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Incidental Swimming with Millstones

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> It would be better for them to be thrown into the sea with a millstone tied around their neck than to cause one of these little ones to stumble.
>
> — Luke 17:2

GENOME AND EXOME SEQUENCING HAVE NOW STARTED TO BE USED CLINICALLY and are providing definitive diagnoses for 15 to 50% of children with previously undiagnosable diseases (1–3). For these young patients, a diagnosis offers new hope of disease-specific treatment; for families, it is the end of the diagnostic nightmare and the means to plan for the future.

THE MILLSTONE

In March 2013, the American College of Medical Genetics and Genomics (ACMG) recommended that all reports of clinical exome and genome sequencing include clinical interpretations of variants in 57 genes, representing the known and likely causes of 55 diseases. These are diseases that are unrelated to the reason for ordering the test, and the variants are called incidental findings. Further, it was suggested that any procedural deviation be documented in the medical record (4, 5).

THE PREMISE

By detecting rare diseases, such as familial cancer syndromes, before disease onset, patients can elect to receive preventative, potentially life-saving medical or surgical treatments, as recently exemplified by the Angelina Jolie mastectomies. This reasoning is also the basis of the public-health success of mandatory newborn screening for 29 diseases (6). However, there is currently insufficient evidence to make objective statements about the benefits, harms, or costs of these new recommendations (4, 5).

THE PRACTICALITIES

At present, genome and exome sequences are of sufficient quality to permit clinical interpretation of ~70% of nucleotides that can be sites of pathogenic mutations. At these locations, ~50% of mutation types are detectable in genome and exome sequences with

SUPPLEMENTARY MATERIALS
www.sciencetranslationalmedicine.org/cgi/content/full/5/194/194ed10/DC1
Table S1. List of ACMG-recommended genes and diseases.

sufficient accuracy and precision for clinical interpretation. Thus, the real-world nuance is that although disease diagnoses are possible, diagnostic rule outs are not.

The sink-or-swim aspect of millstone swimming, however, is not technical but interpretative. Each potentially pathogenic variant in the 57 genes requires visual inspection of sequence alignments and determination of the allele frequency in the appropriate ethnicity, along with literature assessment of the evidence for causality and confirmatory testing by an independent method (7). Currently, the symptoms of the child guide the choice of which protein-coding genes, among the 20,687 present in the genome, are examined in great depth to minimize false-negative results. Considerable familiarity is needed for interpretation of variants in these genes—experience that is critically lacking, in part because of testing monopolies that have only been broken in the last month (8).

There are very few individuals who have the triad of expertise with genomic sequence analysis, qualifications to report molecular diagnostic test results, and familiarity with both childhood and adult onset genetic diseases. My great concern is that the millstone will have the effect of rationing clinical genome and exome testing, or that the quality of interpretation will be compromised because there are too few qualified interpreters. However, the backlog of undiagnosed children is immense, and early-adopter physicians for clinical genome and exome sequencing are critically dependent on accurate interpretation of diagnostic results.

BENEFITS AND HARMS

Most of the potential harms that stem from the ACMG recommendations relate to needless anxiety for patients and families and unnecessary procedures that follow false-positive results. The pretest probability of a true positive result in a disease gene that fits the symptoms of an ill child is high. In this setting, false-positive results are uncommon, and there is usually physician and family support for further confirmatory tests to weed out the few that do occur. In contrast, the pretest probability of a true positive result in these 57 genes in the general U.S. population is less than 1 in 1000. In this setting, there are likely to be 20 false-positive results per true positive. Although well intentioned, the incremental complexity and cost of the ACMG recommendations will have the unwanted effect of physicians choosing familiar genetic testing one disease at a time instead of clinical genome and exome sequencing. The suffering of thousands of undiagnosed children will be prolonged so that future diseases are prevented for tens.

HOW THEN SHALL WE LIVE?

In the interim, the medical genomics community needs swimming lessons. Indeed, the incidentalome genie was freed from its bottle ~405 PubMed articles ago. The number of incidental genes and diseases that are designated material for reporting will increase inexorably with medical genomic knowledge. The guidelines have defined only an initial bright line for interpretation. Scientists who swim with millstones require further guidance:

- We need authoritative public reference databases of pathogenic and nonpathogenic variants in the 57 incidentalome genes to which interpretative guidelines—ACMG or others—are tied (7).

- We need public software for computation of the nucleotide sequences and mutation-harboring nucleotides of the 57 incidentalome genes that have been sequenced sufficiently to merit interpretation on a sample-by-sample basis.
- Physicians, patients, and families of ill children need opt in/opt out provisions. The choice of being tested to diagnose the illness that prompted the physician visit is quite different from that of being incidentally tested for an uncommon future illness. For example, having to report the risk of future cancer syndromes for critically ill neonates or at end of life is absurd.
- An appealing alternative is to perform clinical genome and exome sequencing without ever seeing the incidentalome. There are two ways to do this. One is to sequence only part of the exome-targeted gene panels that comprise only the set of genes that match the child's symptoms. The other is to do this computationally. If the patient's symptoms are entered at test order and bioinformatically matched to all "on-target" disease genes, downstream computational processes can automatically be set to apply to only those genes (1). This is determined by an opt in/opt out box at test order.
- We need new methods for automated genetic variant confirmation other than polymerase chain reaction assays and Sanger sequencing.
- It is critically important that the curator of clinical genomics guidelines—the ACMG— begins to objectively measure the benefits and harms of its recommendations to guide the drafting of future guidelines.

The children are waiting. Let us not cause one of these little ones to stumble.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Biography

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