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Ethics and Genomic Incidental Findings

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Introduction

The American College of Medical Genetics and Genomics (ACMG) recently issued a statement (1) recommending that all laboratories conducting clinical sequencing seek and report pathogenic and expected pathogenic mutations for a short list of carefully chosen genes and conditions. The recommendations establish a baseline for reporting clinically relevant incidental findings and articulate ethical principles relevant to their disclosure. The ACMG acknowledged that the list will evolve over time and is developing a mechanism for community input (2). This paper focuses on the ethical framework for the recommendations, rather than on the choice of which genes to include on the list.

Standards Are Needed

An increasing number of laboratories conduct clinical whole-genome and whole exome sequencing (WGS-WES) (3) and have the potential to seek and report incidental findings, but there are no standards to guide their scope of analysis or reporting. The results a clinician receives depend in part on what laboratory is used, and some laboratories may report incidental findings of limited or uncertain clinical utility. The recommendations set a standard for best laboratory practices, by limiting the obligations of laboratories to incidental findings that meet a high threshold of clinical utility. The recommendations thus aim to discourage potentially harmful over reporting and unjustified variation in reporting practices. The threshold for reporting incidental findings was based on variant frequency, the potential for medical intervention to mitigate disease, the strength of association between specific gene abnormalities and the condition, and penetrance of those genes. The

recommendations authors estimate that only about 1% of patients will receive such an incidental finding (1). Criteria were intentionally set high to include only “unequivocally” pathogenic mutations in genes where pathogenic variants lead to disease with very high probability and where evidence strongly supports the benefits of early intervention” (2). In other words, these are clinically relevant findings, knowledge of which is likely to benefit the patient and promote health.

The recommendations essentially argue that laboratory personnel have a professional obligation to conduct a comprehensive evaluation of available test results to identify such clinically significant findings. This is true in all areas of medicine. To treat genomic information differently would constitute unjustified genetic exceptionalism. This ethical standard already governs clinical genetics practice. For example, if a patient is being evaluated for a hereditary cardiac condition, practice standards for the geneticist dictate that he or she should take a three-generation family history and search for patterns that reveal genetic predisposition to disease. If a predisposition to cancer is recognized, it should be communicated and followed up on. The transition from gene and panel testing to WGS/WES creates the same opportunity and obligation to identify and report clinically beneficial incidental findings.

Respect for Patient Autonomy

The recommendations reflect a core principle of professional medical ethics: The decision about appropriate scope of analysis and judgments about which findings are clinically beneficial are matters of expert professional judgment. Patients retain the decisional right to decline clinical sequencing, but, as is true for other diagnostic and screening procedures, the decision about the minimum list of genes to be interrogated requires professional expertise (4). Some have characterized this as borderline coercive (5) and testing without informed consent (6). This incorrectly assumes that analysis of clinically beneficial incidental findings is a discrete test requiring separate consent, whereas in reality it is integral to the primary interrogation. WGS-WES constitute a single comprehensive assessment using complex analytic algorithms for interpretation. The recommendations state that the ordering clinician is responsible for obtaining informed consent for this test and providing both pretest and posttest counseling “so that the patient is aware of not only the implications and limitations of the primary testing, but also the analysis that is being performed for incidental findings” (1). In other words, consistent with the ethical standards of informed consent and the principle of respect for patient autonomy (7), patients should be informed of the benefits of testing, as well as its risks and alternatives.

The recommendations’ ethical standard for informed consent actually exceeds the legal standard in most states. Most diagnostic and risk assessment evaluations, including genetic testing in the majority of states (8), are performed under a general, simple consent to treat, because it is justifiably assumed that a reasonable patient would agree to a comprehensive evaluation to identify clinically beneficial information.

