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### ► **To cite this version:**

Olivier Putois, Françoise Houdayer, Marie Lise Babonneau, H. Chaumet, Lorraine Joly, et al.. Secondary findings from next generation sequencing: psychological and ethical issues. Family and patient perspectives. Focus groups final.pdf. European Journal of Medical Genetics, 2019, 62, 10.1016/j.ejmg.2019.103711 . hal-03005204

**HAL Id: hal-03005204**

**<https://hal.science/hal-03005204>**

Submitted on 13 Nov 2020

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# Secondary findings from next generation sequencing: Psychological and ethical issues. Family and patient perspectives

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## ARTICLE INFO

### Keywords:

Secondary findings

Next generation sequencing

Exome sequencing

Psychology

Ethics

Developmental disorders

## ABSTRACT

Access to active search for actionable secondary findings (SF) in diagnostic practice is a major psychological and ethical issue for genomic medicine. In this study, we analyzed the preferences of patients and their families regarding SF and identified the reporting procedures necessary for informed consent. We interviewed parents of patients with undiagnosed rare diseases potentially eligible for exome sequencing and patients affected by the diseases listed in the ACMG recommendations. Four focus groups (FG) were formed: parents of patients with undiagnosed rare diseases (FG1, n = 5); patients with hereditary cancers (FG2, n = 10); patients with hereditary cardiac conditions (FG3, n = 3); and patients with metabolic diseases (FG4, n = 3). Psychologists presented three broad topics for discussion: 1. Favorable or not to SF access, 2. Reporting procedures, 3. Equity of access. Discussions were recorded and analyzed using simplified Grounded Theory. Overall, 8 participants declared being favorable to SF because of the medical benefit (mainly FG1); 11 were unfavorable because of the psychological consequences (mainly FG2, FG3, FG4); 2 were ambivalent. The possibility of looking for SF in minors was debated. The 4 key information-based issues for participants ranked as follows: explanation of SF issues, autonomy of choice, importance of a reflection period, and quality of interactions between patients and professionals. Examining equity of access to SF led to philosophical discussions on quality of life. In conclusion, individual experience and life context (circumstances) were decisive in participants' expectations and fears regarding access to SF. Additional longitudinal studies based on actual SF disclosure announcements are needed to establish future guidelines.

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<https://doi.org/10.1016/j.ejmg.2019.103711>

Received 22 October 2018; Received in revised form 4 June 2019; Accepted 28 June 2019

## 1. Introduction

Next generation sequencing (NGS), in particular Exome and Genome sequencing (ES and GS), offers new diagnostic opportunities in the context of rare diseases. It can lead to more frequent primary diagnoses, particularly in congenital anomalies and/or intellectual disability, but also to the discovery of so-called secondary findings (SF), actively sought though not related to the indication for testing. In 2013, the American College of Medical Genetics and Genomics (ACMG) published a list of genomic variants that can be acted upon if found early (Green et al., 2013) (revised to a total of 59 in 2017 (Kalia et al., 2017)): it recommends systematically identifying and disclosing these variants regardless of patient age - if the patient or family agrees - when ES or GS have been prescribed. The European Society of Human Genetics (ESHG), on the contrary, has issued recommendations suggesting the use of gene panels to avoid the question of SF (van El et al., 2013), (Matthijs et al., 2016). In 2015, the Canadian College of Medical Geneticists (CCMG) (Boycott et al., 2015) recommended a cautious approach. They do not endorse the intentional clinical analysis of disease genes unrelated to the primary indication, even if the Results might be medically actionable, until the medical benefits have been established. The CCMG also acknowledges that the magnitude of potential risks has not been empirically determined. A lively debate took place in France in 2018 on this very subject. In the context of the revision of the French bioethics laws, the French Federation of Human Genetics (FFGH) published a document (Contribution de la Fédéra, 2018) in support of the CCMG recommendations, and the French Biomedical Agency is currently drafting recommendations regarding incidental and secondary findings. Mackley et al. (2017) published a meta-analysis of studies examining hypothetical SF preferences for all groups (professionals, patients, relatives, the public) in a clinical, care or research context. The 15 selected quantitative studies reported a widespread desire (95–100%) to receive or recover clinically actionable data. According to previous studies, between 52% and 100% of participants wanted to be able to access all SF, regardless of whether they could be acted upon. In France, the SEQUAPRE study (Chassagne et al., 2019) performed a quantitative analysis of the preferences of 513 parents of children with undiagnosed developmental disorders with respect to the disclosure of hypothetical ES results. The results indicate that the parents wished to receive exhaustive information, including SF. At the same time, presymptomatic diagnostic surveys of families at risk of carrying a genetic predisposition to breast cancer or heart disease have revealed a much lower percentage of patients actually willing to undergo additional genetic testing when the molecular basis of their condition has been identified. In a study of hypertrophic cardiomyopathies at risk of sudden death, for which the fitting of a defibrillator is a possible solution, only 39% of the 235 eligible individuals came in for testing (Christiaans et al., 2008). Ropka et al.'s (Ropka et al., 2006) meta-analysis of 40 studies focused on presymptomatic diagnosis in the context of hereditary breast cancer found that only 59% of the eligible population followed through with testing. Offering patients access to SF currently recognized as actionable is still a debated topic in Europe, particularly in France. This question raises new psychological and ethical issues that require more in-depth investigation. The present study, named PADAP (Possibilité d'Accéder aux Données secondaires, Approche Psychologique), is the first French study seeking to evaluate these questions in different population groups. Our two main objectives were: 1. to learn more about people's motivations and expectations with respect to SF, and 2. to identify people's desire for information and support in these novel clinical situations. The input of parents of children with undiagnosed rare diseases and individuals affected by the pathologies covered by the ACMG recommendations is very important for the future development of national guidelines.

