OPINION

Incidental findings

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Every physician or scientist who sequences whole genomes, either as part of patient care or research, has had to grapple with the question of how to deal with ‘incidental findings’ — genetic variations that may increase a person’s risk of disease but are unrelated to the disorder under study. How much should people be told?

On one side of the debate lie those who believe that patients and research participants are entitled to any and all information about their genomes. On the other side are those who worry that disclosing incidental findings, given the uncertainty of their meaning, could trigger undue anxiety and perhaps excess medical costs, as physicians search for signs of a disorder that may never arise.

No consensus guidelines yet exist to delineate which mutations to report, though some members of the clinical genetics community have called for the development of a list that classifies variations as high or low-risk.

A new study, published online 15 March in *Genetics in Medicine*, **explores the variability of**

opinion among different experts on the types of genetic findings that should be reported back to an individual's physician.

Researchers gave 16 clinical geneticists or molecular lab directors — physicians and scientists on the front lines of genomics — a survey listing 99 common genetic conditions and individual genes and asked them whether or not they would report the information to the individual's physician.

For each condition or gene, the experts were asked to make a decision based on a number of potential conditions: that the individual is an adult, that he or she is a child, that the variation is a known mutation that has already been linked to the disease, a mutation that truncates a protein and is therefore assumed to be linked to the disease, or a mutation that is predicted to disrupt the protein and thus likely to be linked to the disease.

The specialists did not consult with one another and were asked to assume that the individual under study had no clinical features of the disease, that no family history was available, and that the sequencing data were perfectly accurate.

The list of genes and disorders in the survey included those linked to Rett syndrome and **fragile X**, as well as deletion of 22q11.2, which has been **linked to increased risk of schizophrenia** but not other autism-linked mutations or **copy number variants**.

According to the findings, specialists agreed on many counts: All 16 favored reporting information on 21 conditions to adult patients. Most of these were variations that increase risk of cancer or metabolic disorders, such as phenylketonuria, a rare inability to break down the amino acid phenylalanine.

They also tended to agree that information should be returned to a physician when the patient or research participant is an adult, and when there is the opportunity to intervene to decrease the risk of the potential disorder, such as a predisposition to cancer.

But there was less agreement over how to deal with findings pertaining to children, including mutations that increase risk of neurodevelopmental disorders, mutations with only a presumed or predicted risk, and disorders without the potential for direct medical intervention.

Individual specialists varied significantly in their opinions. For example, one thought results from only 30 percent of the genes or disorders in the study should be reported, whereas two others thought that the physicians who ordered the test should get 100 percent of the information.

As the authors point out, the study has significant limitations. Most physicians won't make decisions in a vacuum, without information on family history or patient preference. (Some people want to know more about uncertain medical risk than others.) And the authors did not attempt to survey a representative sample of genetics experts.

But hopefully the findings will trigger a more exhaustive discussion of how to deal with incidental findings in genomics, a problem that is only going to grow as the cost of sequencing drops and whole-genome sequencing becomes a more common tool in medicine.

The **Medical Genetics Laboratories** at Baylor College of Medicine in Houston, Texas, for example, now offers exome sequencing — reading the DNA of the gene-coding part of the genome — as one of its clinical services, with whole-genome sequencing not far behind.

The researchers say the next steps will be to learn what patients and research participants want to know about their genomes, and to better understand why specialists' opinions vary so widely.