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Premature guidance about whole-genome sequencing

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Recently, several success stories about clinical use of whole-genome sequencing (WGS) and/or whole-exome sequencing (WES) have been reported. In some cases, sequencing led to improved decision-making and prognosis, and in at least a few cases, led to successful therapeutic interventions. Importantly, in each case, sequencing was performed on an individual with a serious clinical problem and the results returned related to the disorder.

At the American College of Medical Genetics and Genomics (ACMG) meeting in Phoenix (AZ, USA) in March 2013, the ACMG presented new recommendations on the return of incidental findings in clinical care. It recommended that incidental findings be sought out and reported regardless of age and that the results be reported to patients (or surrogates), regardless of their preferences. These recommendations were made despite the drafting Working Group's acknowledgement "that there was insufficient evidence about benefits, risks and costs of disclosing incidental findings to make evidence-based recommendations" [1].

It is our opinion that the ACMG recommendations clearly contravene respect for patients and shared decision-making at the clinical level and represent a setback to evidence-based

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medicine and the responsible development of societal policy. This article addresses five related issues:

- Guideline development;
- ‘Incidental’ findings;
- Informed consent;
- The ‘best interest of the child’ standard;
- The wider implications of the recommendations.

Guideline development

In 2011, the Institute of Medicine published guidelines for developing standards for objective, scientifically valid and consistent practice guidelines [2]. The Institute of Medicine standards related to eight key issues in guideline development [2]:

- Transparent process;
- Conflicts of interest;
- Composition of group developing guidelines;
- Systematic reviews;
- Evidence quality and recommendation strength;
- Articulating recommendations;
- External review;
- Updating.

The ACMG guidelines do not meet most of these standards. First, the ACMG failed to ensure the participation of many relevant stakeholders, such as primary care physicians, patients and parents. Second, the Working Group members disclosed numerous conflicts of interest. Merely reporting conflicts of interest does not eliminate the biases that may result from them. Third, the ACMG acknowledged the lack of evidence on which to make these recommendations and ignored potential costs: returning additional findings could lead to a diagnostic odyssey, long-term medical surveillance, involvement of family members in testing, iatrogenic harm and psychosocial consequences. Fourth, the recommendations do not consider who will be responsible for coordinating or paying for follow-up, and whether there is a need to recontact individuals as the list of conditions to report expands over time. The ACMG appears to assume that the return of results is an unqualified good that is cost-free or at least cost-irrelevant; either position is unrealistic. And yet, recommendations from an expert group have the potential to become the *de facto* legal standard of care, creating a situation in which even physicians who disagree with the recommendations will feel compelled to follow them.

Incidental findings

The ACMG recommends the active pursuit of specific ‘incidental findings’ – those related to 57 genes (revised to 56) identified by the Working Group as associated with significant and actionable health conditions [1]. No other findings are to be reported except those that relate to the clinical condition for which testing was performed. It seems an oxymoron to describe this purposeful and targeted analysis of 57 specific genes (revised to 56) as the identification of incidental findings; rather, it is better described as screening based on an assumed ‘duty to hunt.’ It ignores well-established criteria for screening [3], as well as

lessons learned from experience with nondirected population screening (e.g., newborn screening; NBS), in which the genotypic penetrance is often significantly lower than observed in symptomatic patients and may lead to more harm than good. At minimum, outcomes of this screening should be evaluated in controlled studies prior to guideline development.

Consent

The recommendation to override consent and shared decision-making is extraordinarily troublesome because it ignores longstanding principles of informed consent; one of the cornerstones of the physician–patient relationship. The rationale for the ACMG position is:

- It is too hard to counsel people about possible outcomes before testing;
- The results, once obtained, are too valuable for patients and their families to be allowed to refuse;
- Lack of low-cost, genome-based approaches for everyone means that WGS should be used for the benefit of patients and their families [1].

