Crowdsourcing to Define the Clinical Actionability of Incidental Findings of Genetic Testing

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Genome-scale sequencing may soon be cheaper than targeted assays as a clinical diagnostic tool. However, these larger queries will turn up many incidental findings—that is, unanticipated information discovered during the course of testing. Implementation of genome-scale sequencing in the clinical setting will require novel methods for managing these incidental findings.

In order to grapple with our ever-changing knowledge of genetic disease and to make recommendations regarding minimal standards for reporting of incidental findings, a “binning” system for the management of such findings has been proposed; this system is based on both clinical utility and clinical validity [1]. Clinically actionable incidental findings (eg, Marfan disease) go into bin 1; these incidental findings are likely to be rare and would be reported to an individual because of high penetrance and the existence of evidence-based management recommendations. Incidental findings that have clinical validity but no clinical actionability go into bin 2; these findings require informed decision making on the part of the individual and would only be reported to the patient on request. In these cases, there may be a strong association between genotype and phenotype, but no immediate intervention exists; an example is APOE risk alleles that are associated with the onset of Alzheimer disease. As effective evidence-based interventions emerge for bin 2 variants, their classification will change. Finally, most genes currently have no known clinical significance. Variants of these genes go into bin 3, and these incidental findings would not be reported.

Although not strictly analogous, the bin 1 variants described above are similar to the incidental findings included on the minimal reporting list published by the American College of Medical Genetics and Genomics (ACMG) [2]. The ACMG working group that developed this list noted that their recommendations were hampered by lack of data on clinical utility and the need for a process by which recommendations could be updated regularly. The binning system described here tackles the lack of data on clinical utility and creates a process amenable to revision as new literature emerges.

So far, binning of genes has been provisional [3] and has been based on consensus among a small number of evaluators. In order to refine this approach into a more fully transparent, reproducible, evidence-based process, members of the North Carolina Clinical Genomic Evaluation by NextGen Exome Sequencing (NCGENES) team developed a semiquantitative metric that scores an incidental finding based on several key criteria: threat to health, chance of disease, efficacy of intervention, intervention acceptability, and knowledge base. This process yields a minimum total score of 0 (for genes with no known clinical relevance) and a maximum score of 15. A higher total score on this semiquantitative metric correlates with a greater degree of clinical actionability, which will hopefully allow us to
set thresholds for determining placement of an incidental finding into bin 1, 2, or 3.

Reaching consensus regarding medical actionability will require multiple evaluations, and it is neither feasible nor desirable for a single working group to score all genome-scale incidental findings. Instead, having a robust number of evaluators will allow for greater diversity of opinion and expertise.

Crowdsourcing has been shown to be a powerful tool for answering scientific questions that require a wide array of input. Crowdsourcing employs distributed problem solving by engaging the public through open-source interfaces. Proteomics research has been accelerated by utilizing the collective intelligence of the crowd through the online game Foldit, in which players attempt to solve protein structures. Some compelling successes have been achieved using this approach; for instance, players modeled the crystal structure of the Mason-Pfizer monkey retroviral protease, which has provided insights that may be useful in the development of anti-HIV drugs [4].

Other areas of genetic research have also harnessed crowdsourcing. SNPedia is an online, open-access wiki project that allows users to input information about single nucleotide polymorphisms obtained from peer-reviewed journals into a computer-friendly format [5]. In another example of crowdsourcing, the Personal Genome Project aims to pair genomic and health data supplied by participants. The project is approved to study 100,000 participants and shares all information in the public domain, making it available for research [6]; to date, more than 1,800 people are enrolled. Although efforts are made to remove personal identifiers from the data, the Personal Genome Project operates under the premise of open consent, meaning that participants are not given promises of privacy, confidentiality, or anonymity.

We propose that the scoring of incidental findings using a semiquantitative metric could also be amenable to crowdsourcing. Defining medical actionability through crowdsourcing allows multiple annotators to provide scores for a gene-phenotype pair, and information can be updated as new evidence emerges. More genetic conditions will likely become medically actionable over time. It is essential, then, to choose an evaluation process that is highly adaptable to evolving medical research; crowdsourcing offers this flexibility. NCMJ

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