SCIENCE AND SOCIETY

Return of genetic testing results in the era of whole-genome sequencing

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Abstract | Genetic testing based on whole-genome sequencing (WGS) often returns results that are not directly clinically actionable as well as raising the possibility of incidental (secondary) findings. In this article, we first survey the laws and policies guiding both researchers and clinicians in the return of results for WGS-based genetic testing. We then provide an overview of the landscape of international legislation and policies for return of these results, including considerations for return of incidental findings. Finally, we consider a range of approaches for the return of results.

Recent developments in whole-genome sequencing (WGS) technologies are increasingly being applied within both the context of research and of clinical practice. These implementations have allowed for rapid diagnosis of the genetic basis of disease[1]. Increasingly affordable, this technology may soon become part of healthcare systems in both research and clinical contexts[2].

Although the use of WGS has the potential to greatly improve genetic discovery for human disease and to advance clinical care, it also raises several challenges. The analysis of whole-genome sequence data is complicated by the amount of information and challenges in defining the impact of specific genetic variants on health[3]. An alternative option is to use gene panels, which can restrict screening to selected genes or genetic regions. Although using targeted panels for screening may simplify the scale of the analysis and interpretation, incidental findings occur using either approach. These incidental findings may be validated and clinically useful or validated but without any treatment or preventive measures, or have unclear or unknown significance. This raises considerations for whether to return such results as well as incidental findings, when, to whom and how. Furthermore, certain results could be relevant to family members. In addition to the question of what results should be returned to patients, research participants or families, other concerns include the risk of learning one's genetic information, the right to know or not to know, the issues surrounding informed consent, genetic counselling, privacy and the impact on professional duties. A further concern is the impact of return-of-results policies on the healthcare system, in terms of cost and personnel. Questions surrounding the return of results reached their peak in 2014, with geneticists, lawyers, ethicists and sociologists debating the professional duties surrounding incidental findings. Thus, the ethical, legal and social issues (ELSIs) surrounding the return of results and incidental findings merit analysis.

Traditionally, genetic testing was guided by policy developed by professional organizations, such as national geneticists' associations or national ethics commissions, as opposed to legislation. Policy guidance specific to the use of WGS-based genetic testing is beginning to emerge, but legislation regulating research or biobanks is also indirectly affecting the debate. In this article, we discuss current approaches for the return of results from WGS-based genetic testing in both clinical and research settings. We focus on WGS as our exemplar, as this includes broader coverage of the genome than whole-exome sequencing and may continue to become more widespread as sequencing costs decrease[1]. Considering the wide range of contexts and populations in which WGS-based genetic testing will be used, we recommend against a single approach for the issue of return of results. However, we do need to move towards greater harmonization of practices and policies across countries, so as to facilitate international collaborative research.

Surveying guidance

We analysed specific policy guidance and legislation governing the use of WGS-based genetic testing. In order to survey policy guidance from associations and societies, we examined the websites of all members of the International Federation of Human Genetics Societies (IFHGS), which includes 62 members (both national and regional entities) from various continents, and searched for guidelines or policies addressing new genomic sequencing technologies. This was followed by a survey of guidance as found in HumGen, an international database of laws and policies related to human genetics. 'Communication of results' was used as the keyword to search this database. We restricted our research to documents published between 2010 and 2015, when WGS began to emerge. In addition, we searched the websites of key organizations catalogued in HumGen, including the World Health Organization (WHO), the United Nations Educational, Scientific and Cultural Organization (UNESCO), the Council of Europe, national bioethics committees and national medical associations.

A policy was eligible for inclusion in our survey if it was available as: a position paper, reports, guidelines or consensus statements produced by international or national governmental and non-governmental health organizations, bioethics committees or professional associations explicitly addressing, to some extent, genomic sequencing generally. Only guidelines written in English or officially translated into English were eligible for inclusion. For legislation, we included national laws, as found in HumGen, if they contained provisions on

the return of results in genetic research or testing generally, thereby potentially affecting professional obligations concerning WGS.

