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Not-so-incidental findings: the ACMG recommendations on the reporting of incidental findings in clinical whole genome and whole exome sequencing

Megan Allyse and Marsha Michie

Center for Biomedical Ethics, 1215 Welch Road, Modular A, Stanford, CA 94305, USA

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Introduction

The issue of incidental findings in genomics research has been contentious, particularly in whole genome sequencing (WGS) and whole exome sequencing (WES). An incidental or secondary finding has generally been defined as ‘a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conduct – but is beyond the aims of the study.’ [1]. However, as WGS and WES increasingly enter the clinical realm, these concerns are extended to individually relevant findings that are unrelated to the clinical purpose of sequencing. In May 2012, the American College of Medical Genetics and Genomics (ACMG) released a policy statement on *Points to Consider in the Clinical Application of Genomic Sequencing* in which they cautioned that ‘when interpreting secondary findings, or results that are generated in the course of screening asymptomatic individuals, it is critical that the standards for what is reportable be high to avoid burdening the health care system and consumers with what could be very large numbers of false positive results’ [2]. As a result, ACMG convened a working group to offer recommendations on handling incidental findings in clinical sequencing.

The Working Group on Incidental Findings in Clinical Exome and Genome Sequencing of the ACMG (‘the Working Group’) published its *Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing* (‘the recommendations’) in March 2013 [3]. On the one hand, the recommendations take seriously the need to focus incidental findings on only those findings with clear clinical utility and actionable results. They provide a stringently curated list of specific variants that they believe rise to the level of clinical obligation to report. On the other hand, the zeal with which these variants were selected apparently encouraged the Working Group towards recommendations that depart significantly from existing practice and policy. First, they suggest that rather than reporting findings that are incidental to the purpose of the clinical sequencing as ordered, clinical

sequencing laboratories have an obligation to seek out actively the variants as listed in the recommendations and include these findings in the clinical report. Second, they do not recommend considering patient preferences in reporting results. That is, all patients (or their guardians) should receive all recommended results whether they desire the information or not. This recommendation specifically includes sequencing on children.

Although we support the desire of the Working Group to honor beneficence by providing patients with information that may affect their future health, we find these recommendations challenging from both an ethical and a practical perspective. Not only do they redefine incidental findings in a problematic manner, but the implication that individual autonomy should be over-ridden by physicians for the patient's 'own good' is weakly supported in modern clinical ethics.

Incidental findings

Despite acknowledging that the term 'incidental findings' has indicated 'unexpected positive findings' in the past, the Working Group gives it an entirely different meaning: 'we use "incidental findings" in this paper to indicate the results of a deliberate search for pathogenic or likely pathogenic alterations in genes that are not apparently relevant to a diagnostic indication for which the sequencing test was ordered.' [3]. This definition contradicts common usage and confuses the issue of incidental findings. The results of a 'deliberate search' for diagnostically relevant genetic information are generally referred to as 'genetic test results.' Furthermore, predicatively testing asymptomatic individuals with no family history of serious genetic conditions suggests a push towards genetic screening; a practice that has thus far only been supported in newborns and is highly controversial in children [4]. In essence, therefore, the recommendations turn the occasion of WES/WGS, regardless of the reason for the test, into a full diagnostic screen.

This gives rise to several difficulties. First, the recommendations specifically acknowledge that the extra testing will place an added burden on laboratories that 'add significant costs to at least some of their sequencing reports' [3]. Historically, third party payers have supported genetic testing only in the event of symptomatic evidence or an established family risk [5]. It is unclear whether payers will cover the cost of predictive testing for conditions when neither of these conditions apply. Indeed, the recommendations acknowledge that they 'do not know the implications that this may have on reimbursement for clinical sequencing' [3]. Laboratories are unlikely to bear the increased cost themselves, making the practical implementation of these recommendations uncertain.

