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Opportunistic genomic screening.
Recommendations of the European Society of Human Genetics

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Abstract

If genome sequencing is performed in health care, in theory the opportunity arises to take a further look at the data: opportunistic genomic screening. The European Society of Human Genetics (ESHG) in 2013 recommended that genome analysis should be restricted to the original health problem at least for the time being. Other professional organizations have argued that 'actionable' genetic variants should or could be reported (including American College of Medical Genetics and Genomics, French Society of Predictive and Personalized Medicine, Genomics England). They argue that the opportunity should be used to look for secondary findings – so-called opportunistic screening. From a normative perspective, the distinguishing characteristic of screening is not so much the context in which it is performed (whether public health or health care), but the lack of an indication for having this specific test or investigation in those to whom screening is offered. Screening entails a more precarious benefits-to-risks balance. The ESHG recommends a cautious approach to opportunistic screening. Proportionality and autonomy must be guaranteed, and in collectively funded health-care systems the potential benefits must be balanced against other health care expenditures. With regard to genome sequencing in pediatrics, ESHG argues that it is premature to look for later-onset conditions in children. Informed consent is and should be a central ethical norm. Counseling should be addressed. Depending on developing evidence on penetrance, actionability and available resources, OGS pilots may be justified to generate data for a future, informed, comparative analysis of OGS and its main alternatives, such as cascade testing.

1. Introduction

Also depending on the development of total costs of clinical sequencing, it is expected that in the near future many individuals with an indication for genetic testing will have their exome or now increasingly their entire genome sequenced (henceforward will undergo 'genome sequencing'). Of course, genome sequencing still allows targeted bioinformatics analysis of the raw sequencing data (including uninterpreted data e.g. in VCF files) by using "virtual panels" that are targeting genes most likely associated e.g. with symptoms of an individual. During such a targeted analysis one may "stumble across" incidental findings, which are unsolicited. Recently, debate has started about the pros and cons of broadening the analysis by actively looking for variants unrelated to the initial purpose of testing which however could be important for the health prospects and/or reproductive choices of the patient or the patient's family (so-called 'secondary findings'; SFs). Such discussions deal with medically 'actionable' information associated with SFs which could help prevent a disease from occurring, or later enable the management a disease once it develops (e.g. utilising 'precision medicine' approaches), diagnose a disease which is already present but has not manifested clinically, thus far, or inform reproductive decisions.

Previous recommendations issued by the European Society of Human Genetics (ESHG) on 'Whole genome sequencing in health care', did not explicitly address exploration and analysis of SFs. The ESHG document states that within the health care context, genomic sequencing should focus on the original test indication aimed at the identification of the underlying genetic etiology of a disease and be 'as targeted as possible'; at least for the time being (van El et al., 2013). Furthermore, cautionary policy statements were issued at that time also by several national societies and authorities, such as the German Society of Human Genetics (2013) and the Health Council of the Netherlands (2015). The recent document of the French Agency of Biomedicine (2020) is a further instance of this.

However, concurrently the American College of Medical Genetics and Genomics (ACMG) recommended a deliberate search for and routine analysis of a predefined set of 'actionable ' genomic variants in each case of exome or genome sequencing irrespective of the medical indication for such testing (Green et al., 2013). ACMG uses the term 'opportunistic screening' for this purpose, with the word 'opportunistic' referring to the opportunity arising with the availability of the raw genome sequencing-based data of individuals undergoing some form of genome sequencing in the context of health care for 'secondary analyses'. In the wake of the ACMG recommendations, variations of this approach have also been proposed or implemented in different European countries, including the United Kingdom (100,000 Genomes Project) and France (Pujol et al., 2018). These initiatives have sparked debate about the ethics of these strategies, also leading to research projects aimed at charting the ethical, legal and social issues (ELSI) linked with opportunistic screening in genomic medicine.

Opportunistic screening should be distinguished from the use of selected multi-gene test panels in a diagnostic context. These are still currently utilized in order to decrease analytical-, bioinformatic- and data-storage related costs and/or to increase specific target sequence coverage and thus the analytical robustness of genetic testing. An example may illustrate this distinction. If the indication for sequencing, involves an oncological problem which could be part of a specific rare genetic tumor risk syndrome, the applied test panel comprises multiple disease genes associated with such

syndrome thereby reflecting clinical / laboratory and genetic knowledge at a specific time point. However, such broader scale genetic analysis still remains within the frame of the diagnostic purpose of such testing. By contrast, testing for 'cancer predispositions' not linked with the suspected tumor syndrome(s) in question would amount to 'opportunistic screening'.