It is important to note the absence of a common definition of 'results' returned for WGS in the context of either research or clinical genetic testing found in the literature[4] or our review. 'Results' often refer to findings that are directly relevant to the indication (that is, a specific research question or the clinical indication) for which the sequencing test was ordered. However, 'results' also include incidental findings, which refer to information identified through the use of WGS, but beyond the indication for which the test was ordered. We use the term 'incidental findings', as our international review concluded that this is the more commonly used term.

Legislation and policies

There are a range of international approaches to address the ELSIs raised by WGS-based genetic testing. It is important to be mindful of the organizational context of any regulation, as there is the necessary distinction to be made between laws and policies. Policies serve mostly as interpretable guidance, whereas laws dictate certain professional behaviour. Ironically, although legislation usually provides clear direction, WGS could be included under the general rubric of genetic testing even though it was not specifically mentioned or even available at the time of the adoption of the law. We address the general legal and policy landscape (TABLES 1,2) before turning to the issue of the return of results (TABLES 3,4).

Table 1 | **Policy landscape for WGS-based genetic testing**

Jurisdiction	Domains	Scope	Contexts	Populations	Issues addressed
Canada (CCMG)	Clinical application in monogenic diseases, 2015 (REF. 10)	National	Clinic	Adult and paediatric	Provide criteria for return of results, consent, counselling and confidentiality versus communication to family members
Denmark (Danish Council of Ethics)	Genome testing: ethical dilemmas, 2012 (REF. 13)	National	Research and clinic	Adult and paediatric	Consent, counselling and confidentiality versus communication to family members
Europe (ESHG)	WGS in health care, 2013 (REF. 38)	Regional	Clinic	Adult and paediatric	Provide criteria for return of results, consent and counselling
Germany (German National Ethics Council)	Genetic diagnostics, 2013 (REF. 27)	National	Research and clinic	Adult and paediatric	Provide criteria for return of results, consent, counselling and confidentiality versus communication to family members
Multijurisdictional (P^3G)	Population biobanks, 2013 (REF. 43)	International	Research	Adult	Provide criteria for return of results and consent
Multijurisdictional (P^3G)	WGS in paediatric research, 2014 (REF. 11)	International	Research	Paediatric	Provide criteria for return of results, consent and confidentiality versus communication to family members
Multijurisdictional (P^3G, ESHG, HUGO and PHG Foundation)	WGS in newborn screening, 2015 (REF. 41)	International	Clinic	Paediatric	Provide criteria for return of results, consent, counselling and confidentiality versus communication to family members
United Kingdom (MRC and Wellcome Trust)	Health findings, 2014 (REF. 17)	National	Research	Adult and paediatric	Provide criteria for return of results, consent and counselling
United Kingdom (PHG Foundation)	Genomics, 2014 (REF. 1)	National	Clinic	Adult	Provide criteria for return of results, consent and confidentiality versus communication to family members
United Kingdom (UK10K)	Ethical governance, 2010 (REF. 12)	National	Research	Adult and paediatric	Provide criteria for return of results, consent and confidentiality versus communication to family members
United States (ACMG)	Incidental findings, 2012 (REF. 44);2013 (REF. 36); 2013 (REF. 45); 2013 (REF. 46); 2015 (REF. 9)	National	Clinic	Adult and paediatric	Provide criteria for return of results, consent, counselling and confidentiality versus communication to family members
United States (Presidential Commission for the Study of Bioethical Issues)	WGS and privacy, 2012 (REF. 47)	National	Research and clinic	Adult and paediatric	Consent, counselling and confidentiality versus communication to family members
United States (Presidential Commission for the Study of Bioethical Issues)	Incidental findings, 2013 (REF. 25)	National	Research and clinic	Adult and paediatric	Provide criteria for return of results, consent, counselling and confidentiality versus communication to family members
United States (ASHG)	Genetic testing in children and adolescents, 2015 (REF. 37)	National	Research and clinic	Paediatric	Provide criteria for return of secondary findings, consent, counselling and confidentiality versus communication to family members

ACMG, American College of Medical Genetics; ASHG, American Society of Human Genetics; CCMG, Canadian College of Medical Geneticists; ESHG, European Society of Human Genetics; HUGO, Human Genome Organisation; MRC, Medical Research Council; PHG Foundation, Foundation for Genomics and Population Health; WGS, whole-genome sequencing.

