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ARTICLE

Stakeholder views on opportunistic genomic screening in the Netherlands: a qualitative study

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Abstract

Genome sequencing can be used to actively search for genetic variants unrelated to the initial clinical question. While such 'opportunistic genomic screening' (OGS) has been proposed in the USA, a European discussion on the ethics of OGS is only starting. Should testing for selected 'secondary findings' be offered to patients who need genetic sequencing? Using focus groups and interviews, we explored views on OGS in adults and minors from three perspectives: policy experts ($n = 9$), health professionals ($n = 8$) and patient representatives ($n = 7$). A thematic approach was used to analyze the data. There was consensus that OGS should be evaluated in terms of the classical 'screening' framework, rather than as a form of 'good patient care'. Accordingly, stakeholders agreed that professionals do not have a 'fiduciary duty' to look for secondary findings. Adding screening to clinical care was only conceivable with the patient's informed consent. In general, stakeholders were reluctant towards OGS. Arguments for regarding OGS being premature included lack of evidence regarding its clinical utility, also in view of uncertainties regarding general population penetrance, and concerns about both its psychosocial impact and respect for autonomy. All groups agreed that OGS means unequal access, which was seen as problematic. Yet, despite their concerns, stakeholders felt that offering screening for certain actionable pathogenic variants with known high penetrance could potentially be valuable in certain contexts for both adults and minors. Pharmacogenetic variants were regarded as a category by itself, for which OGS could potentially be beneficial.

Introduction

Technologies such as whole-exome and -genome sequencing (WES/WGS) are rapidly increasing in patient care due to their decreasing costs [1]. Genome sequencing and analysis can clarify the cause of rare and complex disorders [2]. In addition to identifying findings related to the clinical indication, genome sequencing can also identify other variants. These variants may be accidentally discovered (incidental findings, 'IFs'), but could also deliberately be searched for (secondary findings, 'SFs').

The expanding use of clinical sequencing in patient care has stimulated a widespread debate on whether or not the opportunity of having the patient's raw data available should be used to actively search for selected pathogenic and actionable SFs beyond the patient's clinical indication. Policy statements of national and international professional organizations reflect different views on this issue. The American College of Medical Genetics and Genomics (ACMG) advocates the routine search of SFs in all adult and minor patients who have undergone clinical sequencing, on the basis of a predefined list of medically actionable variants associated mainly with hereditary cancer or cardiac diseases [3]. A partly similar proposal was made by the French Society of Predictive and Personalized Medicine (SFMPP), using a different list consisting of only oncogenetic disorders, and limiting the search for the relevant variants to adult patients only [4]. Notably, there are diverse perspectives regarding the search for SFs in France, with part of the professional community taking a critical stance towards such proposals [5]. A more reticent approach has also been advocated by the European Society of Human Genetics (ESHG). Whereas in an earlier document the ESHG recommended more generally that clinical sequencing should be as targeted as possible [6], a recent policy statement specifically drawn up as a contribution to the

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present debate insists that for the time being, the active search for SFs should only be considered in the context of pilot and evaluation studies to determine whether its benefits outweigh its harms (i.e., proportionality) [7].

Following ESHG terminology, we refer to the active search for selected SFs in clinical sequencing as 'opportunistic genomic screening' (OGS) [7]. The opportunity that arises with the availability of raw data to look for SFs in patients undergoing clinical sequencing is what makes it opportunistic, whereas the search for SFs beyond the patient's indication for testing is what makes it screening.

The proportionality of OGS is contested in view of the fact that the evidence for the penetrance of the relevant variants is based on patients with a family history of the disease, meaning that the risk of carriers of such variants in the general population may be overestimated [8]. Further questions pertain to issues of informed consent and justice considerations. For instance, does it suffice in terms of the principle of respect for autonomy that patients are offered the ability to 'opt-out' from the analysis of SFs, as proposed by the ACMG? Should perhaps a form of dynamic consent be offered, as proposed by the SFMPP? [4] And how to evaluate the fact that only patients who happen to need clinical sequencing are given the option of OGS, whereas their a priori risk of being a carrier of the selected variants is not higher than that of the general population?