The ESHG regards it as its professional responsibility to contribute to this ongoing debate. The present document specifically discusses the pros and cons of opportunistic genomic screening, understood as the deliberate search for genetic variants unrelated to the diagnostic question. The wider discussion of dealing with incidental findings in genomic medicine is beyond the scope of the analysis presented here. This new ESHG position statement contains relevant background information, ethical reflection and updated recommendations. A writing group of the ESHG's Public and Professional Policy Committee (PPPC) prepared the draft, which was then discussed by PPPC and experts from the ESHG-EuroGentest Committee and Quality subcommittee (eurogentest.org). It is posted online on the ESHG website to solicit comments from experts and the ESHG membership from 20 April until 20 May 2020. The authors then will integrate all expert suggestions where appropriate. The Board of ESHG will be asked to approve the final version mid-2020. In view of rapid developments in the field and given the need for further reflection, these Recommendations will need regular evaluation in the future.

2. Opportunistic screening in genomic medicine

2.1 'Opportunistic screening' and 'secondary findings'

The concept of opportunistic screening is not new. For instance, in Family Medicine, general practitioners make use of patient-initiated consultations to test routinely for e.g. high blood pressure or analyze serum glucose / cholesterol concentrations when screening for the metabolic syndrome. When such tests are performed in patients without a clinical indication for such testing, this amounts to a form of screening. What makes it 'opportunistic', is that those who might benefit from testing are only those who happen to contact medical services for whatever reason. Opportunistic screening differs from programmatic screening, where all members of a predefined target population are systematically invited for a uniformly organized and externally evaluated screening service.

For the tested individuals, opportunistic screening does not necessarily entail undergoing medical / laboratory procedures that they would otherwise not be subjected to. It may imply carrying out an extra test (e.g. determining the blood pressure) or extra venipuncture (e.g. examine serum glucose / cholesterol concentrations). It may also consist of an extended analysis of the data resulting from indicated testing, as for instance when a doctor instructs the laboratory to check for a wider range of disease markers in a blood test than those needed in view of a specific medical indication for which the test was ordered. Opportunistic screening as recommended by the ACMG, is of the latter kind: it involves a wider analysis of the raw sequencing data that come available with clinical sequencing.

In genomic medicine opportunistic screening consists of a routine search for SFs, so called to mark the difference from those answering (or partly answering) the clinical question ('primary findings'). Conceptually, SFs are also to be distinguished from 'incidental findings' (IFs). Although both terms (SF and IF) refer to results unrelated to the original reason for testing, SFs are actively sought for, whereas IFs are not. Because in the context of NGS, IFs are not necessarily rare, the ESHG has suggested that 'unsolicited findings' (UFs) may be a more appropriate term for what is meant by IFs

(van El, et al. 2013). In this document we use the term 'opportunistic genomic screening' (abbreviated: OGS) to refer to the active or deliberate search for SFs in the context of genome sequencing in health care.

2.2. Selected OGS-proposals and practices

This section summarizes three examples of OGS-proposals and practices, starting with the relevant recommendations of the ACMG, as these may be considered as an initial frame of reference. The two further examples of OGS are drawn from France and the United Kingdom.

ACMG recommendations

The original ACMG proposal recommends that laboratories performing genome sequencing seek and report to the physician a minimum list of highly penetrant, actionable variants in preselected candidate genes, regardless of the indication for which the clinical sequencing was ordered and irrespective of the age of the patient (Green et al., 2013). Almost all variants on the list are predisposing to selected oncologic or cardiovascular diseases. Although the relevant ACMG's Working Group recommended reporting only variants with a high likelihood of causing disease, it recognized "that there are limited data available in many cases to make this assessment", i.e. there is currently little information on respective variant penetrance and/or expressivity. While the minimum list originally entailed 57 genes, the list has later been decreased to 56 and then subsequently enlarged to 59 (Kalia et al., 2016). The ACMG recommends refining and updating this list at least annually, based on developing scientific and medical evidence. Depending upon the specific genetic risk factor or variant, its carriers can make use of individualized preventive options, including early or long-term medical imaging-based monitoring, colonoscopy, prophylactic surgery and utilization of implantable cardioverter-defibrillators.

Apart from terminology (the original ACMG recommendations confusingly referred to IFs rather than SFs), an important ethically relevant modification since the first version of the their recommendations regards the scope for patients to make a decision about whether or not to have their raw genome data analyzed for variants within the 'recommended disease gene list' (ACMG Board of Directors, 2015). Whereas in the original proposal patients could not decline OGS but by losing their entitlement to be tested at all, criticism of this position as being at odds with respect for patient autonomy has led to a revised proposal advocating an 'opt out' for patients who only want information relevant to the original indication (i.e. 'purpose') for genome sequencing. Such analysis in unaffected individuals (parents of affected infants, index cases affected with phenotypic anomalies now analyzed for other SFs) has been criticized since SFs have not been validated for general population screening, where the penetrance might be lower in the absence of family history (Nussbaum, 2019). Moreover, it needs to be noted that pathogenicity of most of genetic variants was assessed based on their presence in clinically diagnosed cases, which may overestimate their penetrance, as is becoming increasingly apparent from population genome programs. Currently, this shortcoming is being addressed by multidisciplinary collaborative efforts focused on more complex classification of variants, at least now in the most commonly tested genes.