Table 2 | **Legislative landscape for WGS-based genetic testing**

Country	Legislation	Scope	Context	Populations	Issues addressed	Refs
Estonia	Human Genes Research Act, 2000	National	Research	Adult and paediatric	Consent	5
Finland	Biobank Act 688/2012, 2012	National	Research	Adult and paediatric	Consent and counselling	8
Spain	Law 14/2007 of 3 July on Biomedical Research, 2007	National	Research	Adult and paediatric	Provide criteria for return of results, consent and confidentiality versus communication to family members	6
Taiwan	Human Biobank Management Act, 2010	National	Research	Adult and paediatric	Consent and confidentiality versus communication to family members	7

WGS, whole-genome sequencing.

Legislation. In 2000, Estonia was the first country to address genetic testing in its Human Genes Research Act[5], albeit only in the context of research and with a focus on consent for the donation of tissue and data to the Estonia biobank (TABLES 2,4). Interestingly, the right to withdrawal, the right to access personal health information on request and the right not to know genetic data were protected. Spain followed in the legislative footsteps of Estonia in 2007, but under the more general rubric of a law on biomedical research[6]. Although again emphasizing consent, not only access by individuals to results was foreseen but also the communication of such results by researchers to a close family member where necessary to avoid "serious damage" (REF. 6) to the health of the participant or biological family members (when the participant has exercised the right not to know). Such a legal duty to warn relatives is rare, but its scope may well be expanded with the increased use of WGS-based genetic testing and the possibility of incidental findings. In 2010, Taiwan introduced a law on biobanking, with an emphasis on consent to genetic testing. It maintains that a participant "shall be informed of … [a]ny possible impacts of the genetic information derived from the biological specimens on the participant, and his/her relatives or an ethnic group" (REF. 7) (TABLE 2). Finally, Finland's 2012 Biobank Act[8], although legally recognizing the validity of broad consent, stresses counselling and offers the right to receive health information on request, which could include WGS-based testing results and incidental findings. However, it does not mention return of results to family members (TABLES 2,4).

Policy guidance. By contrast, over the past 5 years, several professional organizations, think tanks and foundations that provide policy guidance have addressed WGS-based genetic testing (TABLE 1). These guidelines or recommendations generally cover the research or clinical contexts of WGS-based genetic testing, with an emphasis on consent, return of results, counselling and confidentiality. Some guidelines also discuss the implications surrounding the possible communication of incidental findings to family members[1,9–11], if certain criteria are met, such as when there is a potential disease risk for family members[10]. Even in the absence of specific criteria, some policies allow the communication of incidental findings to family members on a case-by-case basis[11]. Other organizations, such as the Foundation for Genomics and Population Health (PHG Foundation) in the United Kingdom, recommend that the consent process cover the possibility that incidental findings returned to the participant could also be relevant to their family members and that potential disclosure will be made to these family members under certain circumstances[1]. The policies of some other organizations simply mention that the communication of incidental findings of clinical significance carry a risk of causing unnecessary harm to the participant and their families[12], without specific recommendations on when to return these results.

Approaches for the return of results

Our survey (summarized in TABLES 1–4) found four different approaches used internationally for the return of results: first, only panels of specific genes or targeted sequencing are allowed, to reduce the potential for incidental findings (although this not always explicitly stated as such); second, results can only be returned when they meet the following criteria: analytical validity, clinical significance and actionability (see the section 'ACA' criteria below); third, an *ad hoc* case-by-case determination; and last, no return. Although returning everything may be an approach for direct-to-consumer testing (which involves either the marketing, and/or the offer, of genetic tests directly to the public)[13], for some research projects (for example, the UK 100,000 Genomes Project, in which participants have a right to access their raw data) or in clinical practice when the patient so requests, returning all results is not found anywhere in the policy landscape of professional societies. There is, however, the ethical obligation to offer to return aggregate or general results, as found in the Helsinki Declaration, which states: "[a]ll medical research subjects should be given the option of being informed about the general outcome and results of the study" (REF. 14).