Given that the ethical debate about these questions is still in its infancy, it is important to explore the views of different stakeholders on OGS. In this paper we report on a qualitative study with patient representatives, health professionals, ethicists, lawyers and policy makers. Our main research question is whether, and if so, under what conditions, stakeholders in these groups find it acceptable to offer OGS to patients undergoing clinical sequencing?

Methods

Study design

We conducted three focus groups and three one-to-one interviews in May 2019. The use of focus groups allow for the exploration of group dynamics to stimulate the discussion and are therefore most suitable for exploring people's opinions and views on a certain topic [9]. The first focus group was conducted with policy experts ($n = 9$). The second focus group was conducted with health professionals ($n = 5$). The third focus group was conducted with patient representatives ($n = 7$). The focus groups lasted about two hours. Three additional in-depth interviews with health professionals (one cardiologist, one pharmacist and one paediatric oncologist/clinical geneticist) were conducted. These were held with professionals who had wished to participate in the focus group, but had not been able to do so due to their busy schedules. These in-depth interviews lasted about 30–60 min.

This study was reviewed by the Medical Ethical Committee of the VU University of Amsterdam and waived from requiring formal approval under Dutch law. Informed consent was obtained from all participants prior to conducting the interviews and data were handled in accordance with the General Data Protection Regulation.

Participant selection and recruitment

Participants for this study were recruited via a purposeful sampling technique to recruit at least seven stakeholders per group [9]. Stakeholders were invited based on their experience with the topic under study. Policy experts and health professionals were recruited from different institutions, departments and (academic) hospitals in the Netherlands, using the social network of the authors (AW, WD, GdW). The first focus group with policy experts included ethicists, health lawyers and policy makers. The second focus group with health professionals included two clinical geneticists, one clinical laboratory geneticist, one paediatric oncologist and one molecular biologist. For the third focus group, patient representatives (of patients with paraganglioma, lynch syndrome, hereditary cardiac diseases, hereditary cancer, neurofibromatosis, von Hippel-Lindau, and Marfan syndrome) were recruited from the Dutch Patient Alliance for Rare and Genetic Diseases (VSOP). VSOP is a Dutch national patient umbrella organization for rare and genetic disorders with a membership of approximately 70 disease-specific patient and parent organizations [10].

Data collection and analysis

Two focus groups with policy experts and professionals were moderated by AW, GdW and WD. The focus group with patient representatives was moderated by AW and WD. The three one-to-one interviews were conducted by AW. Travel costs for all stakeholders were reimbursed. Patient representatives were also reimbursed fee attendance money.

The focus group interviews and one-to-one interviews were audio recorded and transcribed verbatim. Data were analyzed using MaxQda Version 2018.1.

An interview topic guide was developed on the basis of screening criteria by Andermann: proportionality, autonomy, justice and societal aspects [11, 12]. For example, to examine stakeholders' views on autonomy, AW presented the following statement: 'The offer of OGS by professionals meets the requirements of respect for autonomous choice' (see Supplementary File 1).

We analyzed the focus groups using a hybrid approach (inductive and deductive) of thematic analysis [13]. This approach enabled us to summarize and classify data within screening criteria by Andermann [11], while also allowing for themes to emerge directly from the data using inductive coding [13]. Our thematic analysis included six stages: (1) familiarization with the data (2), inductive open coding (3), generating initial themes (4), reviewing themes guided, but not confined, by the preliminary screening criteria (5), defining and naming final themes and (6) writing up [9].

Two researchers (AW and WD) independently reviewed all transcripts. AW developed codes in an iterative process, and applied these to the data to identify themes. Throughout this process, AW, WD and GdW met regularly to review and revise the themes.

Results

The results are described according to the six themes that we derived from our thematic analysis: Conceptual issues, Benefits, Harms, Autonomy, Justice and Minors. Health professionals are indicated by 'PRO', policy experts are indicated by 'PE' and patient representatives are indicated by 'PR'. The results showed that different perspectives were most pronounced within the different stakeholder groups, rather than between the stakeholder groups.

