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Incidental Findings in the Era of Whole Genome Sequencing?

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The rise of technologies that can inexpensively sequence entire genomes means that researchers and clinicians have access to ever vaster stores of genomic data, some of which could be of great use to research participants or patients, and most of which, at least for today, will be of little, uncertain, or no use.[1] Those facts are essential features of a new ethical territory we are now entering with genetics research. As we explore that territory, we should try to be as clear as possible about the issues at hand.

In the old territory, researchers and clinicians, in tandem with genetic counselors, were obliged for the most part to help research subjects and patients think about the meaning of one highly penetrant gene for one disease. Not only was the predominant target of "genetic" —not yet "genomic"— investigation different then, but so was the social context. The social institution that is genetic counseling emerged out of reflection on a half-century's worth of physician-endorsed efforts to cleanse the human gene pool, and it aspired to protect vulnerable persons from any similar future efforts. That is a far cry from the territory we inhabit today, where reasonable patients clamor for genetic information and reasonable ethicists argue that, to promote everyone's health, we should think of individuals less as *needing protection from* researchers and clinicians and more as *collaborating with* researchers and clinicians in making contributions to "learning health systems."[2]

Clarity about the ethical issues that delineate this new territory requires that we be wary about too hastily importing into it concepts from the old territory. We want to suggest a way in which the term "incidental findings" can impede our ability to see clearly some of the most important issues we face. To show how that term can sometimes obscure more than it illuminates, we focus on how it is being deployed in the context of research. Although it may have been useful, when considering older forms of genetic research, to speak about researchers stumbling across clinically significant findings, and although that way of speaking has certainly not yet become wholly obsolete, it is ever less appropriate as the technology becomes ever more powerful. As a result, the term "incidental findings" is becoming an obstacle to thinking clearly about when researchers may have an obligation to offer findings to research participants.

"Incidental Findings" in Genomic Research

The deluge of genetic data that research is now generating raises a widely recognized and basic question: Do researchers have an obligation to return any results to research participants, and if so, which sorts of results are they obliged to return? The first part of that question concerns the nature of the researcher's role. Despite ongoing debate about the optimal way to understand what that role entails,[3] there is a good deal of support for the proposition that it entails researchers sharing at least some individual results.[4]

The second, intimately related, but harder part of that question concerns which results researchers are obliged to return. We might say it concerns the nature of the results. There does seem to be an emerging consensus that researchers are obliged to return clinically useful results,[5] even if there is not yet agreement about the definition of clinical utility. (Some observers have a relatively strict conception, which requires that the finding serve as the basis of an intervention that has the potential to change someone's health status;[6] others

have a more expansive conception of clinical utility that extends to information that would facilitate life;[7] and others have a still more expansive view in which the offer of information, regardless of its actionability, is construed as a sign of respect for the individual research participant.[8])

Notice that the answers to the basic questions concerning whether and which results to return have nothing to do with the *intention* of the researcher at the time she collected the data. If researchers are obliged to return data indicating the presence of a mutation that markedly increases the risk of disease, that duty applies whenever such information is in their hands, whether they intended to find it or not. Unfortunately, however, the complicated conversation about which results to return to subjects risks becoming still more complicated if we use a term that gives unwarranted attention to just that: the researcher's original intention.

The term "incidental finding" gained traction in the literature about large-scale genomics research in an important 2008 article by Susan Wolf and colleagues.[9] In that article, Wolf et al. defined an incidental finding as "a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study."[10] They offered the example of a finding "on a genomic microarray suggesting a genetic or chromosomal variant of potential clinical importance beyond the variants of genotype/phenotype associations directly under study." Later in that same paper, however, they acknowledged that in the context of research that explores a large part of the genome at once, the idea that researchers should attend to incidental findings is problematic. When we turn to the sorts of large-scale genomic epidemiology or "discovery research" that biobanks can facilitate, "it is harder to identify what might be an [incidental finding], as any genomic pattern correlating with pathology may be captured and studied."[11] In the context of such research, as Mildred Cho had observed in a short essay accompanying the article, "it could be said that nearly nothing is 'incidental' because very little is outside the scope of the research question."[12] (Since then, other scholars have noted the same problem.[13]) That is, Wolf et al. acknowledge the respect in which the notion of looking for one thing and stumbling upon another—the key idea built into the term "incidental finding"—just may not be particularly relevant or helpful for thinking about the problems that arose with the emergence of many uses for microarray technologies, and that we think are even more striking in whole exome or genome sequencing.