Filters or gene panels with the choice to opt-out. Even when guidance suggests the use of a filter or a gene panel, so as to minimize the occurrence of incidental findings, they may still occur. Most guidelines would allow an opt-out option for incidental findings, as typified by the recent position of the American College of Medical Genetics (ACMG)[9] (albeit after considerable debate) (TABLE 3). This opt-out option is found in both the research and clinical contexts, and stresses pre-test counselling as part of the consent process. European policies base this opt-out option on the right not to know enshrined in the 1997 Universal Declaration on the Human Genome and Human Rights[15] of UNESCO and in the Convention on Human Rights and Biomedicine[16] of the Council of Europe. Thus, in both the research and clinical contexts, incidental findings beyond either the objectives of the research in question or the primary indication for the clinical test can be refused by the participant under this approach.

ACA criteria. The most prevalent approach in the policies reviewed is the use of three baseline criteria to determine whether to communicate individual results generally as well as incidental findings. However, the exact terms and their combination may vary. The following terms that are commonly

Table 3 | **Policies for the return of results from WGS-based genetic testing**

Jurisdiction	Policies	Approaches	Refs
Canada (CCMG)	Clinical application in monogenic diseases, 2015	• Opt-out from receiving IFs (medically actionable IFs) • No opt-out from receiving IFs (if ACA during childhood) • ACA criteria	10
Denmark (Danish Council of Ethics)	Genome testing: ethical dilemmas (clinic and research), 2012	• Opt-out from receiving IFs • ACA criteria • No individual return ("do not have the right to information about individual results")	13
Europe (ESHG)	WGS in health care, 2013	• Opt-out from receiving IFs ("right not to know") • No opt-out from receiving IFs (if ACA during childhood)	38
Germany (German National Ethics Council)	Genetic diagnostics (research and clinic), 2013	• Opt-out from receiving IFs ("right not to know") • No opt-out from receiving IFs (if ACA during childhood)	27
Multijurisdictional (P^{3}G)	Population biobanks, 2013	• Return of general research results, ongoing • Opt-out from receiving IFs (other data) • ACA criteria	43
Multijurisdictional (P^{3}G)	WGS in paediatric research, 2014	• No opt-out from receiving IFs (if ACA during childhood) • ACA criteria • Case-by-case determination by research team (in rare situations, return if potential benefit to family)	11
Multijurisdictional (P^{3}G, ESHG, HUGO and PHG Foundation)	WGS in newborn screening, 2015	• Return all (results and IFs) (targeted only) • ACA criteria	41
United Kingdom (MRC and Wellcome Trust)	Health IFs (research), 2014	• Opt-out from receiving IFs (health-related findings) • ACA criteria • Case-by-case determination by research team	17
United Kingdom (PHG Foundation)	Genomics (clinic), 2014	• Opt-out from receiving IFs	1
United Kingdom (UK10K)	Ethical governance (research), 2010	• Opt-out from receiving IFs • ACA criteria • No individual return ("will not feedback to participants their genome sequence data")	12
United States (ACMG)	IFs (clinic), 2015	• Opt-out from receiving IFs	9
United States (Presidential Commission for the Study of Bioethical Issues)	WGS and privacy, 2012	• Opt-out from receiving IFs	47
United States (Presidential Commission for the Study of Bioethical Issues)	IFs (clinic and research), 2013	• Opt-out from receiving IFs • Case-by-case determination by research team ("assess [IFs] significance, consulting with experts as appropriate")	25
United States (ASHG)	Genetic testing in children and adolescents, 2015	• In general, parents can opt-out from receiving IFs • Case-by-case determination by clinicians (communicate to parents when "there is strong evidence that a secondary finding has urgent and serious implications for a child's health or welfare, and effective action can be taken to mitigate that threat")	37