We believe these justifications are seriously flawed. First, the difficulty of pretest counseling does not justify dispensing with it. In a policy statement released by the ACMG in May 2012 entitled “Points to Consider in the Clinical Application of Genomic Sequencing,” the ACMG supported pretest counseling “by a medical geneticist or an affiliated genetic counselor and should include a formal consent process” [4]. In May 2013, the European Society of Human Genetics released its recommendations regarding WGS, clearly stating the need for the patient to know what he or she consents to, despite acknowledging the complexity of obtaining informed consent [5]. It recommended using targeted sequencing, rather than WGS, whenever possible. It also supported using the concept of ‘grouping’ or ‘binning’ genetic findings into categories to help explore what information patients may or may not want [5,6].

Second, the idea that patients can be forced to get information over their objection is almost unheard of elsewhere in medicine and is not warranted by the unspecified potential of third-party benefit. According to the ACMG, patients have no right to refuse information about specified mutations in 57 genes (revised to 56). Yet, in every state, competent adults have the legal right to refuse further testing or treatment. Thus, laboratories and physicians would be generating and reporting information the patient did not seek and, after receiving, would be free to ignore. Third, the lack of universal access to genome sequencing does not justify overriding the wishes of patients (or their surrogates), especially given the absence of any risk–benefit analysis and the unaddressed issues of payment for follow-up and third-party testing.

Testing children for adult-onset conditions

The traditional tenet of pediatric decision-making is the ‘best interest of the child’ standard, which has existed for decades in all professional statements regarding pediatric genetic testing. In 2013, the ACMG and the American Academy of Pediatrics published a joint policy statement and a technical report on genetic testing and screening of children that reaffirmed this tenet [7,8]. While these documents did not address WGS, they specifically addressed predictive genetic testing of children [8]: “The American Academy of Pediatrics and ACMG continue to support the traditional professional recommendation to defer genetic testing for late-onset conditions until adulthood,” a position affirmed by numerous international guidelines [9,10,101]. The new ACMG recommendations, with their ‘duty to hunt’, directly contradict this joint recommendation issued only a few weeks earlier, without

a persuasive rationale or any consideration of alternatives. Using a child's genetic sequence to inform parents and other third-parties about potential health risks is ethically problematic because it uses the child as a means and not as an end [11].

Wider implications

We believe there are a number of implications of implementing the ACMG recommendations that were not addressed. First, the ACMG recommendations imply that when a physician orders sequencing for any patient, it is a minimal burden and cost to search for other potentially actionable genes and to report the results to physicians and patients without explicit, prior consent. However, hunting for the 57 genes (revised to 56) is not minimal burden. It will require the laboratory professional to compare the participants' data to reference samples to identify unexpected variants and then compare these variants with the existing published literature to ensure that the variants are disease-causing [12]. Several reports suggest that the amount of time, effort and resources can be quite extensive [13,14]. How this will be reimbursed and by whom is not addressed.

Second, by recommending mandatory testing and disclosure of some rare disorders, genetic professionals will be increasingly interposed into sequencing ordered by numerous physicians, including sequencing for increasingly routine matters, such as pharmacogenomic testing. This will require a larger number of genetic professionals despite the fact that demand already exceeds supply [15]. Third, the ACMG statement has major implications for pediatrics given the breadth of conditions already included in universal NBS. If NBS evolves to employ genomic technologies and the NIH currently have a request for applications to this effect [102], then NBS will trigger the same 'duty to hunt' at the population level despite lack of evidence of the utility of this information in the general population. The European Society of Human Genetics recommendations considered the use of WGS/WES in neonatal screening and forewarned that "... the introduction of WGS/WES may widen the scope of testing beyond what can be justified in terms of the current classical screening criteria" [5].

Finally, if the ACMG recommendations for screening and mandatory disclosure beyond clinical indication are applied to all emerging fields such as proteomics, epigenomics and microbiomics, the result will be a dramatic expansion of screening in advance of an adequate evidence base. This is clinically and ethically unsound. We believe that the ACMG recommendations must be withdrawn. A broader, more deliberative and inclusive process to develop evidence-based guidelines is needed.

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