Conceptual issues

A primary question in the focus group discussions was: how should offering a search for selected SFs to patients undergoing clinical sequencing be conceptualized? Across all three groups, there was consensus that OGS is indeed screening, since patients are addressed who have no clinical indication to be tested for the relevant conditions. All stakeholders took the view that the acceptability of OGS should therefore be assessed in terms of the classical normative framework for screening, as (initially) formulated by Wilson and Jungner [14] and Andermann [11], rather than as a form of clinical care in which physicians have a 'fiduciary duty' to actively search for SFs.

Although the majority of stakeholders agreed that the professional duty of care should be limited to the primary clinical question, a few of them discussed whether there is a duty to analyze raw data and report on other relevant information that is obtained with clinical sequencing. One professional and one ethicist stated that this is the case with regard to actionable pharmacogenomic variants. According to them, this should be seen as 'good patient care'. However, discussions about the professional duty of care were typically dominated by confusion about responsibilities regarding IFs versus SFs:

PRO1: '*If medically relevant information obtained from clinical sequencing seems of importance to the individual, should that not be reported'?*

PRO2: *'But you don't see this information'.*

PRO3: '*The point is, you do not analyse this, you do not interpret it. This is outside the area of interpretation. So, you don't have this relevant information'.*

In addition, there were unclarities about the conceptual difference between screening and diagnostic testing. One patient representative, for instance, argued that SFs would allow for a better understanding of the primary condition.

Potential benefits

When discussing potential benefits of OGS, all three groups cited actionable variants with highly known penetrance for which there is a possibility of prevention and treatment: '*I think, oophorectomy for BRCA and [surgical intervention] for APC [Adenomatous Polyposis Coli], that is very evident, since there is no doubt that APC will result in death. You will be too late, and the chances of dying are high'* (PRO).

Moreover, respondents' accounts further pointed to a wider understanding of 'medical actionability' in terms of the possibility for prevention or treatment. Pharmacogenomic variants were viewed as a category by itself and potentially beneficial as these are 'not prognostic' and 'only relevant when a patient needs medication'. A number of stakeholders also reported benefits in terms of reproductive decision making, depending on a person's age: *'I think that it is relevant to consider to what age group someone belongs to. If there are young people with a child wish, then the information about Von Hippel-Lindau could be relevant because they can do PGD [preimplantation genetic diagnosis], but in another phase, they might not want to know'* (PR).

Others stated that personal utility could also be relevant. One patient representative, for instance, argued that certain conditions could have important implications for planning one's lifestyle: *'There are so many more actions that you can do that are not purely clinical. What do we mean with actionable? It could also mean that you can change your lifestyle or things like that'* (PR). Nevertheless, the majority of the stakeholders agreed that the benefits of searching for SFs should be limited to the possibility of medical interventions for the individual patient.

Potential harms

Despite the aforementioned benefits of OGS, the overwhelming majority of stakeholders was in general reluctant towards the implementation of OGS in the

Netherlands. Numerous stakeholders mentioned the lack of evidence for a favourable balance between benefits and harms. A specific example was provided by the professionals with regard to the actionability of genetic variants associated with cardiomyopathy: *'There are not many [cardiogenetic] variants of which you know what they mean'* (PRO).

The most frequently cited arguments against OGS included psychological risks and medical risks in terms of overdiagnosis and unnecessary treatment. Various stakeholders often raised the concern that the current evidence is based on penetrance estimates in patients with a family history of disease, implying that the penetrance of pathogenic variants is overestimated in the general population: '*The other thing that is important is that the knowledge that we have about these genes is based on patients with a family history of disease. The 3% where we will find these [SFs], if those are all unaffected families, the question is if that has the same effect [in the general population]'* (PRO).

With regard to psychological risks, stakeholders feared that OGS may do more harm than good as patients are confronted with genomic risks with which they are unfamiliar. In addition, the context in which OGS is offered to patients who are already preoccupied with their primary indication was believed to be problematic: *'So, someone has symptoms that are serious enough to justify genetic sequencing, and he is pretty much stressed out, and the doctor that helps him, tells him, 'we can also look at this and this.' Is that offering a free choice?'* (PE).