ACA, analytical validity, clinical significance and actionability; ACMG, American College of Medical Genetics; ASHG, American Society of Human Genetics; CCMG, Canadian College of Medical Geneticists; ESHG, European Society of Human Genetics; HUGO, Human Genome Organisation; IFs, incidental findings; MRC, Medical Research Council; PHG Foundation, Foundation for Genomics and Population Health; WGS, whole-genome sequencing.

used singly or in combination are: 'scientific and clinical validity or utility'; 'availability of prevention and treatment'; 'predictive value' (REF. 17); 'severely or moderately life threatening and clinically actionable' (REF. 18); 'personal utility' (REF. 19); or 'are clearly of essential relevance to health' (REF. 13). For this overview, we regrouped these concepts under 'ACA': analytical validity; clinical significance and actionability. There are often additional considerations such as approval of the return-of-results plan — based on these criteria to be included in the research protocol — by a research ethics committee as well as the need in the research context to confirm results before returning them. It is important to note that both the research and clinical contexts require pre-test consent of the participant to the return of incidental findings.

Case-by-case determination. A more traditional approach to the communication of incidental findings, used in both research and clinical settings, is an evaluation on a case-by-case basis of whether to return these results to the participant. In research settings, this is 'context based' (REF. 17) and usually means consulting a research ethics committee when the return of research results or incidental findings was not foreseen. In the clinical setting, the clinician can consult a colleague and, depending on the clinicians' knowledge of the particular context of the patient (including their age, prognosis and personal circumstances), could communicate incidental findings outside the primary indication of the test.

A case-by-case approach provides flexibility but raises potential concerns. Both results and incidental findings may be put in the medical record, thereby transferring

any further deciphering to the physician, who may be ill-prepared to interpret them. In research, a case-by-case approach could also be problematic for several reasons but mainly because researchers in specialized fields may not be able to define 'clinical significance'. Participants have often provided consent for their data and samples to be stored in a biobank and to be used for future research: that is, as a resource for other researchers and irrespective of the type of genetic testing or technology. Moreover, as opposed to disease-specific biobanking[20], longitudinal biobanks provide general results but usually do not communicate individual results[21]. This may have to change, however, as researchers accessing longitudinal studies will increasingly obtain findings that would meet the ACA criteria.

No return. Offering to return individual results for WGS-based testing within the research context can be seen as creating a therapeutic misconception, as the goal of research is to produce generalizable findings[21]. Offering the possibility of future information as a form "of consideration for taking part" (REF. 13) in research sends mixed messages. Nevertheless, without further clarification, the 2013 World Medical Association Declaration of Helsinki states that:

> *"[r]esearchers … have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available"* (article 36 in REF. 14).

As illustrated by this quote, the Declaration refers to an ethical obligation to publish and share aggregate results and does not directly address either the return of results or the no-return issue. Today, some projects also provide lay descriptions of the project as well as any aggregate results on websites or in media releases. Research results by their very nature are not necessarily of a clinical standard[12,22].

Particular considerations

In our survey of legislation and policies on WGS-based genetic testing, we have discussed the narrowing distinction between the research and clinical contexts. This has important legal implications not only for adults but also for the rights of children and incompetent adults. The duties of physicians or researchers are also affected. In addition, there is increasing interest in the issue of incidental findings in the context of public health: in particular, in newborn screening (NBS) programmes.

Research versus clinical context. The physician–patient relationship has a long tradition of deontological parameters that are largely circumscribed by the duties to inform, to treat, to follow and to keep confidential[23]. There is no doubt that the use of WGS as a diagnostic tool will gradually enter the clinic and is already being used in newborns presenting with conditions of unknown aetiology[24]. The possibility of incidental findings from WGS testing means not only that the clinician's duty to inform the patient will expand but also that there will be the need to offer choices to the patient as to whether they want to be so informed. The duty to follow will also be affected as the significance of such results becomes clear over time. Although there is no duty to hunt, the delimitation of the duty to follow one's patient over time is a topic for urgent discussion. Professional guidance is also needed, as reflected by the 2013 Report of the Presidential Commission for the Study of Bioethical Issues[25] and the subsequent 2014 discussion of the ACMG guidance[26]. The German National Ethics Council[27] has also called for standards, as has the UK PHG Foundation[1] and the Canadian College of Medical Geneticists[10]. In short, professional guidance on the return of incidental findings should be obtained before ordering WGS, even in the clinical context.