The French Society of Predictive and Personalized Medicine (SFMPP) recommendations

The SFMPP published its "Guidelines for reporting secondary findings of genome sequencing in cancer genes" in August 2018 (Pujol et al., 2018). It discusses multi-gene panels aimed at familial tumor syndromes, including variants unrelated to the patient's tumor. The document speaks of SFs as "the results of a deliberate or incidental (sic, *authors*) screening for alterations in genes that are not relevant to the diagnostic indication for which the screening was ordered." As a consequence, the guidelines fit in with the concept of OGS, as defined in the above. Using the criterion of 'actionability', an evaluation of the relevant risk and the level of evidence, the SFMPP provisionally recommends reporting information on 36 (so-called 'class 1') genes related to specific forms of cancer in adults. While there is significant overlap with the 'cancer genes' on the ACMG list, the SFMPP lists additional genes, for instance *PALB2*. An important difference with the ACMG approach is that the SFMPP proposal insists on an explicit informed consent procedure, rather than a mere opt-out procedure. The document recommends a system of multi-step ('dynamic') consent. The first step is in the context of pretest counseling where patients are asked to indicate whether they want to be informed about SFs in the panel or not. The second step is when patients are being informed about the primary results. Here, they are given the opportunity after further reflection ("with more autonomy") to confirm or refuse access to the information resulting from the search for SFs. This two-step counselling approach was proposed by patient associations in order to limit the potential psychological impact of OGS. The SFMPP recommendations are limited to OGS in adults, pending further debate and reflection on the acceptability of OGS for cancer-related genes in minors.

We here present the SFMPP guidelines as an illustration of a further OGS-proposal, while being aware that in France, as elsewhere in Europe, the debate about the pros and cons of OGS is still going on. Thus, the French Agency of Biomedicine has recently adopted a draft of recommendations for good practice regarding additional data generated by NGS (French Agency of Biomedicine, 2020), which are about to be published by the French Ministry of Health, stating that "At the present state of scientific knowledge, it is recommended not to propose, in a diagnostic setting, a systematic analysis of genes that are not related to the initial indication based on a pre-established list".

100,000 Genomes project and NHS England Genomic Medicine Service

The UK 100,000 Genomes Project (100KGP) was initiated in 2013 with the aim of developing the implementation of DNA sequencing technologies and thereby embedding genomic medicine into routine health care. Recruitment into 100KGP was primarily of patients with undiagnosed rare disease or with specific cancers and this ceased in 2018. The NHS England Genomic Medicine Service is being instigated, building on learning from the 100KGP, and introducing whole genome sequencing as a clinical test in the NHS in England (NHS, 2020). In October 2018, the UK Health and Social Care secretary stated an ambition to achieve the sequencing of 1 million genomes by the NHS and the research project UK Biobank over 5 years, including those with rare diseases and cancers, including a population cohort (Hancock, 2018).

Participants in 100KGP gave consent for genome sequencing with return of results related to their presenting condition and the use of their data for research. Those recruited were also offered the return of a limited set of additional 'looked for' findings which would be confirmed by accredited clinical diagnostic laboratories and then usually returned to the patients by the specialist who had

recruited them to the 100KGP. These SFs would be generated via a separate bioinformatics analysis on the genomes of all those who had consented. There were two classes of SFs: (i) medically actionable information and (ii) information of reproductive significance. Participants could make the same or different decisions about the two categories of SFs and they could also change their minds at any time. Consent is sought for findings that were described as actionable rather than specific, named conditions and participants were informed that any conditions tested for would be serious and that prevention or treatment was available in the NHS. The offer to participants in relation to reproductive findings (i.e. carrier status) was framed as looking for variants that would not affect the individual but could affect their future children (Genomics England, 2020). A decision regarding whether a similar process of returning additional 'looked for' findings will be offered in the NHS Genomic Medicine Service has not yet been made, thus far.

It was decided to be much more conservative in deciding what disease genes would meet the criteria for inclusion than the ACMG had been but to keep this list under review. In addition to questions of 'actionability', other factors were considered in drawing up the list of SFs. Only those disease genes were included which comprise high penetrance variants and where the association with disease and/or the evidence for the efficacy of interventions was strongly substantiated; where it would be technically possible to reliably detect variants in these genes using genome sequencing, variants would only be reported where there was a high confidence that they would be pathogenic or likely pathogenic. In addition, evidence of clinical benefit from application of the genomic information would be required, not simply the validity of the information. This takes account of the potential burden on NHS staff in validating and returning findings, and whether care pathways for patients are established within the NHS. However, the scenario of OGS crowding out resources for indication-based pathways remains a matter of concern in collectively funded health-care systems, such as in the UK.

The release of additional findings from 100KGP has been delayed for logistic reasons, but is expected to go ahead in 2020. In line with current recommendations on genetic testing in children, the search for additional health related findings in minors is restricted to conditions where benefit could be assumed during childhood and carrier testing is not offered.