A second difficulty arises from the assertion of the Working Group that clinicians ordering WES/WGS are responsible for both pre-test and post-test counseling for both the primary testing and 'the analysis that is being performed for incidental findings' [3]. The lengthy list of mandatory gene tests in the recommendations, and the acknowledgement that it will continue to grow, suggests that such counseling will be extensive and costly. Furthermore, 'clinical sequencing may be ordered by specialists who may not feel comfortable discussing incidental findings...thus generating additional consultations and medical costs' [3]. Given that reimbursement for genetic counseling has been uneven, there is potential for

considerable unreimbursed cost associated with this sudden increase in medical interaction [6]. These additional costs could create an even larger gap between those with the financial resources to receive high-level medical care such as WES/WGS and those without.

Patient autonomy and preferences

The Working Group also recommends against patients choosing whether to receive incidental findings, because ‘clinicians and laboratory personnel have a fiduciary duty to prevent harm by warning patients and their families about certain incidental findings and... this principle supersedes concerns about autonomy’ [3]. These recommendations include reporting test results for adult-onset conditions to parents of children undergoing WGS/WES, regardless of parent preferences.

This recommendation runs counter to previous guidelines on sequencing from ACMG and others [2,7]. Furthermore, it contradicts ethical clinical practice in general. By policy and practice, clinicians or other surrogates may only make decisions on behalf of a patient in situations in which (s)he is incapable of exercising judgment [8]. Rarely, the courts may over-ride parental decision making about the medical treatment of a child when a parent is invalidated as an appropriate decision maker. In other circumstances, physicians may have a fiduciary duty to offer incidental findings, but these are generally limited to physical abnormalities, for example, potentially operable tumors. Such situations are qualitatively different than forcing a patient to learn about a future disease risk.

The further assertion of the Working Group that respecting patient preferences would be ‘unwieldy’ is unconvincing, especially in light of the additional costs generated by providing incidental findings. In evaluating the return of genetic test results, the recommendations set up a false dichotomy between ‘genetic libertarians’, who advocate for full return of all genetic information, and ‘genetic empiricists’, who argue against sharing incidental findings because their significance is unclear. This dichotomy ignores the considerable work that has been done in the middle ground of tiered consent and patient-centered return of results [9–11].

Even if one accepts that laboratories should proactively screen for certain genetic variants and provide those results to the clinician, it seems far from obvious that, during the complex process of deciding the relevance of this genetic information, a clinician should be incapable of serving as a gatekeeper for the information the patient has consented to receive, as long as the patient is clear in his/her refusal of additional information. The assertion that ‘patients have the right to decline clinical sequencing if they judge the risks of possible discovery of incidental findings to outweigh the benefits of testing’ [3] borders on the coercive. It argues that patients should be offered potentially life-saving sequencing for a condition they do have only if they are willing to accept additional, potentially devastating genetic testing information about a condition they might someday have, regardless of whether they perceive that additional information as desirable [12]. Nor does this construction address the possibility of patients refusing all incidental findings, thus saving the laboratory the expense of looking for them and any complications in selecting which results to report. This ‘one

size fits all' approach to consent also ignores the observed differences between social and ethnic groups in their desire for genetic information [13–15].

Concluding remarks

Without a doubt, a majority of physicians would agree that the conditions included in the recommendations are serious and, to a varying extent, actionable and thus advanced notice of their potential presence may provide important guidance surrounding future care. We do not disagree that most patients or parents would prefer that their physician tell them about serious, life-threatening conditions for which they may be at risk. What the recommendations seem to suggest however, goes beyond targeted testing or true incidental findings to suggest that anyone undergoing WES/WGS should automatically be screened for a growing list of genetic conditions. Indeed, because there is no evidence that those undergoing WES/WGS are at any greater risk of the listed conditions than the rest of the population, the further implication may be that we should be implementing population-based testing for serious medical conditions. At the same time, the Working Group suggests that although the cost of additional testing, laboratory time, reporting, interpretation, and reporting will be manageable, it is simultaneously too burdensome to respect patient preferences about additional testing and receiving results. This, it seems to us, is both dubious and problematic. We suggest that a broader social and professional debate is desirable, in order to gain insight into whether we – as test providers, clinicians, and patients – are really ready for mandatory genetic testing.

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