## 2. Subjects and methods

Study design: The Focus Group (FG) method (Kitzinger et al., 1999) (Morgan, 1993) is a qualitative research method that allows semi-structured discussions to be conducted using pre-defined questions. When conducted by professionals used to handling potentially conflicting views or positions and preventing tacit consensus formation, they can facilitate the expression of a variety of opinions while preventing restriction, hierarchy or consensus building.

Collected data are illustrated by powerful paradigmatic verbatim statements which reflect the depth of content that can be collected using this method.

This process allows a better understanding of how and why certain behaviors are adopted.

In order to collect information about individuals' specific attitudes and desire to access SF, we formed 4 discussion panels. The first was parents of children with undiagnosed rare diseases who were potential candidates for genome-wide sequencing with the possibility of accessing SF, and the other three panels included individuals affected by the 3 main categories of genetic predispositions listed in the ACMG recommendations for SF (hereditary cancers, hereditary cardiac conditions and metabolic diseases).

Study population: The relevant patient organizations for each of the four conditions (undiagnosed rare diseases, hereditary breast cancer, hereditary cardiac disease, and metabolic disease) were contacted. We sent an email explaining the context of the study and offered additional explanations by phone if requested by potential participants. Patient organizations participated on a voluntary basis and chose their own representatives. Participants were not initially told what they would be discussing, since the objective was to obtain spontaneous reactions. They were informed that the discussions were being recorded in order to acquire a full record of the dialogue; it was mentioned that the collected data would remain anonymous. Participants were asked to sign a consent form. Overall, 21 individuals from 13 patient organizations were included; they all had personal experience in genetic testing, either as patients (groups 2 to 4) or as patient relatives - spouse or parent (group 1). Before joining a FG, participants were required to attend a 2-h information session to ensure that everyone had a similar minimum level of information. The first 1-h session provided basic information regarding genetics, transmission and new technologies, and the second 1-h session defined SF, presented the different attitudes in various countries and the general Results of population surveys. Participants were presented with the fundamental notion of medical actionability, and the fact that the risk/benefit balance of accessing SF results has not yet been proved. They were told that some countries consider the medical benefits of SF to be questionable, that the potential risks have not yet been determined in situations where there is no family history, and that the long-term prospects of patients with positive SF results is not known. The afternoon was devoted to FG discussions. Participants were grouped into four FG categories: FG1, parents of patients with an undiagnosed rare disease (n = 5); FG2, patients with hereditary cancers (n = 10); FG3, patients with hereditary cardiac conditions (n = 3); FG4, patients with metabolic diseases (n = 3).

FG and data collection process: Each FG was led by an experienced clinical psychologist (the moderator), accompanied by an observer; all had prior experience in genetics. The collected verbatim statements concerned hypothetical situations since no participant had had any direct experience with the disclosure of SF from ES or GS. Each group met for a 2-h discussion. Each moderator insisted that everyone was entitled to their opinion and that they should not be afraid to diverge from other participants: the goal was not to reach a consensus.