3 Ethical exploration

In view of an ethical evaluation of OGS as exemplified in the above proposals or practices, a preliminary question is how they should be conceptualized for normative purposes. There is more than one way of doing so, depending on which elements are regarded as normatively relevant.

Firstly, the fact that OGS is carried out in the context of individual patient medical care makes it a kind of in-between concept: 'screening' in so far as the active search for SFs goes beyond the original indication for testing, and 'individual care' in so far as this search is aimed at enhancing the medical benefits of a clinical test for the patient. The ACMG strongly emphasizes the latter perspective (Green, 2013). It stresses that its recommendations ought to be regarded as part of medical doctors' fiduciary duty, i.e. as just a matter of providing good clinical care to the patient, who would naturally expect the doctor to actively look for (actionable) information relevant to his or her health. To the extent that this does amount to screening, this is seen as different from the kind of screening to

which the normative framework applies that was developed by the WHO ('Wilson & Jungner') and other national and international authorities (Andermann et al., 2008). The difference being precisely that this framework was meant for organized screening programs targeting population groups in a public health context (Brothers et al., 2019), rather than for the clinical context for which OGS is being proposed (ACMG Board of Directors, 2019). However, this may be too swift a dismissal of the wider relevance of this framework also for OGS. From a normative perspective, the distinguishing characteristic of medical screening is not so much the context in which it is performed (whether public health or health care), but the lack of an indication for having this specific test or investigation in those to whom screening is offered (Juth & Munthe, 2012). As the non-indicated nature of screening entails a more precarious benefits-to-risks balance in comparison to indication-based testing, the core requirements of the framework include 1) evidence that for those being screened, this balance is clearly favorable (proportionality) and 2) explicit informed consent by those to whom the screening offer is made (autonomy). Moreover, especially when screening is offered in the context of collectively funded health care it requires 3) a justification in terms of considerations of distributive justice.

Secondly, given that what we are dealing with here is the wider analysis of raw sequencing data that have come available as a result of testing, a further possible understanding is that providing this information is a matter of the individual's right to information that others have obtained about him or herself. However, this seems to ignore the difference between raw sequencing data and whatever meaningful genomic information can be extracted from those data, either with clinical or personal utility. Even if the patient has a right to his or her raw data (including e.g. VCF files), it doesn't follow that medical professionals should perform the analysis needed to turn that data into information. If they decide to do so, as proposed in the ACMG and SFMPP recommendations, this requires a separate justification, which leads back to the above discussion of OGS as a form of screening in the context of clinical care.

We intend to contribute to further debate about the conditions for responsible OGS by considering how such an offer relates to the three core requirements of the screening framework: proportionality, autonomy and justice, while differentiating between OGS as offered to adults and as offered to children (or minors) (De Wert & Dondorp, 2019).

3.1. OGS as offered to competent adult patients.

3.1.1. Proportionality

Because OGS is offered to those who do not have a medical problem or medical history-based reason for having the relevant sequencing data analysed, and because generating medical information may also have adverse effects, it is not obvious that a specific OGS proposal is on balance beneficial for those to whom the offer to search for SFs is made. Whether it is, can only be determined based on scientific evidence - not just considering the potential benefits that it may yield, but also specifying the possible harms that it may bring. Given that OGS is a form of genetic screening, any benefits and harms may affect not just the individual whose genome data are analysed, but their genetic relatives as well. Notwithstanding the requirement that the proportionality balance must be positive for the screenee in the first place, these 'third party' effects do count in the balance as well.

<u>Possible benefits</u>

The possible benefits of OGS are primarily medical. First and foremost, OGS is aimed at yielding information allowing the primary or secondary prevention of serious genetic diseases, notably forms of genetic tumor risk syndromes and cardiogenetic disorders, not only in the screened individual with a 'positive' result, but also their genetic relatives. In a recent study it was found that no less than 2.6% of healthy individuals would be shown to carry an increased risk for a severe dominant disease if routinely screened for variants in the ACMG minimum list of genes (Haer-Wigman et al., 2019). The health benefits following from this may be considerable, depending, however, on several factors. The positive predictive value of the secondary findings targeted in the OGS panel must be high, the effectiveness of the preventative interventions or measures recommended to those found to be at risk should be scientifically proven, and access to those interventions as well as to relevant counseling must be guaranteed. Whether the latter conditions will be appropriately met, is contextually dependent on the health care system.

A second type of medical benefit regards a more favorable risk-benefit ratio of medical interventions or treatments that the patient might have to undergo somewhere in the future. Think of screening for genetic variants causing serious adverse reactions to anesthetics (already included in the ACMG list) or for pharmacogenomic (PGx) variants. As argued in one of the updated versions of the ACMG recommendations, the latter may be especially relevant where concerning "variants related to commonly prescribed medications as well as medications associated with serious adverse events for which there is greater urgency surrounding actionability" (Kalia et al., 2016).

