



Revealing the results of whole-genome sequencing and whole-exome sequencing in research and clinical investigations: some ethical issues

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ABSTRACT

The introduction of new sequencing technologies whole-genome sequencing (WGS) and whole-exome sequencing (WES) that are much less finely targeted than previous genetic tests has resulted in ethical debate about what should be done with clinically significant findings that may arise during the sequencing process. In this piece we argue that, in addition to whether the finding has been intentionally sought or arises incidentally, the ethical issues concerning what should be done with WES and WGS findings are also influenced by whether sequencing occurs in a clinical or research setting. We argue that decisions about the disclosure of WGS and WES findings generated in the clinical context are much less ethically contentious than decision making about the feedback of research results. We conclude by calling for greater transparency about the purpose of sample collection, more explicit protocols for transitioning between research and clinical contexts and patients and research participants to be warned of the potential for incidental findings to be generated, their potential significance and the actions that might be taken as a result.

PERTINENT VERSUS INCIDENTAL: THE STATUS OF GENETIC FINDINGS GENERATED DURING WHOLE-GENOME SEQUENCING (WGS) AND WHOLE-EXOME SEQUENCING (WES)

In recent years, a number of commentators have distinguished between genetic findings that have been intentionally sought as part of the diagnostic process or to answer a particular research question—pertinent findings—from other clinically significant findings that are generated in the course of the WGS and WES sequencing, but have not been deliberately sought, namely, ‘incidental’, ‘unsolicited’, ‘coincidental’ or ‘secondary’ findings.^{1–7} These incidental findings emerge because WGS and WES screening techniques are less finely targeted than more classical genetic tests. In some cases, the term ‘incidental findings’ refers to findings that are discovered accidentally, in others it is used to refer to findings that are deliberately sought in addition to the patient’s presenting complaint (see for example, the American College of Medical Genetics (ACMG) recommendations⁶) or to the primary research question.

While we acknowledge that ethical debate about the status and disclosure of ‘pertinent’ versus ‘incidental’ findings in genomic sequencing is important, this paper focuses on another issue that we believe is as important when it comes to making decisions concerning the disclosure or feedback of

the findings of WGS and WES, namely, the context in which sequencing takes place—the research or clinical context.² This paper will, therefore, discuss some of the ethical issues that concern the disclosure or feedback of findings generated by WGS and WES in the clinical context and the research context.

Before we address the issue of disclosure or feedback, we need to consider what we mean by *sequencing* and *the findings of WGS and WES*. Genome sequencing comprises a set of interrelated activities that follow on from the generation of the sequence of the base pairs across the entire genome/exome. These activities include (a) the identification of defined variants in the sequence as compared with some reference sequence, (b) the selection of those areas of the genome that contain variants that are pertinent to the clinical or research question and (c) the interpretation and analysis of the data within those selected areas.⁸ It is at the final stage when the sequence variations are interpreted that judgements are made about the meaning of the variants that exist in the analysed sequence.⁹

Findings generated by sequencing may be designated as scientifically significant, or not. ‘Scientifically significant’ findings are those findings for which there is statistical evidence of a relationship between the genotype (genetic variation) and a particular phenotype (eg, disease symptoms/risk factors). If there is insufficient evidence to support this relationship, then the finding is often designated a ‘variant of uncertain significance’ (VUS). Labelling a particular genetic variant as a VUS does not necessarily mean that the genotype–phenotype relationship does not exist, but rather that it has not been confirmed statistically at this time in this population. WGS generates a large amount of data, and many observed variants will be of uncertain significance. Further clinical investigation may be required to determine their significance, and this may necessitate disclosure to patients or feedback to research participants for the purpose of gathering more data (eg, biospecimens and phenotypic data from other family members).¹⁰ While we acknowledge that whether or not to disclose VUS in clinical or research settings raises a number of interesting ethical issues,¹⁰ this paper will primarily consider the disclosure or feedback of scientifically significant findings that are known to have health implications.

What are the criteria for assessing whether or not a variant has health implications? A variant with ‘health implications’ will include those where



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there is a probability that the variant will impact negatively on health, not only on the individual, but also on their future offspring or extended family. So in this paper we use the term WGS and WES findings to refer to those scientifically and clinically significant genetic variations that emerge during either clinical or research investigations that, according to the literature and current knowledge, are thought reasonably likely to have a modest or significant impact on an individual's (physical or psychological) health either now or in the future. A number of additional factors may need to be considered when assessing the clinical significance of a finding, including the timing of potential health impact—when this will come about, now or in the future; its scale—whether its impact upon health is significant or trivial; treatability—whether it is a treatable or preventable condition, and the probability of impact—whether the variant is completely penetrant or only marginally so.