When Wolf et al. published their second major paper, in 2012, they were even more keenly aware of concerns about the helpfulness of using the term "incidental finding" in the context of large-scale genomic research. They wrote that "in large-scale discovery research it is difficult to identify what is 'beyond the aims of the study' because the entire genome is under scrutiny and the research is inductive … rather than … driven by discrete hypotheses."[14] But they defended their continued use of the term with two examples in which it remains wholly pertinent. The first example is of a genomics researcher who during the enrollment phase of a study discovers that a potential participant has elevated blood pressure. The second is of a researcher who, using a genome-wide association study to investigate breast cancer, stumbles upon a mutation associated with colon cancer. Their point is important: the fact that "incidental findings" cannot illuminate all of the new territory does not mean that it is now useless.

In a further clarification, Wolf et al. formally distinguish between incidental findings and what they call "individual research results." They continue to define an incidental finding as a finding of potential health or reproductive importance beyond the original aims of the study, and now define an individual research result as a finding "discovered in the course of

the research, when the finding is on the focal variables under study in meeting the stated aims of the study."[15] That is, individual research results are also defined in terms of the researchers' intention: if the researcher was not looking for the finding, then it's an incidental finding; if she was, then it's an individual research result. This distinction surely has a place. We are merely calling attention to the way in which its emphasis on the researcher's intention can distract us from the more salient issue: the nature of the result, and the question of which results should be offered to research participants.

It bears repeating: we fully recognize that genomic researchers today do not always screen an entire genome for all pathologic variants. They often restrict their analyses to identifying polymorphisms or mutations associated with the disorder that is the focus of their study. In such cases, they may indeed stumble across clinically actionable findings, and the term "incidental finding" will remain pertinent. For studies in which larger sections of the genome are interrogated, the scope of potential findings will be broader and the notion of "stumbling upon" results less pertinent. As screening and interpreting data become simpler and more accurate—and as analysis pipelines are built to automate detection of known disease-associated mutations throughout a genome—the likelihood of uncovering many variants relevant to a large number of disorders will become the rule rather than the exception, and the term "incidental finding" will not be pertinent. Some observers have already begun to ask if researchers have an ethical obligation to look actively for all known significant variants[16]—a practice that, if adopted by regulation or professional consensus, will render the discovery of actionable findings less contingent on the procedures of a given study and diminish the importance of the distinction between incidental findings and individual research results. Once researchers are aware of having readily identifiable, clinically significant findings, how they got there is not material to the question of their disposition. It is the nature of the findings, not the original intention of the researcher, that matters.

The Future of "Incidental Findings"

So much for the research context. Another way of seeing the infelicity of "incidental findings" is to look at recent recommendations from the American College of Medical Genetics regarding the *clinical* context.[17] Those recommendations say that clinical labs should now be required to analyze fifty-seven genes that increase the likelihood of diseases for which there is an intervention, regardless of the specific disease that the clinician intended to investigate when she ordered the sequence. If laboratories are essentially required to look for variants that are clinically actionable, then it is rather hard to see in what sense those results are "incidental." Although the authors of the ACMG recommendations seemed tacitly to acknowledge this problem when they parenthetically added "or secondary" to modify "findings," they apparently were not yet prepared just to leave "incidental" behind, even though, in that context, it obscures more than it illuminates.

As we move forward, attempting to craft policies that efficiently and ethically promote the health of everyone, we have to remember that the technology in use today, which in principle can, with a few key strokes, investigate every published disease-associated genetic variant, is different from the technology in use when the term "incidental finding" was more pertinent. Our approaches have to take into account the real costs associated with generating and reporting such information (for example, with using laboratories that meet the standards of the Clinical Laboratories Improvement Amendments and with advising patients about the implications of the findings). We may have to give up our current model of allocating one counselor to help one patient or research participant think about what findings regarding one gene and disease will mean for her. Not using "incidental findings" when it is no longer

pertinent is one way to signal that we know we're in uncharted territory, and that we need new terms to illuminate it.

We highly doubt that there is a single, new term that will all at once illuminate this new territory and make our policy conversations more coherent. If pressed to recommend a term to *supplement* "incidental findings"—for those cases in which a result has in no sense been stumbled upon—we would tentatively suggest "individual genomic result." The term avoids the problem of giving undue attention to the researcher's or clinician's intentions. To the extent that the term is vague, the vagueness may be a virtue. It reminds us of the real, difficult work that remains: articulating criteria to distinguish between individual genomic results that do—and do not—warrant an offer to return to research participants or patients.

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