In addition to direct or future health benefits, OGS may, thirdly, provide reproductive benefits, in so far as any positive findings allow the screenee or their relatives to make reproductive decisions aimed at avoiding the birth of a child with a serious genetic disorder. The inclusion of CF-carrier status in the OGS approach taken in the UK represents a limited step in this direction.

A further increase of possible benefits is conceivable if more variants will be found to meet the criteria of pathogenicity and actionability and the list would be expanded. Apart from single genetic variants, future incorporation of genome-wide polygenic risk scores (GPS) might be considered if these would be shown to have clinical utility in order to reduce the risk of developing common disorders like diabetes type 2 and coronary heart disease (Khera et al., 2018). Likewise, the reproductive benefits of OGS may be enlarged by including carrier status for a potentially large number of serious recessive disorders.

Risks

The potential harms and disadvantages of OGS are of different but interrelated kinds: psychological, social, and medical. Some of these are of a more general nature, linked with OGS per se, while others depend on the context, content and conditions of specific OGS-practices.

Both psychological and medical harms may arise when OGS is introduced based on insufficient evidence regarding the health impact (pathogenicity, penetrance and expressivity) of variants in the listed disease genes (Burke et al., 2013; Holtzman, 2013). Clearly, the penetrance of some of the variants on the ACMG list has been overestimated. While, for instance, in 2004 the penetrance of pathogenic variants in the *SDHB* gene (succinate dehydrogenase B, causing pheochromocytoma and paraganglioma) was estimated to be 77% by 50 years of age (Neumann et al., 2004), two recent papers concluded that in healthy relatives ("non-probands") it is closer to 20% by 50 years of age

(Rijken et al., 2018; Andrews et al., 2018). Given that those to whom OGS is offered are a general population with regard to the SFs on the list, penetrance figures based on data from affected families may overestimate their risk of actually developing the disorder (Turner & Jackson, 2019). Overestimation of the health risks related to OGS findings may lead to unnecessary anxiety. It may also lead to the screenees being unnecessarily exposed to iatrogenic harms of invasive procedures undertaken as diagnostic or preventive measures. For instance, significant harm was caused to those who were prompted to have an implanted cardioverter defibrillator on the mistaken assumption of being at a high risk of sudden death (Manrai et al., 2016). This is not to deny that the penetrance of genetic variants in the general population (although lower than their penetrance in affected families) may still be sufficiently high to warrant their inclusion in OGS. But if so, the lower magnitude of risk may well require preventive strategies that reflect a different proportionality balance as compared to prevention in affected families.

Precisely in order to avoid screenees being confronted with the psychological burdens of being told to be at risk of developing a serious disorder for which no options for treatment or prevention exist, OGS proposals rightly insist on the condition that to qualify for OGS, SFs should also be 'actionable'. However, psychosocial harms may still ensue when actionability is too easily assumed (Isidor et al., 2019), or when only limited actionability is taken as a sufficient reason for inclusion in the list of targeted SFs. A good example of this is the only 'partial' actionability of (germline) p53 pathogenic variants predisposing for Li-Fraumeni syndrome (Elmore, 2018).

Assuming that OGS is only offered for SFs where there is sufficient evidence of both a significant health impact (in terms of pathogenicity and penetrance) and a clear actionability (in terms of options for treatment and prevention promising to considerably ameliorate the health prospects for those with positive findings), OGS still comes with psychosocial concerns and challenges, given that little is known as yet about how people unfamiliar with the relevant disorders will deal with positive findings and related options for prevention and reproductive choice (Isidor et al., 2019). Needless to say, counseling should be provided by a professional with relevant expertise regarding the additional finding. However, how can OGS be offered in a way that empowers people rather than undermines their confidence in their health? What are their counseling needs in connection to OGS-findings, also with regard to the possible sharing of genetic information with relevant family members? Given the different setting, premature extrapolations from (mostly reassuring) psychological research in (non-) carriers in affected families should be avoided. Though a small recent study of the psychological impact of receiving 'positive' secondary findings seems to be reassuring (Sapp et al., 2018), more research is crucially important. These questions are even more important if OGS would be offered at a time when patients are trying to cope, deal with and give meaning to the totally different genetic problem for which they are having indicated clinical sequencing – think, for example, of such sequencing after sudden cardiac death in a child.

The societal risks of OGS, in addition to the potential transformation of everyone who undergoes genetic testing into a "patient-in-waiting" (Timmermans & Buchbinder, 2010), primarily regard possible adverse consequences for access of people 'at high genetic risk' to particular insurance schemes (Mohammad, 2017), or to specific jobs. Taking account of the recent report that variants related to sudden cardiac death were found in 1% of asymptomatic individuals (Khera et al., 2019), professions at stake in this regard include bus drivers, aircraft pilots, etc.. Several studies suggest that there is only little evidence for such societal repercussions, especially when the disorders for which

people prove to be at high risk are preventable or at least treatable (Joly, et al., 2014). In view of the highly different jurisdictions regarding the legal protection of applicants for jobs and insurances, these societal risks are probably to a considerable extent contextual.