TO DISCLOSE OR FEEDBACK OR NOT TO DISCLOSE OR FEEDBACK, THAT IS THE QUESTION

Traditionally research and clinical investigations have been understood as different types of activity, stemming from very different motivations. In theory, the former is carried out independently of individual patient's interests, is hypothesis-driven and primarily aimed at answering a research question. The latter is motivated by individual patient's needs, and its prime purpose is to benefit individuals not the wider patient population.

Distinguishing research from clinical activities is seen as critical from an ethical standpoint¹¹ as the actors involved in these different activities are seen as having different rights and duties; but in reality the boundary between these activities is becoming increasingly indistinct particularly in genetics and genomics.^{4 12 13} The result is that patients and research participants may find it difficult to distinguish between research and clinical activities, particularly when their clinician is also a researcher interested in investigating their condition¹⁴ or the research participant is also a patient.¹³ Moreover, clinical activities are increasingly regarded as having a research element.¹⁵ This confusion may lead to research participants and researchers viewing research interventions in genomics, as well as in other areas of medicine as being motivated primarily by clinical intent.^{16 17} But notwithstanding this ambiguity, in every clinical encounter there is always a primary problem brought by the patient to the clinician that needs to be solved, and although the context in which research and clinical care takes place is now increasingly indistinct, it is important, and it should be easy, to be clear and transparent about the primary purpose of any encounter.

The setting, whether clinical or research, provides an important starting point for deciding what findings should be disclosed to patients or fed back to research participants; however, as we shall demonstrate, there are a number of additional factors that may be taken into account, for example, age of disease onset, disease severity, the potential for treatment or prevention, and who may be affected (the patient, the family or future offspring).

CLINICAL CARE AND THE DUTY TO DISCLOSE WES AND WGS FINDINGS GENERATED DURING CLINICAL INVESTIGATIONS

In general, the disclosure of WGS and WES findings within the clinical setting is not perceived as contentious. Disclosure decisions are subject to clinical judgement, and therefore, driven by the professional obligations of beneficence and non-maleficence. Clinicians are duty bound to do the best for their patient and

will choose to disclose any clinically significant findings, when, in their opinion, the benefits disclosure outweigh the harms that may arise from disclosure. It has been argued that clinicians should advise patients that in addition to the findings that are deliberately sought for diagnostic purposes, WGS and WES may generate a range of additional findings that may affect their clinical management now or in the future and that, unless they indicate otherwise, some of these findings may be disclosed.^{4 7} Disclosure of any WGS and WES findings in addition to those sought for diagnostic purposes requires clinicians to determine which findings should be disclosed in any particular instance. This decision requires them to assess the benefits and harms of disclosing particular findings in addition to those that were sought for a diagnosis, and this will need to be informed by their knowledge of the patient and the clinical context. As we have noted before,² when deciding whether the disclosure of any particular finding is in the patient's best interests, clinicians will consider a number of clinical factors such as whether the finding is diagnostic or predictive, age of disease onset, severity of disease, penetrance of the mutation, potential for prevention or treatment and customary medical practice regarding disclosure of this finding. Other non-clinical factors may also be relevant, including the age of the patient or whether the patient is a child, knowledge of the patient's health and other comorbidities, social and family circumstances, and the individual patient's wishes concerning disclosure. Within the clinical context decision making concerning disclosure of pertinent findings will usually be straightforward; however, deciding whether or not to disclose incidental findings, particularly those that are unexpected or accidental, will be more difficult and may be greatly influenced by the clinical significance of the finding (including both actionability/treatability and severity of the condition in question).

While we would argue that decision making about the disclosure of additional information in clinical contexts should be driven by clinical judgement, recent research carried out in the USA⁷ suggests that patients can play a role in these decisions. Shahmirzadi *et al*⁷ informed the patients in their study that their diagnostic exome sequencing might generate a number of 'secondary' findings and asked them to choose what type of additional findings they received. Even though the clinical team in this instance made the initial judgement about which categories of additional findings could be disclosed (ie, carrier status for recessive diseases, cancer predisposition mutations, early-onset disease and late-onset disease) and which specific findings fell into these categories in any particular case, this study demonstrated that it is possible to incorporate some form of shared decision making in the disclosure of WGS and WES findings in a clinical situation despite the ACMG recommendations on clinical sequencing, which advised against offering patients such choices.⁶ It is also interesting to note that 16% of adult patients in this study opted out of receiving additional findings in one or more categories. This observation suggests that non-disclosure of some findings that are unrelated to the original diagnostic question is valued by some patients.⁷