Researchers are often not provided with clear guidance or standards regarding incidental findings. With the exception of longitudinal studies, researchers usually have no long-term relationship with participants. Conditions for the return or not of incidental findings would have to be approved by the ethics review board that approves the protocol. Even so, both the ethics review board and researchers (unless they are also clinicians) may not be sufficiently trained for this type of doctor-to-patient interpretation and communication role — taking this on would alter the relationship. Moreover, consenting to research under the impression of receiving potential personal benefits could be considered as inducement.

Minors and legally incompetent adults. When minors or legally incompetent adults receive WGS-based genetic testing, their legal representatives act on their behalf and in their best interests. For incompetent adults, there may be indications of what their personal preferences are because they may have expressed them during their lifetime, before the loss of their capacity.

Children are generally considered to lack the capacity to consent on their own. Parents are legally obliged to protect their children and to act in their best interests, with an increased participation of minors in decision making as they mature[28]. WGS is particularly helpful as a diagnostic tool for children. For example, it has been used

Table 4 | **Legislative approaches for the return of results for WGS-based genetic testing**

Country	Legislation	Approaches	Refs
Estonia	Human Genes Research Act, 2000	Opt-out from receiving IFs ("right not to know"; "right to access personally their data … [but] do not have the right to access their genealogies")	5
Finland	Biobank Act 688/2012, 2012	No individual return (but "right to receive, upon request")	8
Spain	Law 14/2007 of 3 July on Biomedical Research, 2007	• Opt-out from receiving IFs • Case-by-case determination by research team ("exclusively limited to the data necessary [to avoid a serious damage]") • No individual return ("make public the general results")	6
Taiwan	Human Biobank Management Act, 2010	No individual return	7

IFs, incidental findings; WGS, whole-genome sequencing.

in the paediatric population in order to establish the diagnosis of a sick child or to exclude the possibility of a rare genetic disorder[29,30]. WGS-based testing has also been used within research contexts to identify the gene responsible for an unknown syndrome[31]. Within clinical contexts, WGS has been used in combination with pharmacogenomic studies in order to increase the treatment success rate[32–34]. Finally, WGS has been used within prevention strategies, in order to identify and to anticipate future health problems[35]. However, when incidental findings are identified, should these results be returned to parents and, if so, under what conditions? This was one of the issues in the 2014 ACMG recommendations[26], according to which, at first, parents of children, like other adults, could not opt-out of receiving any results concerning their children from the 56-gene panel[36]. It was considered the duty of the physician ordering the panel to report all 56 genes and any clinically significant findings as well as "to provide comprehensive pre- and posttest counseling to the patient." (REF. 36). In addition, the ACMG recommended that the findings "be reported without seeking preferences from the patient [that is, no opt-out] … and without considering the limitations associated with patient's age." (REF. 36).

The final ACMG recommendations of 2015 (REF. 9) allowed for an opt-out by adults and by parents on behalf of their children. By contrast, on 2 July 2015, the American Society of Human Genetics (ASHG) declared that:

> *"when there is strong evidence that a secondary finding has urgent and serious implications for a child's health or welfare, and effective action can be taken to mitigate that threat, ASHG recommends that the clinician communicate those findings to parents or guardians regardless of the general preferences stated by the parents regarding secondary findings."* (REF. 37).