Moreover, the group with policy experts and patient representatives stressed that genetic results are far less deterministic than generally believed by the population. They held that the growing availability of genomic screening conveys the sense that *'life is manufacturable'* (PE) and may create false reassurance. Mentioning of anxiety and the psychological burden of learning about genomic risks recurred in all groups. Accordingly, a substantial number of stakeholders questioned whether knowledge of SFs is truly empowering. This was exemplified by the following quote from a patient representative with long QT syndrome, who stated to be pleased to have learnt about her genomic risk only at a later age: *'I discovered long QT syndrome when I was 27 years old. But I have worked at the fire department for 10 years, which would not have been possible had I known about the disease at the age of four. Then I would have never learned how to swim. Fortunately, nothing happened. My childhood was pretty easy because I didn't know'* (PR). In addition, patient representatives mentioned the psychological impact that SFs may have on family members: *'The result is that when they find something in you, it will have consequences for your children'* (PR).

Autonomy

Opt-out versus opt-in

In all groups, several concerns about an opt-out procedure (as proposed in ACMG recommendations) were mentioned. Stakeholders feared that this procedure does not reflect patients' information preferences and ability to understand the complex information. Consequently, stakeholders anticipated that patients might too easily provide consent with an opt-out: *'I wonder whether the majority of the people understand what is actually being tested. One can emphasize the need to inform, but we all know that many of them don't understand this, and they will just say 'yes' to the offer*' (PRO).

Nevertheless, a number of perceived benefits of opt-out were named. These included higher uptake of genomic screening and ensuring equal access by offering a uniform test package. One patient representative explicitly reported to have no objection to opt-out. Moreover, with regard to pharmacogenomic variants, one professional stated that an opt-out would be acceptable: *'For [actionable] pharmacogenes, I would favour an opt-out. Since there are guidelines and it is good care, you can almost turn it around. You could say: you should have a very good reason not to search for those variants'* (PRO).

In contrast, an ethicist wondered whether patients who are offered OGS by their health care provider may be less likely to choose actively against such offer: *'It's also the question whether opt-in will meet the requirement of autonomy. This assumes that the patient is able to make a choice, but the way in which the doctor presents the information or places it in a certain context, highly influences the patient's choice. So that raises the question whether people are truly able to decide for themselves'* (PE).

Anticipated decisional regret was mentioned by one patient representative: *'But if you have a mutation [variant] in your 'backpack', it's like a bomb in your 'backpack'. You can decide, I am not going to look into the backpack, but the mutation [variant] is there. So, one could say, I prefer not to know, but if you get cancer, then people's attitude changes. If only I would had known, then I could have prevented this'* (PR).

The majority of stakeholders agreed that an opt-in would be a better approach than an opt-out and that the 'right not to know' should at all times be respected. Only a small number of stakeholders mentioned that individuals have a right to the information. One patient representative, for instance, emphasized respecting the 'right to know': *'The information is so important to me, I would wish for everyone to know this information. For example, familiar hypercholesterolemia, it's actionable and the risks for*

related conditions can be reduced. For me, it's almost unethical to keep this information from people' (PR).

Informed consent

All groups mentioned the importance of informed consent. But stakeholders were unsure how detailed the information should be. Whereas professionals and policy experts stated that SFs should be discussed pre-test to enable informed decision making, one patient representative mentioned that positive results can just be explained post-test, since patients do not have to know all the details to make an informed decision. Concerns regarding the complexity of OGS for patients as well as for professionals were mentioned by all three groups. A professional, for instance, remarked that clinical sequencing will increasingly be ordered by non-genetics specialists who have limited knowledge to perform genetic counselling.

Other concerns about unrealistic or wrong expectations of genetic screening among patients was raised in all three groups. Professionals said that patients would be falsely reassured when no pathogenic variants are identified. They feared that patients might as a result forego participation in existing population-based screening programmes (e.g., for breast or colorectal cancer), or ignore advice pertaining to a healthy lifestyle.