A distinctive trait of our approach was the use of open-ended, general questions. In view of pre-existing patient expertise, the morning information sessions, and the novelty of the hypothetical situations, we deliberately chose questions that would allow participants to spontaneously imagine situations associated with access to SF, both

individually and as a group. This study thus differs from that of Christenhusz et al. (2015) where FG on SF revolved around structured, scenario-based discussions. Overall, our goal was that participants themselves would determine what truly matters (Smithson, 2000) (Smithson, 2000).

In order to focus the discussion on the objectives of the study, the three following questions were asked directly:

**Question 1.** What do you think about access to actionable SF identified by ES for patients with developmental diseases who have not yet received a genetic diagnosis?

**Question 2.** How do you view the information to be given to patients in the context of proposed access to actionable SF by ES?

**Question 3.** In your opinion, is the restriction of SF Results to patients with an indication of ES (as opposed to general population) an issue with respect to equity of access?

At the end of the session, two debriefings were held: 1. Between the moderator and observer of each group; 2. Between all 8 moderators and observers. Recorded FG discussions were transcribed, and data underwent qualitative analysis by two experienced psychologist researchers (FH and OP). The interviews have been conducted in French; we translated specific passages into English for publication.

Data analysis: to analyze data from a single, parallel FG session, we relied on a simplified version of Grounded Theory – a form of bottom-up categorization rooted in field data (Morgan, 1993). Grounded Theory allows researchers to exploit data collected over the course of FG sessions (Hennink, 2014), (Foley and Timonen, 2015), (Glaser et al., 2017). This method generally requires 2 researchers to code data into categories and subcategories in parallel, and then compare their Results and work to reconcile their independent coding schemes (cf. e.g. Klitzman, 2009 (Klitzman, 2009) for this type of use of Grounded Theory). Since our goal was to provide an exploratory assessment of the most salient preoccupations emerging in this novel context, we reasoned like Bennette et al., 2013 (Bennette et al., 2013) and did not aim for standard, complete saturation but to identify the most frequent themes.

We therefore simplified the principles of Grounded Theory. First, we sought to organize the ideas on a single level (according to “themes”); second, we coded the FGs independently but in the same, randomly picked order (starting with FG3) to then see whether the themes emerging from FG3 data also emerged in other FGs – and, if so, to what extent.

In view of our explicit and constant efforts to ensure that all participants felt comfortable expressing their opinions, we considered that the significance of a theme was reflected by the number of times it was brought up during the FG discussions.

Thus, in addition to numbering participants in favor of, against or ambivalent to the ideas raised in the questions, we ranked the themes present in their answers by the order of frequency.

### 3. Results

Of the twenty-one volunteer participants, eighteen were women and three were men (one in FG1 and two in FG2); median age was 49 years (35–80). In FG1, all participants (n = 5) were parents of children with

an undiagnosed rare disease; in the other three FGs (n = 16), fifteen participants were patients and one man was the husband of a patient.

3.1. Results for question 1. What do you think about access to actionable SF identified by ES for patients with developmental diseases who have not yet received a genetic diagnosis? (Table 1)?

Overall, 8 participants were in favor of access to SF, 11 were against it and 2 were ambivalent. When the participants' opinion was favorable, it was motivated by the notion of prevention or treatment possibilities. In FG1, parents confronted with their child's lack of diagnosis were very eager to have access to SF: “Additional Results, in any case, can only be positive. There's nothing worse than not knowing” (FG1, P2). Two mothers also mentioned the value of testing for SF if it would allow them to live longer in good health so that they could care for their disabled child for as long as possible. A participant in FG2 (P1) said: “I would know what I have hanging above my head, [...] to do something, you know, not just to be passive.” Participants referred to individual experiences to justify their choices. For example, one participant (FG3, P1) said: “In Marfan disease, it's useful to be informed of the diagnosis as soon as possible”.

When participants were not favorable to SF, they put forward the psychological consequences of this type of diagnostic disclosure (for the patient, the couple, the siblings, or the extended family), and the recommended increase in medical supervision. Diagnosis actionability was sometimes viewed negatively. One participant (FG1, P4) who was against SF said: “the choice they give you to avoid [the disease] is mastectomy and ovary removal [...] It's so huge that I think I still have to maintain my position against it.” One participant said (FG2, P6): “we've already experienced this trauma once, though, so reliving it for something else ...”. Another participant said (FG2, P8): “maybe the general population would actually like to see what they have, but we already have a problem and we know all about it. We know what it's like to know.” Two women from FG2 (P6, P7) explained that opting for prophylactic surgery was “the only way to make it stop.” The complexity of treatment was also mentioned by one FG4 participant, citing the example of Fabry disease.