This latter position of the ASHG is in conformity with that of the paediatric platform of the Public Population Project in Genomics and Society (P^3G)[11], the Public and Professional Policy Committee of the European Society of Human Genetics[38,39] and the Canadian College of Medical Geneticists[10] (TABLE 3). They maintain that findings that are medically actionable during childhood should be returned, so that such children can receive medical care. This latter position of 'childhood medical actionability' is indicative of the more protective attitude towards children in Europe[38] and Canada[10], as opposed to the deference to parental authority and autonomy of the ACMG[9]. Irrespective of this difference, in all jurisdictions, upon reaching maturity, children can make their own decisions and determine their preferences. The policies also illustrate some flexibility as to the communication of incidental findings found in children that would prevent serious harm to the health of family members. For example, this could be the case if, following WGS in a minor, he or she is identified as being carrier of a mutation in *BRCA1* or *BRCA2*. Although knowing this information will not lead to the initiation of treatment or preventive measures during the childhood or adolescence, the incidental findings can have significant consequences on the health of the child's parents and adult siblings or other biological family relatives for whom it will be possible to undertake effective preventive measures.

Newborn screening. Nowhere is the concept of *parens patriae* — that is, the obligation of the state to protect the vulnerable — more evident than in the public health system-mandated screening of asymptomatic newborns for conditions that are immediately treatable. Recent controversies in NBS surrounding the storage of newborn blood-spots or their use in later research seem to be minor when contemplating the possible future use of WGS-based genetic testing in NBS[40]. Is the current paediatric routine standard of newborn care that uses a targeted approach to NBS with confirmations and notifications and a possible opt-out by parents for research or storage transposable to WGS-based genetic testing?

The European Society of Human Genetics, the international paediatric platform of P^3G, the Human Genome Organisation and the UK PHG Foundation endorsed a statement on the continued importance of a targeted approach in NBS programmes[41]. They are advocating that the responsible use of WGS-based genetic testing within a public health programme such as NBS should not be technology driven but rather be adopted on the basis of its public health potential. They argue that the primary justification for performing WGS-based genetic testing within the context of NBS should continue to be the health interests of the child. Like the most recent ASHG position[37], they highlight the advantage of adopting an approach using targeted sequencing, as this will limit the number of incidental findings. Nevertheless, they recommend that any incidental finding indicating a serious health problem for the child should be reported to the parents in cases in which treatment or preventive measures are available during childhood[41]. In the context of NBS, this cautious approach would limit WGS-based genetic testing to targeted sequencing or gene panel approaches. This is consistent with the European[38] and Canadian[10] positions on returning medically actionable results during childhood.

Conclusions

We provide an overview of the international policy and legal parameters surrounding the use of WGS-based genetic testing in both the research and clinical contexts. We find that there is a lack of agreement in guidance for the return of results and that there is a need to establish a clear direction on how to develop more harmonized guidance across countries.

Although the application of WGS-based genetic testing may be in hyperdrive[42], establishing the clinical relevance of results remains difficult. Even though such uncertainties affect the interpretation of the content and scope of the laws and policies on the matter, this is not surprising considering the broad array of research and clinical endeavours. It is difficult to adopt comprehensive guidelines or laws to cover all contexts, but at a minimum policy should be specific to the inherent characteristics of the research or clinical domains and to differing contexts.

Rare are the laws and policies that actually differentiate the role of the individuals involved in the management of the return of research results and incidental findings. More specifically, only a few establish the criteria that would help non-clinician researchers to delineate their role with regard to participants whose findings may or may not be returned. Management of expectations by those spearheading research activities is paramount. Although currently laws and policies are not harmonized, the tools used to manage the return of results and incidental findings can be developed to be interoperable across jurisdictions. To that end, the database of generic clauses of the P^3G's International Policy interoperability and data access Clearinghouse (P^3G-IPAC) provides a useful tool for stakeholders when preparing their internal policies and agreements concerning the feeding back of information to participants or not. While we are moving forward in our understanding of interpreting the clinical relevance of

results from WGS-based genetic testing, the question of whether to return is becoming how to return, who should return and when to return. This requires anticipatory governance and interoperable policies, as well as sound management to ensure that the resources, both financial and professional, are in place to undertake such a task. Irrespective of these issues, considering the speed of the integration of WGS-based genetic testing in research and clinical contexts, we hypothesize that the future question may well soon become: what should we not return?

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Competing interests statement
The authors declare no competing interests.

FURTHER INFORMATION
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