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'Pandora's box' of incidental findings in brain imaging research

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The title of Grossman and Bernat's editorial[1] 'Incidental research imaging findings: Pandora's costly box' captures perfectly the discussion, and sometimes heated debate, about the complexity of handling such findings in research. The debate centers on a scenario involving an imaging protocol and a research subject who has a brain anomaly. If the subject is a healthy control, the anomaly is unexpected. If the subject is a patient, the anomaly is unrelated to the purpose of the imaging study.

The important choices about what to do with such a finding are indeed all potentially costly. The choices can be appreciated in relation to axes of an imagined 3-dimensional problem space: incidence and significance (*x*-axis), disclosure (*y*-axis), and duty of care (*z*-axis). I will discuss these dimensions in terms of ongoing work and the state of the current discussions and argue that, although the scientific community must vigorously continue its solution-seeking efforts, there will ultimately be no single approach to the problem space defined by these dimensions. A minimum set of practice standards are needed to enable investigators to protect their participants, to insure that participants understand the limitations of those protections, and to promote trust and reciprocity in the research process.

The discussion about clinical findings discovered in brain-imaging research was sparked by a series of publications about their incidence and significance. Tens of thousands of brain-imaging research studies are performed each year. Current data suggest that about 15% of asymptomatic research subjects have a brain anomaly; in 2–8% of all asymptomatic subjects, the findings are clinically significant.[2–4] These data reflect higher rates than some population studies,[5,6] but seem to vary consistently with age, gender, and even with the geography of the data taken. Procedures for handling these findings in the research environment vary substantially, and range from strict protocols to ad hoc procedures.[7] Subjects have reported that they expect that if an abnormality is present it will be discovered and disclosed to them.[8]

Assume that following a series of empirical studies of false-positive rates, the established upper limit is 2%; is this frequency sufficient to justify ongoing concern or an investment in practice standards? This figure is higher than the adverse event frequency of greater than 1% that necessitates a warning on drug labels in the US. But what are the costs—financial and personal—of findings that are found on follow-up to be inconsequential? On the other hand, what if even one subject per year is affected by a missed finding? Varying appreciation among investigators of the different cost : benefit ratios reflects an important source of ongoing debate.

In a workshop co-sponsored by several institutes of the National Institutes of Health (NIH) and Stanford University, broad consensus was reached over certain fundamental principles governing the approach to incidental findings in brain imaging (J Illes, unpublished data). Among these principles was that researchers must respect the subject's right to privacy—the right to know and not to know—and therefore anticipate the possibility of detecting brain anomalies in their research. The methods for dealing with this possibility must be clearly articulated in Institutional Review Board protocols and consent forms. A majority of the group favored disclosure of an incidental finding, but these members also recognized the right of a participant to opt out of disclosure—two different points on the continuum represented by the *y*-axis. A minority of participants articulated that incidental findings in research should not be disclosed, given the current state of knowledge and the possible consequences of false positives. Although among the majority group, I remain wary about the subject opt-out option, even though it has precedent in the genetics and medical-screening literature. In the event of a life-threatening finding—however frequently or rarely this occurs—withholding this discovery does not seem realistic, even

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if the subject opted out of disclosure when providing informed consent. This is an option that assumes a great deal of *a priori* knowledge about the brain and brain scans on the part of volunteers. Potential medical urgency represents a case where paternalism may well prevail over subject autonomy.

Duty of care, on the *z*-axis, is inherent to the medical profession. Some have argued that only neuroradiologists are competent to clinically review images of an incidental finding detected in research, especially because subtle abnormalities can be particularly difficult to detect. Others have argued that subspecialists from other medical disciplines who routinely handle brain images can serve this function. This might be, in part, a turf battle that is not uncommon in medicine. Of far greater importance then, assuming that the criterion of competence is met, is the ensuing obligation of the physician involved. As a gatekeeper whose function is confined to research, a collaborating physician is obliged to determine only whether a detected finding requires clinical evaluation. A report is made to the Principal Investigator or to his or her designate, stating whether a finding requires follow-up. Duty of care in the context of research has been fulfilled (unless the Principal Investigator is a physician who elects to lead the clinical evaluation, in which case, duty of care continues). The benefits of this approach are efficiency and expediency. Although medical training does not guarantee good bedside manner, a legitimate question is, however, whether a PhD-trained Principal Investigator who has had no medical training is skilled to communicate clinical and potentially sensitive information to a subject. The difficulty of this situation could be heightened by the stress on subjects when they have to wait to learn whether a finding is clinically significant, and by possible downstream financial costs that might be incurred during follow-up. Even if the communication issue is resolved, a conundrum remains about whether all scans should be read by a physician or whether sheer numbers make this prohibitively expensive. Compounding the potential burden of physician involvement is the issue of access to physicians at an imaging facility not affiliated with a medical center.

The discovery of incidental findings in clinical medicine and in research raises difficult questions. The questions are particularly acute in the research setting and are not easily resolved. Besides imaging, incidental findings have arisen in a number of other research contexts, most notably blood donation and genetic testing. There are no standards for how to deal with such observations. Pleiotropy—associated or secondary effects—makes the problem even more acute.[9]

It is important to emphasize the early stage of these efforts in understanding the impact of incidental findings in imaging on researchers and practitioners, and on their research participants, institutions and sponsors. Specific details about solutions notwithstanding, costs will be best contained and benefit maximized with the guidance of a good framework, and with a professional community that is open to all perspectives and is forward thinking through these endeavors.

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Competing interests

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