What, then, about the proportionality of OGS? The ACMG is convinced that their proposal meets the criterion of proportionality, because the health benefits are large and the risks are minimal. In a later clarification document, the ACMG even stresses that not offering such OGS would be unethical and unprofessional (American College of Medical Genetics and Genomics, 2013), while McGuire et al. state in their supporting paper that the ACMG Recommendations may count "as evidence of the standard of care" in the case of malpractice litigation (McGuire et al., 2013). The ESHG wants to underline that the proportionality prerequisite is inherently linked with what has been termed the 'evidentiary model' (Wilfond & Nolan, 1993). At least for the moment, there are simply too many questions, unknowns, uncertainties and concerns to justify the conclusion that current OGS-proposals clearly meet the proportionality criterion – let alone that they would define the standard of care. This holds *a fortiori* for the suggestion to extend the concept into incorporating genome-wide polygenic risk scores (GPS) in clinical care (Khera et al., 2018), also given the current apparent bias towards European-derived populations (Duncan et al., 2019).

3.1.2. Respect for autonomy

According to the original ACMG recommendations, patients should not be given the option of having genome sequencing without OGS. The only way to avoid OGS for those not wishing to have it carried out would be for them to decide not to have indicated sequencing at all, thus seriously undermining their own health interests. The main argument for making OGS a so-called 'coercive offer' was that the fiduciary duty of health professionals to prevent harm would trump the patient's right to decide about having or not having OGS (American College of Medical Genetics and Genomics, 2013). This view has rightly been criticized as being at odds with 'respect for autonomy' as a core principle of medical ethics (Wolf et al., 2013). In response to this, the revised ACMG position allows patients who want to have indicated sequencing without having their raw sequencing data searched for SFs, to opt-out from OGS if they so wish. Although a clear improvement, this still falls short of the normative framework for screening, according to which the non-indicated nature of any screening offer requires those offering it to seek the full and explicit consent of those to whom the offer is made (Andermann et al., 2008). The problem with an 'opt out' for OGS is that patients may be insufficiently aware of the fact that the search for SFs is unrelated to the indication for genome sequencing, and that whether or not to have OGS is therefore something that needs separate consideration. Moreover, even when patients understand that OGS is indeed a form of screening, the message connected with offering it as a default procedure that only some might want to opt-out from, still might entail a significant pressure to accept the offer and may as such stand in the way of helping the patient to make a truly autonomous decision.

The SFMPP recommendations insist that "the patient's autonomy and desire to know or to ignore SF results must be respected" and stress that the patient "could decline at any time to be informed about the SF's even if they previously gave their approval" (Pujol et al. 2018). Pujol et al. differentiate between a first step at which written consent for SF is given, a second step in which this consent is renewed and primary findings are discussed, and a third step in which the actual SFs are discussed. Such an approach may well help avoid a professional conflict of duties; it is a different matter not to

screen for certain genes out of respect for the patient's right not to know, and not to report available findings of great relevance for the patient's own health or that of his or her close relatives (Dondorp et al. 2012). Ideally, one should try to avoid burdening professionals by generating health information that the patient does not want to receive. Although this cannot be completely avoided in the genomic era, an adequate informed consent procedure for OGS should try to minimize this problem as far as possible (like in other contexts of genetic testing). For example, the raw data might only be analysed after the second step of the SFMPP approach. This would allow tested individuals to become better informed and allow them additional time for reflection and might thereby reduce the chance that the patient later claims the right not to know about SF's after an initial consent given for the generation of such findings, possibly generating the conflict of duties mentioned.

If genome sequencing were offered as a package of enrolment combining health care and research in a hybrid offer, where sequencing was only available if consent to research was given, then there could be concerns about so-called 'undue inducement', as Dheensa et al. (2018) have discussed for the 100kGP. The aims of sequencing could be blurred: both research and care are at stake. The hybrid offer might lead people needing sequencing in a health care setting to decide to participate in sequencing because of potential advantages outside of the initial medical indication, such as receiving SFs, while also influencing them to participate in research. The hybrid nature of such initiatives raises questions concerning the consent process by distracting potential participants from its core elements and potentially violating the principle of respect for autonomy (Dheensa et al., 2018).

A final issue is whether patients should be given the option to decide for themselves whether to be screened for only part of the list of SFs targeted in a specific OGS offer. The updated ACMG recommendations insist that for practical reasons, this is not possible and that the decision regarding OGS must therefore be an 'all or nothing affair' (ACMG Board of Directors, 2015). However, a categorical rejection of allowing any form of 'personalization' of OGS seems at odds with the principle of respect for patient autonomy. Acknowledging this principle would seem to require professionals to as much as possible respect patients' wishes with regard to controlling what information to receive as a result of being tested. For instance, patients may want to limit the search for SFs to pharmacogenomics variants or to carrier status for recessive disorders. What patients would regard as meaningful choices in this regard and whether providing those choices would be feasible in practice is a matter for evaluation in the context of future OGS-pilots.

