later. The illness is dominantly inherited, which means that also some of your relatives may have the same disease, for instance your children, siblings, or parents. If one has this disease, diet alone will not affect the cholesterol level. Efficient statin medication is always needed, and often also another complementing medicine, to achieve a cholesterol level that is close to normal.

We recommend you contact the laboratory of your healthcare center to make an appointment to have your cholesterol level measured. Please take this letter and the attached referral with you to the laboratory. After this, please book an appointment with internist (cardiologist) to evaluate medical and other treatment and to possibly organize further examinations in your family. Please take this letter and the referral with you also to the doctor’s appointment.

[VERSION LONG QT SYNDROME:]

Your recently analyzed results indicate that you may have a hereditary susceptibility for certain types of cardiac arrhythmia.

The condition is a hereditary heart arrhythmia, so called long QT syndrome, which predisposes to certain types of arrhythmia. The susceptibility is dominantly inherited, which means that also some of your relatives may have the same susceptibility to arrhythmia, for instance your children, siblings, or parents. Most carriers of the syndrome in Finland have no symptoms. However, there are preventive methods and medical treatment for the arrhythmia. Need for treatment is evaluated individually.

We recommend you contact the laboratory of your healthcare center to confirm the diagnosis and to make an appointment for ECG (’heart film’). Please take this letter and the attached referral with you to the laboratory. After this, please book a doctor’s appointment at the healthcare center or occupational healthcare, to evaluate the need for treatment and to possibly organize further examinations in your family. Please take this letter and the referral with you also to the doctor’s appointment.

[VERSION LYNCH SYNDROME:]

Your recently analyzed results indicate that you may have susceptibility to a hereditary colorectal cancer syndrome.

The condition is a hereditary cancer syndrome called Lynch syndrome, which means susceptibility to e.g. early colorectal cancer, and endometrial cancers in women. The susceptibility is dominantly inherited, which means that also some of your relatives may carry the same susceptibility for cancer, for instance your children, siblings, or parents. Often there are more people with cancer in the family than usual. Colorectal cancer can be prevented through regular examinations.

We recommend that you telephone the genetics clinic of a university hospital, to confirm the diagnosis and to book an appointment for genetic counselling. During the counselling session you will receive more information on the disease, its heritability, and preventive surveillance. Please take this letter and the referral with you to the appointment.

[VERSION LI–FRAUMENI SYNDROME:]

Your recently analyzed results indicate that you may have susceptibility to a hereditary cancer syndrome.

The syndrome is called Li–Fraumeni syndrome, which is a rare syndrome causing susceptibility to several cancers. The susceptibility is dominantly inherited, which means that also some of your relatives may carry the same susceptibility for cancer, for instance your children, siblings, or

parents. The cancers typically occur at a relatively young age and they may sometimes recur. Tumors associated with Li–Fraumeni syndrome include, among others, soft tissue sarcoma, breast cancer, and brain tumour.

We recommend that you telephone the genetics clinic of a university hospital to book an appointment for genetic counselling. During the counselling session you will receive more information on the disease, its heritability, and preventive surveillance and treatment. Please take this letter and the referral with you to the appointment.

[COMMON TO FOUR VERSIONS:]

If you have any questions, you can contact the healthcare personnel below.

[Hypothetical contact details for personnel at the university hospital]

Please imagine this situation and write down what You would think and do in this situation.

(Open responses)

We ask you to imagine being in the situation described in the letter until you come to the focus group discussion, and to think about how you would react to the letter.

Table II. Diseases discussed in four focus groups.

Focus group	Cardiovascular related letter (N=12)	Cancer related letter (N=11)
A	Long QT syndrome (N=4)[1]	Lynch syndrome (N=3)
B	Familial hypercholesterolemia (N=3)	Li−Fraumeni syndrome (N=3)
C	Familial hypercholesterolemia (N=2)	Lynch syndrome (N=2)
D	Long QT syndrome (N=3)	Li−Fraumeni syndrome (N=3)

[1]number of focus group A participants who wrote their first reactions to long QT syndrome. In focus groups, participants could comment on both vignette letters under discussion.

Table III. Descriptive characteristics of study participants who completed a writing task.

Disease in the letter	Familial hyper-cholesterolemia	Long QT syndrome	Lynch syndrome	Li−Fraumeni syndrome	Total
Vignette letter in writing task (n)	5	8	7	9	**29**
Attended focus group (n)	5	7	5	6	**23**
Females (n)	5	7	6	9	**27**
Parents (n)	1	5	4	6	**16**
University degree (n)	3	3	2	4	**12**
Mean age (years)	43	50	49	50	**49**
Age range (years)	20−61	28−64	32−63	30−61	**20−64**

Appendix. Topic guide for focus groups.

We (MV & KA-C) welcome all participants and introduce ourselves. We tell the participants that they need not tell their names, and the interview is recorded and transcribed so that the researchers can analyze the conversation. We remind them that participants' names will not be linked to citations. All citations will be made so that anonymity is secured. The transcribed data will be stored behind locked doors.

Participants are told they no longer need to imagine themselves as the recipient of the letter. They can comment it from whichever position they like.

We tell them that each participant read a letter, but under the present discussion there are two versions of it, i.e. risk information on two different diseases. In the present group the participants have received letters concerning diseases x and y (see table below), and we will go through them together.

Focus group		
A	Long QT syndrome	Lynch syndrome
B	Familial hypercholesterolemia	Li−Fraumeni syndrome
C	Familial hypercholesterolemia	Lynch syndrome
D	Long QT syndrome	Li−Fraumeni syndrome

The participants may ask questions and interrupt the interviewers freely. The interviewers appoint speaking turns if needed. Lastly, the participants are told that there are certain themes to be discussed during the allocated time frame.

Opening the discussion

1. **Instant reactions or spontaneous comments on the letter**

How do you feel at the moment/What do you think about the letter or the finding it concerns?

What was your first reaction after reading the letter?

Was there something scary/threatening?

Was there something relieving?

How did the letter appear in general?

How would you change the letter?

How would you like to know about the finding?

Have your thoughts changed after the first reaction?

2. Disease and understanding of susceptibility

- At some point of the discussion, the participants are told more about the two diseases (slide show), and also other diseases if necessary. When need for this knowledge arises, the participants are asked to first describe what they have learned about the diseases so far. After this, they are told what is known about the diseases in the medical field. This is why delivering knowledge on the diseases is not strictly fixed to any particular phase of the interview.

What did the disease seem like?

Could someone interpret the letter to mean that they already have the disease instead of only susceptibility?

How do you define susceptibility and illness?

Based on the letter, what kind of disease is this? How likely is it?

3. Search for knowledge

Did you try to find out information on the disease after the letter?

If you did, where did you find information?

What did you find out?

What did you try to find out?

Did the disease seem different after searching information, how?

4. Family and heritability

At which point did the letter raise thoughts about family?

What kind of thoughts and questions arose concerning family?

Do you have previous experience on heritable diseases?

Why did you choose to participate this study?

5. Recommendations for practical implication

What kind of diseases or susceptibilities would you like to be informed of in the future?

How should this information be delivered?

6. Consent to receiving information

If you imagine having consented to receiving information on genetic susceptibilities during a medical appointment, would you like to decline this sort of information after receiving this letter?

In practice, how should consent be obtained, when dealing with issues like this?

(We may tell them how consent is obtained, for instance, in the Finnish biobank research register.)