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Genomic Medicine and Incidental Findings: Balancing Actionability and Patient Autonomy

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In March 2013, the American College of Medical Genetics and Genomics (ACMG) released recommendations on how to handle incidental findings (IFs) for the clinical application of whole exome or whole genome sequencing (WES/WGS).[1] The ACMG recommended that clinical laboratories "actively search,"[1] evaluate, and report pathogenic or likely pathogenic variants in 56 genes and report these findings to the ordering clinician, who could then "contextualize any incidental findings for the patient in light of personal and family history, physical examination, and other relevant findings."[1] The 2013 recommendations did not provide guidance for laboratories to offer patients of any age the ability to opt out from the reporting of IFs. The 56 genes are associated with 24 genetic cardiovascular disorders or predisposition to cancers for which confirmatory diagnostic approaches are available as well as some preventive or treatment measures that can be offered. The ACMG recommended further that those who did not agree to learn of these IFs could choose to forego the entire test. These recommendations generated much controversy, most of which focused on patients' ability to opt out of receiving unwanted results.[2-9]

Illustrating its commitment to participating in broad, public discussion, the ACMG Board of Directors surveyed its membership in early 2014 to ascertain how the members viewed the 2013 recommendations. In addition, the ACMG surveyed attendees of the 2014 ACMG annual meeting. The responses suggest that most members support allowing informed patients to opt out of receiving information about some or all IFs (presented at the 2014 annual ACMG business meeting). The ACMG also held open forums to discuss the recommendations, including one at each of the 2013 and 2014 annual ACMG meetings. These activities resulted in the Board revising their 2013 recommendations to allow clinical laboratories and clinicians to offer patients the ability to pursue genetic testing but opt out of receiving results covering these 56 genes.[10] In addition, the ACMG has established a new committee that will create a mechanism for evaluating changing evidence of genetic variants for inclusion on subsequent lists of actionable variants. Although challenges remain for implementing genomic medicine, including how to effectively and efficiently discuss IF options with patients,[11-13] this new position by the ACMG acknowledges the importance of tailoring the reporting of results obtained from clinical WES/WGS of each individual patient. In this article, we describe the ethical and clinical rationale for our strong agreement with this position, highlighting how the ACMG's position more fully preserves patient decision making and autonomy in the era of next-generation sequencing (ie, massively parallel high-output sequencing of nucleic acids in which multiple DNA templates are sequenced simultaneously, enabling cost-effective analysis of large numbers of target sequences at one time).

The initial ACMG statement has been an important first step in developing national consensus on managing clinical IFs from next-generation sequencing. It generated an intense discussion about a patient's "right not to know" about IFs. The statement also established a starting place for considering what should be included in a list of clinically actionable genetic findings from WES/WGS. Although the discussion has been ongoing in the context of genetic and genomic research for more than a decade, with the rapid movement of next-generation sequencing into the clinical arena, initiating a

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broader conversation on how to handle clinical IFs is even more germane.

When the 2013 ACMG recommendations were released, commentators[2,4,8,9,14] voiced concern about the lack of provisions for patient choice in decisions about the receipt of health-related information. These concerns were consistent with our experiences at Mayo Clinic's Individualized Medicine Clinic.[15] In that context, we are conducting studies characterizing patients' preferences regarding IFs. Our findings reveal that those preferences are diverse.[16] That is, some patients do not want to know about findings that are unrelated to their primary condition, while others want to learn about all IFs, extending even to those findings that may not have apparent clinical implications. The contextual uniqueness of each patient can play a critical role in how individuals make decisions. In this sense, the initial 2013 ACMG recommendations appeared to be inconsistent with the heterogeneity and diversity of patient preferences with respect to receiving information on IFs and the importance many patients assign to individual choice.

The revised 2014 ACMG position places greater weight on patient autonomy and shared decision making. Many clinicians encourage patients to be actively involved in health care decisions, and many patients *expect* to play an active part in decisions concerning their health. Indeed, although the 2013 recommendations stated 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,"[1] this "all or none" approach about WES/WGS was incongruent with the spirit of individualized medicine. One can imagine that a patient may wish to undergo genomic testing for a specific indication, such as selection for an approach to cancer treatment, and yet may choose not to go forward with this approach once informed that additional unrelated information would also be disclosed.

The 2013 recommendations raised other concerns that the most recent revision has addressed. For example, the 2013 recommendations implicitly obligated clinical laboratories to search for pathogenic or likely pathogenic variants in the 56 genes identified by the ACMG. When ordering clinicians receive the results, they must determine how best to return these findings to the patient. Although the original recommendations duly noted that the ordering clinician could decide not to return these findings to the patient, placing the clinician in a gatekeeper role, the results of clinical testing would likely be entered into the patient's medical record, raising the potential for another clinician, unaware of the patient's wishes, to divulge that unwanted information to the patient. In addition, some clinicians may feel a legal responsibility to share IFs with the patient, especially once reported by the laboratory, creating a potential tension between their legal and ethical duties.

The 2014 revision also partly addresses the challenging question of what genes and diseases should be included on the list. For example, one could argue for the addition of genes such as *CDH1* (associated with hereditary gastric and breast cancer) or *PTCH1* (associated with Gorlin syndrome [basal cell nevus syndrome]) to the list but against *TP53* (associated with Li-Fraumeni syndrome, a rare genetic condition that greatly increases the risk of several types of cancer but with limited genetic testing—related actionability for those cancers). Indeed, the original list contained 57 genes, and one (*NTRK1*, associated with familial medullary thyroid cancer) was removed shortly thereafter. With the inclusion of the opt-out provision, those patients who may have reservations about the implications of learning about some of the variants on the ACMG list have a way to proceed with WES/WGS. Still to be addressed is what to do for many other genes for which a limited degree of evidence exists or not as compelling data are available on their clinical importance and actionability. The pre-event probability of a given clinical outcome depends on the clinical scenario of the patient population seeking genome sequencing: currently, a substantial proportion of clinical WES is being conducted in the setting of advanced cancer with a life expectancy limited to 2 years or less. The likelihood that a pathogenic variant that has not yet manifested itself will subsequently do so in the short time remaining is likely small. For some patients as well as their families, learning about this information may create an unnecessary burden. No doubt, for others the information may be a way for the patient to pass a legacy of potentially useful information on to surviving family members. We allow patients to make decisions about other