3.1.3. Justice

As OGS is screening in the context of health care, involving the further analysis of raw data that come available because of indicated testing, the costs are relatively lower in comparison to programmatic screening programs. Nonetheless, bioinformatics analysis of detected variants (when manual variant curation and their assessment will still be necessary) will still be costly in the near future despite rapid progress in machine learning-based procedures for variant prioritisation. Moreover, genetic counseling costs may still be considerable especially given the potential need to recontact and repeatedly counsel tested individuals as new evidence gradually accrues on variants of unknown / unclear clinical significance. These aspects need to be taken into account especially when OGS is offered in a way that would as much as possible acknowledge the principle of respect for autonomy.

Costs of OGS will further increase if one would engage in subsequent cascade screening among relatives of people with 'positive' OGS-results. The fact that OGS will lead to downstream costs for the health system is not *per se* problematic. However, it is a further reason for only offering OGS for variants with a proven health impact, so as to avoid the costs of unnecessary interventions and deal with the concept of 'overdiagnosis' as documented e.g. in the field of radiology (Booth, 2018). Moreover, in solidarity-based health-care systems, the scenario of OGS crowding out resources for indication-based care pathways raises concerns about just prioritization (Severin, et al. 2015).

In view of the costs of OGS it is important to consider if alternative approaches would be more cost-effective. Most notably, currently, cascade testing (CT) targeting the relatives of a proband in case of clearly pathogenic, highly penetrant, and actionable variants, is still underutilized. Whether CT, OGS or a smart combination of both should be given priority from a distributive justice perspective is an important question that may allow for a different answer in countries that have already implemented CT for a larger number of the relevant conditions in their health system, as compared to those that have not. Where regarding OGS for genetic risk factors that allow for prevention through lifestyle modification rather than medical interventions, collective measures, such as general health education or measures of health protection targeting the environment or the workplace may be considered as alternatives (West et al., 2017). The case for prioritizing such measures, if proven effective, is strong, especially in less resourced countries. Whilst in more affluent countries, distributive justice may allow for combining collective prevention and well-defined OGS.
It also needs to be noted that there remains a strong bias towards European-derived variant frequencies currently present in broadly used variant databases with data from less-resourced countries still generally missing (Bentley et al., 2017).

OGS also raises a question about formal justice. OGS is only offered to individuals who happen to have an indication for genome sequencing. However, with regard to the SFs targeted in OGS these patients do not have a higher *a priori* risk than other members of the general population, who are not offered screening for the same conditions. This could be considered as a morally problematic inequality of access to a health service that ideally should be avoided. However, as stressed by the ACMG, offering the same benefits to all would come with the much higher costs of setting up the infrastructure for programmatic screening, which would be far less cost-effective than OGS (Green et al., 2013). Given the opportunity costs of population screening for the same set of variants, the only way of securing equality of access may well amount to denying access to all. Such 'leveling-down' justice ('if not all can profit, then no one should') is clearly not in anyone's interest. Moreover, it could be argued that the formal justice problem of OGS is mitigated by the fact that chances of becoming a patient with an indication for clinical sequencing are equally distributed in the population. However, people who achieved higher education and income are often over-represented when applying for genetic counseling (van der Giessen 2017).

Further justice considerations arise with the different health care settings in which OGS could be offered. For instance, if 'actionability' consists of costly treatment that many people could not afford, screening for the relevant variant will be more beneficial for some than for others.

3.2. OGS in children

Traditional guidelines state that predictive genetic testing of children should be limited to conditions where options for treatment or prevention are available that must be initiated already during childhood (Clarke, 1998; De Wert, 1999; Borry et al., 2009). All further predictive testing should be postponed until children are old enough to decide for themselves about undergoing genetic testing. Arguments for this position are of two kinds based on moral rights or on morally relevant consequences. Relevant arguments of the former kind refer to the child's right to informational self-determination (as part of 'the child's right to an open future'). Consequence based arguments point to how the burdens of risk status information may harm the child for example by overshadowing its psychosocial development.

To the extent that these recommendations should also apply to OGS, this significantly limits the list of variants that children's sequencing data could be screened for, at least where young children are concerned that have not reached sufficient maturity to decide about OGS for themselves. Although OGS for certain conditions that are actionable early in life (such as MEN type 2A, hereditary arrhythmias such as long QT and Brugada syndrome) and for pharmacogenomic variants including variants modifying the individual reaction to anesthetics could still be possible, this would rule out OGS for most of the ACMG list.