The psychological discomfort of asymptomatic carrier status was widely discussed in FG2, FG3 and FG4. For example (FG3, P3): “with such screening, an asymptomatic patient status is created. You already have one foot in the coffin.” It was described as a “cleaver” (FG2, P2, P9) and “sword of Damocles” (FG2, P4, P6, P7, P8 and FG4, P2). The impact on quality of life was highlighted in FG2, in which participants spoke about losing their “joie de vivre” (P4) and “insouciance” (P8, P9, P10).

The two ambivalent participants (FG4) were sensitive to both the medical benefits and potential negative repercussions of SF. The notion of benefit was also mentioned for diseases which are currently not well understood.

Lastly, we observed that the views of some participants evolved over the course of the discussion: 7 participants out of 21 (in all combined FGs) ended up adopting more nuanced positions. A person who was initially not favorable to looking for SF said (FG3, P3): “You completely convinced me that for Marfan we can do it.” Another participant, initially in favor of SF, added (FG4, P1): “In the end, I can imagine that sometimes it's not a gift.” Two people (FG1, P2 and FG2, P5) questioned the notion of actionability: “Well, if there are preventive measures that are less radical ... that is, there's a question of degree.”

Table 1  
Results to question 1.

Name of the FG	Favorable to the search for the SF	Unfavorable to the search for the SF	Ambivalent
FG1 Parents of patients with undiagnosed rare disease (n = 5)	4/5	1/5	0
FG2 Patients with hereditary cancers (n = 10)	2/10	8/10	0
FG3 Patients with hereditary cardiac conditions (n = 3)	1/3	2/3	0
FG4 Patients with metabolic diseases (n = 3)	1/3	0	2/3
TOTAL (n = 21)	8/21	11/21	2/21

FG1, FG3 and FG4 discussed the prospect of looking for SF in minors when the Results do not entail a risk of developing a disease until adulthood. Six participants were in favor, concluding that it was the parents' responsibility. In FG4 for example (P1): "they make the decision for him, especially if there is an actionable interest behind it." Three participants were ambivalent. In FG1 for instance (P4): "it depends on the cases, the age, whether they can think for themselves." In FG3, one participant was against it because of the legislative issues around the subject of presymptomatic tests for minors in France. In this same group, the impact on the parent-child relationship was a concern (FG3, P2): "if, in addition, someone comes to tell me that there is a risk of sudden death, am I going to continue to love him?" It was also pointed out in FG1 (P1) and FG4 (P1) that choosing for the child "deprives him of choosing tomorrow." Two participants in FG1 (P3, P4) considered the idea of requesting medical information but not transmitting it to the underage child. The outcome of the parents' choice was discussed in FG4 (P3): "in a few years, you may find yourself at odds with your child's point of view", whatever the parent's choice may have been.

3.2. Results for question 2: How do you view the information to be given to patients in a context of proposed access to SF by ES?

FG participants held fairly convergent opinions for this question. Four key recommendations were expressed by a majority of participants.

1. Thirteen participants highlighted the need to explain the implications of SF beforehand. For example (FG3, P2): "it's not enough to say: 'you want to know or you don't want to know?', that's not informed consent. We need to explain to them what knowing implies." 2. The next issue was the importance of autonomous patient choice, which was raised by twelve participants. For example, (FG2, P5): "you have to let people say yes or no, I want to know, or I don't want to know." 3. The importance of a reflection period was another priority, and it was discussed in the light of individual experiences. Overall, ten participants were in favor of such a period, for example (FG3, P1): "there is such a quantity of information to ingest that today any lucid person should say to himself: 'I cannot make him sign the same day'." Two participants were unfavorable after their own experience in oncology (FG2, P9, P10): "if there is one thing that is unbearable – or at least it was to me – it's waiting." 4. Finally, eight participants stressed the importance of meaningful, satisfactory interactions with four specific interlocutors, namely physicians, genetic counsellors, psychologists and patient associations (FG4, P3): "it is important not to see necessarily only the doctor but also genetic counsellors, psychologists and why not even patient discussion groups." In addition, the current written consent document has been criticized for holding too much information for the limited reflection period, especially if information about SF is added. The possibility of re-analyzing the data over time also brings current practices into question. One patient (FG3, P2) said: "when you give consent, it's for that particular time, not 10 years later."