Due to the complexity of weighing up personal benefits and harms, one professional explicitly mentioned the need for face-to-face counselling in addition to providing written information. In all groups, stakeholders believed that the information should be tailored to personal preferences and literacy. They further cited that informed consent should pay attention to the patients' age, phase of life and family history of disease: *'It is difficult to catch all the personal ifs and buts in that [counselling]. You have to look at the age group that people are in and their phase of life. For whom is this information important? Do people have brothers or sisters? Do people have children? That is information that is important for people's choice. What is people's background, their religious beliefs?*' (PRO).

The option of two counselling moments, in which the primary indication and SFs are discussed independently, was also mentioned by a professional and patient representative. Yet, questions were raised about the feasibility of such a form of dynamic consent: *'So, counselling will be reserved for the primary indication and then a second conversation will be planned during which you can discuss this [OGS]. Eh, the question is whether this is feasible. I do not know if people are willing to go to the hospital twice. Also, I wonder whether this is feasible for us to organize this'* (PRO).

Test package

With regard to medically actionable genes, there was support for the offer of a personalized 'menu' or subset as a means of supporting patients' autonomy. One patient representative explicitly suggested that medically actionable genes could be categorized according to penetrance. However, stakeholders questioned whether the offer of a 'menu' would enable informed decision making: *'Categories can also be debated. What belongs to which category? It seems like a pretty difficult task to me. Even within the category actionable, there are big differences related to the chance that people will actually develop a disease. Take cancer for instance […] The type of cancer also matters. How big are the benefits of early detection and how big is the chance that people will actually die? What should the intervention be if the disease is detected at an early stage and what happens when it is detected at a late stage?'* (PRO).

Accordingly, there were discrepant opinions about whether patients should have a choice regarding the content of the test package. Whereas some were convinced that having a choice about a 'package' is required for respecting patients' autonomy, others were also worried that this might lead to inequalities: *'That is not fair. That will mean that people who are naturally well-informed [have more access]'* (PR).

A small number of respondents mentioned the possibility of offering patients 'non-medically actionable' genes. Yet, one professional raised the concern that the creation of different types of SFs might not be feasible, as this could overburden laboratory specialists and professionals: *'Then you will have to tailor the analysis. I don't know how that is feasible—logistically—for the lab […] If someone does not want to know whether he has Huntington* ['s disease]*, but the total analysis is already being done, you will know this as health care professional, and then you will have a problem'* (PRO).

Justice

Stakeholders' accounts illustrated questions around formal justice (i.e., similar cases must be treated similarly) and distributive justice (i.e., scarce resources must be fairly distributed). Unequal access to genomic screening was seen as an important formal justice issue. A number of stakeholders called it 'unfair' to offer it only to those who undergo sequencing for diagnostic purposes, as the a priori risk for SFs is the same for everyone: *'It is absolutely arbitrary. It has nothing to do with the primary indication'* (PR). The majority of the respondents believed that genomic screening, if on balance beneficial for the screenees, should ideally be offered universally. Statements concerning such universal genomic screening were largely

influenced by a sense of moral rights. One ethicist for instance stated that genomic screening should be made widely available as individuals have a right to health information, but individuals would have to pay for it themselves, since it does not yet meet relevant quality requirements.

With regard to distributive justice, professionals discussed whether alternatives, such as cascade screening, would be more cost-effective compared to the offer of OGS. Cascade screening is an approach to finding at-risk persons in families by targeting the relatives of a proband in case of clearly pathogenic, highly penetrant and actionable variants. Yet, we found strong agreement that this would not be a sufficient alternative to OGS as de novo variants would be missed with cascade screening: *'There are APC mutations [variants] that can also be de novo. You will not be able to find all of those with cascade screening'* (PRO). With regard to cardiogenes, one professional pointed out that cascade screening would indeed be more cost-effective, since most of Dutch families with cardiac disorders are already being found through cascade screening.