Some mistakenly infer from the recommendations that patients have no choice about which results they receive, thus violating a patient’s right not to know. The right not to know is ethically controversial, and most of the relevant literature relates to findings for which no clearly beneficial interventions are available (9). Nonetheless, the recommendations explicitly state that the clinician-patient interaction is the appropriate place for incidental findings to be managed (1). Although the recommendations set a minimum standard for analysis and reporting, the physician and patient may decide together whether additional analyses and disclosures would be beneficial. There may be rare circumstances in which a physician, in consultation with the patient, decides not to follow the recommendations; for

example, where WGS-WES will likely be beneficial to the patient for his or her primary clinical concern, no other test alternative is available (e.g., targeted testing is unavailable, has been tried, or is too expensive), and the patient insists that he or she does not want to be informed about incidental findings, even if disclosure could lead to beneficial intervention. When this occurs, the clinician must ensure that the patient's refusal is informed. If refusal persists, and the clinician agrees not to follow the recommendations, then the clinician should document this as a deviation from recommended analysis and disclosure, equivalent to refusing disclosure of any other clinically significant information. The clinician should inform the patient about practical constraints, including the difficulty of keeping the laboratory report out of the electronic medical record.

Treat Children and Adults Equally

Traditional guidance for genetic testing of children, reflected in a joint statement by the ACMG and the American Academy of Pediatrics (AAP), recommends that “predictive genetic testing [of children] for adult-onset conditions generally should be deferred unless an intervention initiated in childhood may reduce morbidity or mortality” (10). It follows that, barring unusual psychosocial circumstances or a request by a mature minor, genetic testing for adult-onset conditions should not be performed even when parents request it. The primary rationale is a desire to preserve the child's ability, when he or she reaches adulthood, to make an autonomous informed decision about testing.

The recommendations suggest that seeking and reporting incidental findings should not be contingent on the age of the person being sequenced. This does not contradict the AAP-ACMG position, because the two statements reflect fundamentally different contexts. The AAP-ACMG statement addresses the child who is known to be at risk of an adult-onset genetic condition for which no intervention can be initiated during childhood. For this child, the relevant alternatives are to (i) offer testing now, or (ii) defer testing until the child can make his or her own informed decision. Whereas option (i) may impose a test on a child that he or she might otherwise have chosen not to undergo, there is essentially no harm associated with option (ii), other than restriction of parental choice and authority. The issue of testing the child can safely be addressed when the child is an adult. In addition, because other at-risk adult family members are presumably aware of the proband's condition and of their own risk, they can elect to undergo testing.

The current recommendations address a very different context, in which the balance of interests, both of the child and of the family, must be reconsidered. In the case of incidental findings, where there is no prior information that identifies the family as at risk, the laboratory can either: (i) seek and report incidental findings included on the list to the ordering clinician, or (ii) not seek or report such findings. Option (i) runs the risk of imposing knowledge on the parents, child, and future young adult that they might nonetheless prefer not to have received, but offers potential medical benefit both to the child and to at risk family members. In contrast, option (ii) withholds information that is potentially lifesaving for the child, one of the parents, and potentially other family members—information that they would otherwise have no reason to suspect (2). Furthermore, because the clinician and family are unaware of the child's risk, deferral of testing is not an option and preservation of the child's ability to make a future autonomous choice—the motivation underlying the AAP-ACMG proscription—is logically precluded. Thus, if the laboratory and clinician do not alert the child and family to the newly discovered risk information, they ignore potentially preventable harm to the child and other family members, fail to recognize parents' obligation to protect and promote the best interests of the child, and prevent them from making informed decisions about their child's and their own subsequent clinical management.

Implications and Next Steps

The recommendations represent an initial attempt to set a professional standard for best laboratory practices that will responsibly minimize variation in laboratory analysis and reporting of clinically beneficial incidental findings. They should be seriously considered by laboratory personnel, but they do not have the force of law. In the event of malpractice litigation, the recommendations may be introduced as evidence of the standard of care. Ultimately, they will be considered in light of all other evidence to determine whether the defendant's actions were consistent with what a reasonable professional might have done. The recommendations set a minimum standard for analysis and reporting of clinically beneficial incidental findings. By setting a high threshold for the reporting of findings with likely clinical benefit, they may also protect against liability for failure to report incidental findings that are not included on the list.

Tremendous investment has been made in studying the clinical utility of WGS-WES, including psychosocial benefits and harms of receiving incidental findings (11). As new evidence emerges, the list of reportable genes will be refined. Careful consideration should also be given to the application of these and/or other recommendations to preconception, prenatal, and newborn sequencing and sequencing of those without symptoms.

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