In the course of the discussion, two other themes emerged: psychological support, and the importance of both timing and circumstances (understood as "life context", as research in quality of life calls them (Lloyd et al., 2017)). Five participants (three from FG3 and by two from FG4) strongly endorsed offering psychological support immediately after the return of the diagnosis and in the aftermath. For example (FG3, P2, P3): "the role of the psychologist is essential; it should be included in the law." "We can't limit ourselves to medical benefit because ... the psychological impact is enormous and can't be measured at any given time; it lasts for years and years." The subject was not mentioned directly by FG2, but this group spent the most time discussing the psychological consequences of diagnoses. Conversely, in FG1, in the absence of an etiological diagnosis, previous negative experiences were reported (FG1, P3): "there are still families who remain in a mindset of: 'it's the parents' fault'."

Concerning the timing of the announcement and life context, it was

discussed more or less explicitly in all the FGs. In FG2 for example (P7): "ten years ago, I would have responded quite differently, since the illness was no concern of mine." In FG4 (P2): "we really need to be in a situation that is adaptable to the disease, the family, the person's experience, his whole history." In FG1, FG2 and FG3, participants highlighted a wish not to know every possible risk and a feeling of uncertainty towards the progress of scientific knowledge. For example (FG2, P5): "They will tell us 'in the current state of research, you are not carriers of anything but come back in 5 years [ ...] the small list will be much longer and we will find more things'. [ ...] I find it unthinkable and irresponsible to announce a risk, a probability, unless we want to be prescribing antidepressants non-stop."

3.3. Results for question 3: In your opinion, is the restriction of SF results to patients with an indication of ES (as opposed to general population) an issue with respect to equity of access?

Restriction of access to exome data was not perceived as a privilege by the parents of patients with undiagnosed rare diseases (FG1). The question even somewhat upset them (FG1, P3): "If you want the same opportunity ... well, you can take my handicap too." Participants in FG2, FG3 and FG4 thought that, while medical application is important, equity would indeed mean providing everyone in the general population with access to SF. The question of challenges and limitations was thus raised by seven participants. For instance (FG3, P2 who has the same pathogenic condition as his child): "How will we live with this degree of knowledge, of prediction ... ?" According to another participant (FG3, P3): "We must go further in our ethical considerations – what kind of society do we want tomorrow?" This question didn't elicit as many detailed responses as the previous ones.

## 4. Discussion

Participants were generally not in favor of access to SF. This study showed that 8 participants were in favor, 11 against and 2 ambivalent.

### 4.1. The benefit-risk ratio

Arguments in favor were mainly related to expected medical benefits for the patient. Conversely, arguments against were mostly related to the potential psychological consequences of a diagnostic announcement of this type. Our Results are consistent with those of Bennette et al. (2013) who identified hypothetical preferences for the return of results from next-generation testing. They showed that some FG participants expressed a desire to know all IF, some preferred to access only selected SF, and others expressed general apprehension about receiving any SF.

Faced with this benefit-risk ratio, participants who were in favor of access to actionable SF believed that the expected medical benefits would outweigh the psychological risks. The subject of actionability is central, and echoes the work of Mackley et al. (2017), Clift et al. (2015) and Christenhusz et al. (2015) for whom interviewed subjects expressed a desire to access SF in the hope of being able to take action (treatment or prevention), and thereby plan or modify future life choices. Interestingly, FG1 (the parents of children with an undiagnosed condition) saw SFs in a considerably more favorable light than the other three FGs. This result is consistent with Shahmirzadi et al. (2014) who found that 93.5% of parents of minors with complex illnesses, including children with severe intellectual disability or in critical condition, wished to receive one or more categories of proposed actionable SF. The authors specify that those affected by an undiagnosed disease are more active in seeking medical information, making them more receptive to obtaining SF than healthy individuals.

On the other hand, participants not in favor of access to actionable SF were those who felt that the psychological risks would outweigh the announced medical benefits. FG2, FG3, and FG4 patients extensively recounted the traumatic nature of their personal and family diagnostic experiences, particularly after disclosure of the diagnosis. Mackley et al.