The fact that the raw data would be already available due to clinical sequencing, thus rendering OGS more 'cost-effective' than alternative approaches was not considered to be a strong argument for OGS. Professionals stated that the 'total package of costs' should be considered, which should be broader than the costs of the analysis: *'It has to be broader than the medical costs. You have to map out really well what are the costs of follow-up testing'* (PRO).

All groups mentioned that more research should be done to gain insight into the penetrance of candidate SFs in the general population and into the psychosocial impact of SFs. Two professionals found that OGS is acceptable in the context of a pilot study, aimed at generating more data about its psychosocial impact. In addition, a professional and patient representative mentioned the option of offering a constricted test package in a pilot study, illustrated by the following quote from the professional: *'If you talk about a research setting, like a pilot, you could start with a small test package. That also makes the [post-test] counselling easier, because it does matter how many people you have to counsel'* (PRO).

OGS in minors

Autonomy

Stakeholders widely felt that respecting the future autonomy of minors is essential. A number of professionals argued that the active search and reporting of some SFs in minors might under certain conditions be acceptable: *'Well, as long as we agree on the principles, if that has been well sorted out, then I think it should be implemented for minors—as long as it is relevant for that age'* (PRO).

There was consensus among the respondents to not actively search for later-onset conditions, like BRCA1, in minors. Early-onset conditions that were mentioned to be relevant for minors at young age included Multiple Endocrine Neoplasia Type 2A (MEN type 2A) and familial hypercholesterolemia. In addition, pre-emptive pharmacogenomic testing was cited to be most cost-effective when done at an early age by a number of stakeholders. One policy maker felt that actionable conditions, such as MEN type 2A, should be included in the new-born heel prick screening. An ethicist emphasized that minors should not be tested for further parental reproductive decision making, as parents could test themselves: *'So, if you want to test your minor children to make reproductive choices, I would think, you should have tested yourself'* (PE).

Discussion

The expanding use of WES/WGS in clinical practice has led to debate on whether selected SFs should be actively searched for. Employing a qualitative study design, we explored views on OGS in adults and minors from three perspectives: patient representatives, health professionals and ethicists, lawyers and policy makers. In line with the recent recommendations by the ESHG [7], there was consensus that the relevant normative framework for assessing the acceptability of OGS should be the classical screening framework with its emphasis on proportionality, explicit informed consent and justice considerations [11, 14]. In all groups, ethical and practical concerns with regard to these three main elements of the screening framework were raised, implying that the implementation of OGS in the Netherlands was perceived to be premature for the time being.

There was consensus that, for the time being, there is too little evidence surrounding the clinical utility and psychosocial impact of actively searching for and reporting SFs. Concerns related to psychological consequences are consistent with previous research [15], which identified these concerns as the most important arguments against OGS among parents of patients. Concerns about the penetrance in the general population are supported by data from a recent review [8]. The results from this review suggest that the evidence base regarding penetrance estimates in the general population is limited and further research is needed to elucidate the ethical consequences of actively searching for SFs. Due to the lack of evidence mentioned above, the French Agency of Biomedicine recently recommended against the implementation of OGS for the time being [16].

With regard to respect for autonomy, stakeholders discussed the possible categorization of genetic variants and the offer of 'packages', reflecting the argument in favour of 'bins' for IFs [17]. However, there was uncertainty as to

how these 'categories' should be defined and whether patients should be given the option to decide for themselves to be screened for a subset of variants, as this 'bottom-up' approach may increase inequalities in access. Assuming the moral weight of personal values in decision making, further research is needed concerning the feasibility of offering 'packages'.

In addition, whereas previous research suggested that patient autonomy would be invoked by offering an 'opt-out' [18], stakeholders in this study queried whether this procedure would truly meet requirements of autonomous choice. Dynamic consent was proposed by some stakeholders to provide patients with a possibility to change their mind about decisions. However, the feasibility of this form of consent was contested from various perspectives. From a practical perspective, there may not be sufficient counselling capacity for this approach. From an ethical perspective, a situation may arise in which a professional finds herself in a conflict of duties, given that the testees' right not to know may clash with their relatives' right to be timely informed about actionable variants. Stakeholders anticipated a tension between the need for explicit informed consent on the one hand and the risk of overburdening the patient with too much complex information on the other hand. In line with previous research, the need for face-to-face counselling and attention to individual preferences and skills was mentioned to be essential in this decision-making process [18]. Future research should explore whether dynamic consent truly lowers the psychosocial impact of SFs and helps patients to become better informed.