However, proponents of OGS in children as recommended by the ACMG argue that the context for which those traditional guidelines for predictive genetic testing of children were drafted, namely pre-symptomatic testing in relatives of a proband, is importantly different from that of OGS (McGuire et al., 2013). In the former context, postponement of testing children for later onset disorders is without consequences both for those children and for their relatives, as no information about their at risk status will thereby be lost. Refraining from OGS in children with an indication for genome sequencing, by contrast, amounts to missing what may well be a one-off opportunity of generating potentially life-saving information both for the children themselves and their relatives.

Whether this reasoning justifies OGS for later onset conditions in children is a matter for further debate. Is there evidence that children may be harmed by telling their parents that they (those children) are at risk of a serious but actionable later onset disorder? If not, are the possible future benefits for the child itself sufficiently weighty to trump the remaining concerns about violating its right to informational privacy? How convincing in this regard is the notion of OGS as a one-off, unique, opportunity that should not be missed, given that children will grow up in an age where genome sequencing may become a routine part of health care? Alternatively, does the argument ultimately rest on the interests that the child's relatives may have in not letting this opportunity for generating important health information be wasted? Then indeed the question becomes one of justifying the screening of children in order to benefit others. Are the interests of family members sufficiently weighty to override the concerns related to the child's right to informational privacy? However, a less antagonistic way of framing this debate is that where the health or reproductive interests of the parents are concerned, serving those interests is also in the interest of the child who depends on the ability of its parents to provide for its daily care.

The suggestion is that in the near future, genome sequencing may become a standard procedure in neonatal screening for serious and actionable congenital diseases which lends further urgency to this debate (Howard et al., 2015 ; Lantos, 2019).

Recommendations of ESHG: Opportunistic Screening in genomic medicine

According to earlier ESHG Recommendations on NGS in health care (Van El et al., 2013), genomic analysis should be as targeted as possible, at least for the time being. Taking account of further reflections on developments in science and clinical practice, this new document confirms that broader analysis than needed to answer the diagnostic question raises complex issues in clinical practice. This is not to say that all forms of OGS are *a priori* unsound. However, if OGS is being offered, it should take the form of pilots combined with rigorous evaluation studies aimed at reducing present uncertainties that yet stand in the way of determining its proportionality as a health care service.

1. Performing a broader analysis than needed to answer the diagnostic question amounts to a form of screening, for which the general framework of screening criteria is applicable. In addressing the question whether such OGS would meet the relevant and widely endorsed criteria for (genetic) screening, ethical principles of proportionality, respect for autonomy, and justice should be considered.

2. Weighing potential benefits and harms for the patient, given the many questions, uncertainties and concerns linked with OGS in genomic medicine, it is premature to consider OGS for later-onset disorders, especially in children, to be proportionate, let alone to recommend that it should define the professional standard.

3. In view of the many uncertainties, directly impacting the required proportionality of any OGS, the ESHG recommends a generally cautious approach. Any OGS should be embedded in adequate pilot and evaluation studies in order to enable optimal decision making about the proportionality of OGS. Priority should be given to well-known, highly penetrant variants, predisposing for genetic disorders which can be adequately and effectively prevented and/or treated. The selection may well be contextual, taking account of both the penetrance of particular variants in a given population, which may differ between populations in Europe, and the capacity of the different health care systems to integrate relevant, complex, counseling and (preventive) treatment services for proven carriers of these variants. Apart from genetic and medical uncertainties, and implementation issues, the psychological impact of OGS merits attention. Crucial questions include how to enable the empowering and address the counseling needs of the patients involved.

4. Clear procedures and criteria are needed for decision making about the composition and extension of the list of genetic variants included in any OGS, and its implementation. A wider debate, involving all relevant stakeholders, especially patients, is of utmost importance. Patients should not be reduced to the object of well-intended medical deliberations and interventions.

5. Informed consent is and should be a central ethical norm in the framework regarding genetic screening generally and OGS particularly. Alternatives such as opting out and, particularly, a coercive offer of OGS are problematic. A multi-step (‘dynamic’) consent approach may be helpful but needs further empirical study. The patient’s right not to know should be respected as far as reasonably possible, while allowing professionals to still inform the patient about specific findings of great importance for the patient’s own health or that of his or her close relatives.

6. When counselling for OGS, the provisional nature of current knowledge on penetrance should be addressed as well as potential crossovers with research and options for recontacting in case new scientific evidence of clinical relevance arises.

7. Depending on developing evidence on penetrance and actionability, but also taking account of the resources available for health care in European countries, OGS pilots may be justified to generate data for a future, informed, comparative analysis of OGS and its main alternatives, namely (the offer of) universal genomic screening for highly penetrant, actionable variants, and (more systematic) cascade testing in relatives of probands affected with (avoidable) diseases caused by highly penetrant genetic variants.

8. OGS in children for later-onset actionable variants needs further ethical scrutiny. There seem to be neither valid principled objections to OGS in children for PGx variants and early-onset actionable variants, nor to OGS for late-onset disorders in children that because of, for example, intellectual disability, will (probably) not become competent later (if such targeted OGS would meet the principles of proportionality and justice).

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