(2017) found that 12 out of 44 selected studies (including 11 qualitative studies) listed the risk of anxiety or psychological harm as the most common reason to not disclose SF findings. These studies show that previous experience with genetic disease and testing leads to greater caution in accessing SF. In particular, when a potential future illness is disclosed, the idea of a 'burden of knowledge' was underlined. One participant in Christenhusz et al.'s study (Christenhusz et al., 2015) wondered whether learning that one is at risk of developing a disease can influence the chances of actually developing it. Gargiulo et al. (2017) raised the same question for patients with a diagnosis of Huntington's disease. From a medical point of view, the patients did not develop symptoms of the disease earlier on, but from a subjective point of view they were more likely to feel sick and anxious about the first signs of the disease.

#### 4.2. SF disclosure to minors

The ACMG advocates making certain SFs systematically available to patients of all ages (Green et al., 2013), and the chronological review of ethical arguments for predictive genetic testing in minors (Mand et al., 2012) suggests a gradual shift in clinical practice towards a broader prescription of predictive genetic testing in minors. The current European guidelines, which date from 2009 (Genetic testing in asympt., 2009), do not include the possibility of actively looking for SF for late-onset diseases which could be treated preventatively. Most of the parents who took part in the qualitative studies by Christenhusz et al. (2015), Townsend et al. (2012) and the present study asserted that parents should decide for their underage child whether to access SF or not. In addition, a child with a developmental disorder/intellectual disability will not, in most cases, be able to give his opinion on such a complex subject. This raises ethical questions about the balance between the best interests of the child and the family, especially if the child is at risk of illness later in life. In our study, parents also focused on the delicate subject of child information. They wondered if it was necessary to deliver medical information to the child while he was a minor – and, if so, when and how? Christenhusz et al. (2015) also stressed the difficult balance between generating Results early enough to provide a medical service to the child while avoiding undue anxiety about the onset of symptoms. Christenhusz et al. (2015) also showed that some parents feared that a knowledge of future illness would negatively influence the parent-child relationship. Finally, we wish to insist on the fact that SF disclosure to minors will put asymptomatic children in a position where they will reveal a genetic risk for their parents and families, most probably unaware of their carrier status". This type of situation is a new clinical paradigm specific to predictive medicine, and it is a matter that warrants further exploration.

#### 4.3. Family involvement

The expression "Pandora's box" was used in FG4 (P2), in the study by Clift et al. (2015) and in the title of the article by Townsend et al. (2012). Opening this box by giving access to SF could summon family-wide anxiety about the uncovered risk. In addition, in France, Decree No. 2013-527, dated June 20th, 2013 (Décret n° 2013-527 du 20, 2013), requires patients diagnosed with a genetic abnormality to inform potentially affected family members as soon as preventive or therapeutic measures can be provided. We can hypothesize that this obligation could have specific unexpected psychological effects on patients who are required to disclose and their family members.

Psychological effects of predictive medicine. The disclosure of medical risk calls into question the future of an individual. Here we find the importance of timing and life context, a theme that emerged spontaneously in the FGs. Gargiulo and Durr (2014) warn us about the risk of "a form of informative illusion when one believes that a genetic test provides pure scientific information, without taking into account the psychological reality of the patient." Moreover, PL Weil-Dubuc (2014) states

that: "to assume that medical science can predict what will happen means, in parallel, to set the goal of preventing it." This is precisely what actionable genes are all about. PL Weil-Dubuc also stresses that predictive medicine reveals "the expression of a desire, that of overcoming uncertainty" – a fundamental part of the human condition. Uncertainty can be painful, but it is at the same time a guarantee of freedom that allows us to detach ourselves from the prophetic dimension of prediction. Biesecker et al. (2014) showed that participants' responses to the uncertainty of genomic sequencing information appeared to reflect their existing epistemological beliefs: those who perceived uncertainty as an opportunity reported feeling optimistic about future genetic outcomes, while those perceiving uncertainty as a threat expressed more pessimistic prospects for the future. The confidence displayed by some participants, believing that they should be allowed to decide for themselves, enters into direct conflict with the paternalistic approach of some geneticists who would like to protect them by giving restricted access to specific SF, as has been shown in studies by Mackley et al. (2017), Christenhusz et al. (2015), Townsend et al. (2012) and Fernandez et al. (2014).

Our study participants and those in the study by Christenhusz et al. (2015) also opened a philosophical discussion on quality of life. While some participants acknowledged trying to control the future to reassure themselves, others agreed that uncertainty is linked to the human condition and to the very act of having children.