Whereas our study generally revealed reluctance among stakeholders regarding the active search for SFs, other studies have reported opposite findings [19]. One explanation for this difference may be our use of group interviews in contrast to administering a survey, as this allowed us to gain deeper insights into stakeholders' opinions and dynamic group processes. Previous qualitative studies showed that participants' attitudes towards SFs changed during the course of the focus group interviews [20].

Similar to previous findings by Houdayer, Putois [15] who described patient and family perspectives on the active search for SFs, a smaller number of stakeholders were not clearly in favour or against OGS. Their ambivalence could be explained by their shared belief that the proportionality of OGS is dependent on the context in which it is offered. Specifically, the fact that, in this context, additional burdensome information is provided to patients who are already confronted with another condition was viewed as potentially unethical. Similar to previous research in the context of IFs, stakeholders discussed the burden of knowing and related anxiety [20]. However, there is a need for more empirical studies on the psychosocial impact of SFs, as to date, most of the studies are hypothetical. Even though one empirical study indicated that patients who received positive SFs experienced minimal psychosocial impact [21], this study was limited by its small number of patients as well as by selection bias towards individuals with positive attitudes regarding participation in research.

Stakeholders also raised justice issues linked with OGS. The offer of OGS was believed to lead to formal justice issues, as members of the general population (with the same a priori risk of being a carrier of any of the relevant SFs) do not receive this offer. To avoid this potential formal injustice, some stakeholders mentioned that genomic screening should be offered universally. However, this suggestion seems to ignore the principle of distributive justice, as this practice in turn has implications for the just distribution of scarce resources in health care. Even if the actual genome analyses costs of OGS are relatively low, there are additional costs, such as the provision of pre- and post-test information and counselling, as well as follow-up costs for the health system, which will have to be dealt with should OGS be offered on a population level [22].

Cascade testing was mentioned to be a sufficient alternative for hereditary cardiac diseases, but not for other hereditary conditions, especially for those characterized by a relatively high contribution of de novo variants, as these would then be missed. Further research should explore the contexts in which cascade testing, or a combination of cascade testing and OGS, may be a more cost-effective alternative.

Supposing that OGS in minors may be justified, stakeholders agreed that early-onset conditions, such as MEN type 2A, as well as pharmacogenomic variants, but certainly no late-onset conditions should be considered. This is in line with the recommendations of the ESHG [7].

As the sample size was limited, the perspectives may not all represent the diverse population of policy experts, health professionals and patients. In addition, this study was conducted in the context of the Netherlands and did not include perspectives of the general population, which might limit the generalizability. Nonetheless, this study is one of the first empirical studies to offer important insights for the discussion surrounding the active search for SFs. Our findings support the argumentation of the ESHG on OGS [7]. We recommend the investigation of stakeholders' views concerning OGS in other countries to enable comparison of findings.

Conclusions

Despite general reluctance towards OGS, numerous stakeholders stated that the proportionality of OGS is dependent upon content, context and conditions. Stakeholders generally agreed that SFs should only be searched for and analyzed under the conditions that there is sufficient evidence that the benefits would outweigh the harms. Across all groups, the

potential value of OGS for actionable genes with highly known penetrance was acknowledged. In addition, pharmacogenomic variants were seen as a promising category sui generis for enhancing patient care. With regard to minors, stakeholders agreed that the search for adult-onset diseases is unacceptable, yet early-onset diseases and pharmacogenomic variants were deemed to be potentially relevant. The need for pilot studies was emphasized to allay practical and ethical concerns around the proportionality, autonomy and justice requirements of OGS.

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Compliance with ethical standards

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