THE FEEDBACK OF FINDINGS FROM WES AND WGS IN RESEARCH PROJECTS

While the disclosure of WGS and WES findings in a clinical setting is relatively uncontroversial, the feedback of individual findings emerging during genomics research has been the subject of a great deal of ethical debate.⁴ Determining the best approach to the feedback of research findings is often seen as more difficult for a number of reasons. First, for technical

reasons any WGS and WES findings generated during the course of research are more likely to be of low diagnostic quality. Second, the required expertise in interrogation and interpretation of particular genetic variants may be unavailable in research laboratories. Thus, all research findings will require further confirmation and validation by experienced professionals in a clinically accredited laboratory. This is a highly resource-intensive practice. Third, the feedback of research findings will require expertise in genetic counselling, and thus, it may be practically impossible to feedback genetic results without extensive resources and this will impact upon research and training budgets. Finally, the relationship between researchers and research participants differs from the clinician–patient relationship to the extent that it is not based upon the same set of professional duties.¹⁸

These observations suggest that a rule-based framework that sets out the basis for feedback of research findings should be put in place for every research project.⁴ In table 1, we list a number of different frameworks that take into account the significance of the finding, its actionability (ie, presence of effective treatment and/or prophylaxis) and disease severity and outline the ethical arguments for and against their adoption⁵ (see table 1).

A number of issues must be noted regarding the options outlined in table 1. First, all of these feedback policies fall along a continuum of decreasing (potential) clinical significance (a combination of severity and actionability) and increasing participant autonomy; ranging from high utility plus low autonomy in B, through high to moderate utility plus moderate autonomy in C, to high through low or non-existent utility and high autonomy in D. Arguably research participants' autonomy is maximised in the feedback policy outlined in E in which research participants are given the choice of which types of findings they receive by opting for a particular feedback policy.⁷ In addition, it must be noted that the extent to which each of these feedback policies seeks to maximise participants' autonomy is related to the burden that feedback puts upon researchers. For example, E may maximise an individual's autonomy by allowing them to

choose which feedback policy is adopted, but it also places one of the maximum burdens on researchers at the point of consent because they would need to explain each option in detail in order to facilitate informed choice. While it could be argued that individual autonomy should trump the burden placed on researchers, in reality the burdens of feedback, in terms of the resources required, need to be balanced against participant autonomy.

Second, allowing research participants to have a greater role in choosing the type of information they receive has recently been supported by Anastova *et al*, who have called for research participant input into the use of filtering algorithms used in WGS research.¹⁹ Arguably, enabling individual research participants to determine which WGS or WES findings are to be returned, if any, opens the door to the personalisation of feedback, which in turn would require personalising consent processes. However, as Kaye *et al* point out,²⁰ despite the scale of some research projects, this could easily be achieved by the use of information technologies and web-based platforms, which could also be used to provide access to different types of research findings. In this scenario, participants would be responsible for determining what level of research participation they consent to, and thus, which results they would access. For example, individuals could opt to receive feedback about the generic results of the research study (we found gene X in our study population), the family's results (we found gene X in members of your kinship) or their personal results (we found gene X in you).²¹

Third, although offering feedback about any and all variants identified by WGS/WES (option D) may seem to promote research participants' autonomy, as was noted above, many variants will be difficult to interpret or uninterpretable and, therefore, be of uncertain significance (VUS). Consequently, disclosing these findings without a clear understanding of their phenotypic expression could generate potentially unnecessary anxiety in research participants.²²

Fourth, any discussion of the feedback of research findings should not overlook more fundamental debates about the

Table 1 Arguments for and against different options for the feedback of research results

Feedback policy	Arguments for	Arguments against
(A) No feedback	Feedback harmful if unexpected; no evidence of benefits; resource implications (clinical validation, no trained personnel); feedback may fuel therapeutic misconception and undermine altruistic research participation	Undermines autonomy; missed opportunity for detection and prevention
(B) Severe, clinically actionable* findings	Enhances prevention and detection of disease; targets scarce resources where they will be most effective	How to determine criteria for feedback; may fuel therapeutic misconception and undermine altruism; undermines autonomy to not know; resource intensive
(C) All health-related findings regardless of severity and actionability	Overcomes criteria problem of B enhances autonomy; enhances prevention and detection of disease	Psychological harm of knowing untreatable risks social and economic harms; undermines autonomy to not know; resource intensive (required clinical validation, no trained personnel); feedback may fuel therapeutic misconception and undermine altruistic research participation
(D) Whole sequence	See C; enhances autonomy; overcomes criteria problem of B	Information may be uninterpretable; see C: no evidence of benefits; resource implications (clinical validation, no trained personnel); feedback may fuel therapeutic misconception and undermine altruistic research participation
(E) Research participant chooses feedback option	Maximises autonomy	Overwhelming choice; informed consent process too onerous; resource implications (clinical validation, no trained personnel); feedback may fuel therapeutic misconception and undermine altruistic research participation