Our study highlights the possible psychological impact, both individual and for the family, of disclosing ACMG-recommended SF diagnoses. Psychological follow-up is clearly appropriate for those who discover their status of mutation carrier. The importance of psychosocial support is also highlighted in some of the qualitative studies selected by Mackley et al. (2017).

On a more general note, the less detailed responses to question 3 could be explained by the novelty of the topic under discussion. It seemed to us that even people as informed as they were still needed time to integrate the novel clinical situations produced by the possibility to access secondary findings; the extra step of reflecting on issues of social justice might have come off as somewhat premature (also in view of their ethical implications), considering a merely relative familiarity with these medical possibilities.

#### 4.4. Limits of the studies

The limits of our study are mostly linked to the small number of participants. This implies viewing our conclusions with caution, even if Grounded Theory considers that less than 6 participants is optimal for deriving conclusions (Foley and Timonen, 2015). The small number of male representatives (3 out of 21 participants) precluded a gender-based analysis. Moreover, participants did not all have the same role (parent, patient, association representative). Finally, some participants were highly informed expert patients who had often already participated in discussions on behalf of their associations or taken part in other ethical reflection processes. This point, associated with an over-representation of patients directly affected by diseases, and in particular of FG2 participants with hereditary cancers, may account for the higher proportion of unfavorable views of SF than those generally published on the subject. This being said, it is important to keep a critical eye on publications reporting the opinions of people regarding SF obtained by ES and GS. Research or diagnostic contexts have different implications for every patient, and studies only present patients with hypothetical SF scenarios. Finally, Mackley et al. (2017) point out clear differences depending on the chosen methodologies. The proportion of individuals favorable to SF is higher in quantitative studies than in qualitative studies. By devoting time to live, in-person discussion and reflection (through individual interview or FGs), qualitative studies enable participants to explore the issues and implications of SF research more thoroughly, and thus to be more cautious, sometimes to the point of changing their initial preferences.

#### 4.5. Perspectives

Offering patients the opportunity to access “actionable” SF in ES or GS implies transmitting a large amount of information to them beforehand, and explaining the notion of actionability in terms of both expected medical benefits and potential psychological risks. This study has clearly demonstrated that individuals without a diagnosis and those affected by inherited genetic disorders have different perspectives based on their subjective experience. It has also underlined the importance of timing and life context in the decision-making process. Taking all of these parameters into account will complicate the drafting of general recommendations designed to guide these new clinical practices. Nevertheless, in order to provide patients with adequate and appropriate informed consent, we wish to stress the importance of the interpersonal interaction between patients, families and professionals. This interaction is essential, not only to share objective and technical knowledge of genetics, NGS and the list of targeted genes, but also to address psychological issues raised by SF research. All this should be done by integrating a patient's unique medical and psycho-affective experience into the individual and family context as much as possible. The proposed period of reflection prior to any decision seems important, though the support provided during this period remains to be defined. Given the rapid progression of genomic science, dynamic consent procedures also need to be developed. In order to fine-tune our thinking, it is now essential to design longitudinal studies in genuine situations of SF disclosure in order to evaluate the medical benefits and psychological consequences. Finally, we wish to insist on the fact that this new clinical context is totally unique. It involves offering access to predictive genetic knowledge (including in children) outside of any presymptomatic diagnostic protocol. All of this requires the utmost caution and calls for interdisciplinary reflection, wherein clinical psychologists have their rightful place alongside geneticists, biologists, genetic counselors, bioethicists, lawyers and patient representatives.

#### Conflicts of interest

The authors declare no conflict of interest.

#### Acknowledgments

The authors would like to thank AnDDI-Rares, CARDIOGEN and l'IDEX Université de Strasbourg (through a starting grant awarded to Olivier Putois), the Conseil Régional de Bourgogne through the plan d'actions régional pour l'innovation (PARI 2016) and the European Union through the PO FEDER-FSE Bourgogne 2014/2020 programs for funding this study. The authors also thank the 13 patient support groups and their volunteers who accepted to be part of the study: ADAPEI 21; ARAPI; Alliance Maladies Rares; HNPCC; APTEPF; BRCA France; La Ligue contre le cancer; ARMYC; La ligue contre la cardiomyopathie; AFSMA; Feux Follets; APMF; VML. Finally, the authors thank Suzanne Rankin from the Dijon University Hospital for translating the manuscript.

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