Introduction
The Challenge of Incidental Findings

Susan M. Wolf

At first, the problem of incidental findings may seem, well, incidental — "unpredictable," "minor."[1] So much attention has been devoted for so long to the challenge of structuring human subjects research, that turning now to the question of how to handle information that is generated unexpectedly in the course of conducting research but may be important to the research participant's health or reproductive decisions may seem very much a side issue. If the brain scan of a healthy adolescent participating in a functional magnetic resonance imaging (fMRI) study of cognition looks abnormal — with a big bright area suggesting a tumor — or the scan of an asymptomatic volunteer in a computed tomography (CT) colonography study shows a 5 mm nodule at the base of the lung, surely someone knows how to handle this. If a family pedigree study aiming to unravel the genetics of an inherited disorder unexpectedly reveals misattributed paternity, there must be some standard approach to handling this potentially explosive information. And as genomics researchers analyze, archive, and reanalyze large stretches of the human genome — indeed, the whole genome in genome-wide association studies (GWAS) — we know that they will stumble upon all sorts of information of potential health and reproductive importance. Surely, someone knows how to handle that.

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The truth is that no one knows how to handle these difficult questions. There is no consensus as yet on how to handle incidental findings in human subjects research. Though a substantial debate has erupted over whether to offer research participants individual research results, especially in genetic and genomic research, much less discussion has focused on incidental findings. Research results and incidental findings are sometimes conflated, but there are important differences. Researchers are likely to be experts in interpreting research results; after all, the goal of their study is to generate just such results. But incidental findings are discovered in the course of doing research yet beyond the aims of the study; the researchers may lack the expertise to interpret them. In addition, the clinical implications of research results may be unclear (achieving greater clarity may indeed be the very point of the research). In contrast, the clinical implications of incidental findings may be quite clear and call for urgent clinical attention.

The problem of incidental findings is intrinsic to human subjects research; we simply have not focused on it systematically. Brain imaging studies report incidental findings in a range from 13 to 84 percent of the scans, depending on the subject population.[2] CT colonography studies reveal extracolonic findings about half the time in asymptomatic subject populations[3] and more than half the time among symptomatic subjects.[4] Family genetic studies regularly reveal misattributed parentage at an estimated incidence of 10 percent, though we lack clarity on the actual incidence in different study populations.[5] And researchers are just beginning to worry about the scale on which we may encounter incidental findings in genome-wide studies using genomic microarrays or gene "chips."

As research becomes increasingly large-scale using powerful technologies, the problem of incidental findings is becoming more serious. Genomic microarrays, scanning technologies, and other research instruments now generate massive amounts of information. Some of that information is the data that the researchers are seeking in order to answer their research question and achieve the aims of their study, but much of that information is incidental. From the moment researchers first encounter a potential participant and begin collecting baseline information to ascertain the person's eligibility to be part of the study, researchers have to face the fact that they may come across incidental information of potential clinical or reproductive significance. And in this era of archived samples, DNA, and information organized by computers into large databanks available for reanalysis well into the future, it is not clear when the problem of incidental findings ends. If secondary researchers reanalyzing genomic information collected for one study stumble upon genetic information suggesting vulnerability to serious side-effects from a commonly used drug, or realize that their dataset sheds light on research participants' vulnerability to avoidable cardiac disease, the problem of incidental findings arises even though it may be years since the samples were first collected.

Confusion over how to handle incidental findings bedevils not just researchers. It is not clear what Institutional Review Boards (IRBs) should demand, what funders such as the National Institutes of Health (NIH) should expect, what professional societies should urge, or most importantly what the human beings who generously and often bravely participate in research should anticipate. The lack of agreement and standards turns out to be a very serious problem. In practical terms, it can mean that researchers unexpectedly encounter a potential clinical problem that may be serious, even life-threatening, and have no idea what to do. They may rightly worry both about failing to report the finding promptly to the research participant and, conversely, about reporting it, prompting anxiety and burdensome evaluation, only to discover that there was nothing really there. For their part, research participants may expect that researchers looking at an organ system or at their genetics will report anything of clinical concern, even though the researchers may not take this view at all. On the other hand, participants who sign on to participate in a certain research study may be flabbergasted to get a phone call later offering information of potentially grave clinical import that seems completely unrelated to the study. Indeed, the clinical benefit of reporting silent cancers or genomic deletions incidentally discovered in research may be far from clear.

All of this means that the problem of incidental findings is serious, ubiquitous, and growing. It is also an enormous challenge. It raises vexing questions of how to protect the scientific enterprise while doing right by human participants. It makes us face the diagnostic limits of research information – the research scan that is not optimized for clinical diagnosis and yet seems to show a serious anomaly, or the genomic information anonymized for inclusion in a databank that nonetheless reveals information sufficiently serious that researchers consider finding a way to recontact the participant. It forces us to rethink the traditional divide between researcher obligations to research participants and physician duties to patients – should the scientist, especially the non-clinician Ph.D., turn away from the sign of potential tumor on the brain scan or the ominous deletion in the genomic analysis? After all, the traditional view of researcher obligations may absolve the researcher of clinical duties to care for the research participant. And from the standpoint of the research participant, being offered information on incidental findings may yield benefit, but may also produce risk and harm.

The problem of incidental findings is thus a ferocious tangle of science, medicine, and ethics. The problem forces us to confront the limits of the research enterprise, its relationship to clinical medicine, and how we conceptualize — or must now reconceptualize — the researcher role. At the end of the day, this is also a problem of law. How should we read the Com-

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mon Rule[6] and federal guidelines governing human subjects research to address incidental findings? And where does potential liability lie? Those universities and researchers that have addressed incidental findings thus far in their consent forms and guidance documents posted on the Internet show widely divergent approaches, from a declaration that information about incidental findings will not be returned to the research participant to a promise to seek expert clinical consultation on incidental findings and report those of significance.[7] Both approaches could do harm. Courts have yet to speak to the problem, but inevitably will.

This challenging tangle of science, medicine, ethics, and law drew my colleagues and I to assemble a national group of expert collaborators for a two-year study of incidental findings funded by the National Human Genome Research Institute (NHGRI) at the National Institutes of Health (NIH). We focused on genetic and genomic research, comparing emerging approaches to incidental findings in imaging research, particularly neuromimaging and CT colonography research. We combined empirical study of how publicly available guidance documents and research consent forms currently approach incidental findings with normative analysis to arrive at a consensus analysis and set of recommendations. Individual project members wrote their own additional analyses to further explore pieces of the puzzle. In May 2007 we convened a major public conference to present and debate our findings and conclusions (see <www.lifesci.consortium.umn.edu/conferences/incidentalfindings.php>). The conference featured not only project members, but also distinguished policymakers and leading scholars, reacting to our analyses and offering their own perspectives.

This symposium is the result of our work. We present here our consensus paper, as well as individual papers from project members and from extremely thoughtful collaborators who presented at the conference. We believe this is the most concentrated, in-depth work to date on the problem of incidental findings. It turns out that this problem has enormous implications for the rights and welfare of research participants, forces a reconceptualization of the role and duties of researchers, and requires IRBs, regulators, and funders to address difficult new questions at the boundary of research and clinical care. In short, it turns out that the problem of incidental findings is not "incidental" at all.

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