*It should be emphasised that the exact criteria for considering whether a variant is considered to be actionable or not and serious or not is context dependent and will be subject to a range of factors (eg, current knowledge, established treatment practices, available and accessible healthcare resources, researchers' judgements and ethical or IRB ruling) and may only emerge during the process of seeking ethical approval for the study.

nature and scope of the consent that should be sought. There is ongoing ethical debate about the requirements of informed consent in genomics research²³; whether it should take the form of a broad-based generic consent to secondary analysis and use of DNA or whether it should be specific or targeted at particular uses.^{24–25} As Shahmirzadi *et al* have demonstrated, it is possible to seek consent from patients to receive broad categories of findings generated by WES.⁷ Whether their consent process could be scaled up to take into account the larger numbers who may be involved in research studies is unknown. What Shahmirzadi *et al* do not report is how the patients understood these categories and what was the impact of receiving the different types of information.⁷ In other words, little is known about the perceived harms and benefits of receiving different types of research findings, a point we will return to below. These reservations apart, we are of the opinion that if researchers opt to feedback research findings, then potential research participants should (a) be warned of the possibility that personal findings may be fed back either now or in the future, (b) be informed of the risks and benefits of receiving personal findings, (c) understand that any research result will require further clinical validation and may require other family members to be so informed and (d) be given the option of opting out of receiving personal research findings.

Finally, it must be noted that research is not, and should not be seen as, a monolithic activity, and thus, we anticipate that different feedback policies could be adopted for different types of research or at different times. In other words, the nature of the research (population biobank/clinical research) or the types of researchers (epidemiologists/clinical geneticists) involved may determine the type of feedback policy adopted. For example, large-scale population biobanks may adopt a different feedback policy compared with small-scale studies in which an ongoing clinical relationship exists between the researchers and the participants or the cultural and sociopolitical context could determine that certain feedback options are much more appropriate than others.

WHAT'S NEXT?

In this piece we have argued that the context of sequencing, whether it takes place in a research or clinical setting, may influence the communication of WGS and WES results. As Wolf and others have observed, it is becoming more and more difficult to distinguish research and clinical activities in genomics.⁴ Indeed, as far as the UK 100000 Genome Project is concerned, while the project will involve diagnostic sequencing of patients in a clinical setting, it is clear that the sequences generated may be the subject of secondary analysis; in other words, they may also constitute research material in the future.

Many opinions have been aired about disclosure and feedback of findings generated by WGS and WES in different settings, but little has been concluded. While the ACMG has lobbied for extensive disclosure of a number of additional key genetic variants following clinical sequencing,⁶ as of April 2014 they have intimated a policy change allowing patients to opt out of analysis of these variants²⁶: this decision brings their position into line with others who have adopted a more precautionary position including the Presidential Commission's 2013 report, which advocates a more nuanced approach.¹ This paper advocates a more pragmatic approach that uses the context for sequencing as a guide to the ethical principles that might apply. There are a number of policy implications that flow from this position. First, that there is greater transparency about whether sample collection and analysis forms part of clinical care or

research. Second, there are explicit and standardised protocols in place for transitioning between research and clinical contexts, including systems for validating research findings that are subsequently applied for clinical use. Third, that regardless of the setting in which sequencing is carried out, patients/research participants should be warned of the potential for incidental findings to be generated, their potential significance and the actions that might be taken as a result (also a key recommendation of the Presidential Commission's report¹).

Finally, advocates of the feedback and disclosure of WES and WGS findings in research and clinical assume that disclosure/feedback of WES and WGS findings will promote individual autonomy.⁶ We suggest that this argument is underpinned by the view that knowledge about one's health is good and more knowledge about one's health is better and overlooks the potential for psychological and/or physical harm that the feedback/disclosure of genetic risk, and subsequent risk-management practices (eg, screening and prophylaxis), may cause. Arguably, this assumption needs greater interrogation at a normative level and, indeed, at an empirical level. The little empirical evidence that currently exists suggests that some, but not all, individuals opt out of receiving some findings following clinical sequencing,⁷ while others feel less than positive about receiving unexpected clinically significant findings discovered in the course of research investigations.²¹ Although we would not suggest that empirical observation should dictate ethical reasoning, we are of the opinion that more empirical research of this type is needed so that we may have an evidenced-based discussion of the harms and benefits for individuals, and thus for society, of the introduction of WGS and WES as clinical and research tools.

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