

Research Malpractice and the Issue of Incidental Findings

Alan C. Milstein

The ability to search for the truth implies also a duty; not to conceal any part of what one has found to be true.

- Albert Einstein

Magnetic resonance imaging (MRI) and functional MRI (fMRI) are important tools for neuroscience research because of their capability for investigating both the structure and function of the brain.¹ The fMRI image extends traditional anatomical imaging of the MRI to include maps of human brain function. The ability to observe brain function opens an array of opportunities to research brain organization, neurological status, and neurosurgical risk.² Neurological research is, thus, burgeoning.³ For example, Columbia University currently has several ongoing protocols investigating fMRI's future role in neurosurgical planning, pain management, and understanding the physiological basis for neurological disorders as well as cognitive and perceptual events.⁴ One can imagine research proposals, both important and trivial, on such topics as whether brain imaging can shed light on the nature of dreams, memory, speech development, love, anger, or addiction.

Consider this fact pattern from one of my case files.

A psychology professor at a well respected university designs a study to explore whether attention deficit hyperactivity disorder (ADHD) is associated with a physiologic defect in the brain. As principal investigator (PI), she recruits potential subjects in poor neighborhoods, offering \$680 to any parent who signs the informed consent document allowing a child to participate. Each child as young as eight is given a single dose of methylphenidate or Ritalin, which the protocol says is equivalent to three cups of coffee. An MRI is then performed to see whether the brains of the healthy children show any physiologic difference from the brains of the children diagnosed with ADHD who had also just ingested the drug. The plan is to include 1000 volunteers, divided equally between those who had been diagnosed with ADHD and those who had not.

The PI and the IRB should know from the scientific literature, in designing and approving such a study, that brain MRI will reveal significant abnormal brain morphology in two to eight percent of the scans exam-

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ined, a subset of the variations that are likely to be revealed in as many as 20 percent of the scans.⁵ These variations can range from relatively benign findings such as chronic sinusitis to serious conditions such as cysts or tumors.

Indeed, recent studies reveal an extraordinary number of incidental findings in neurological research. One such study characterized the frequency and severity of incidental findings in brain MRI and fMRI of 151 adult volunteers.⁶ The results revealed incidental findings in 47 percent of the total number of scans examined, 6.6 percent of which required follow-up.⁷ Of the total findings, 9.8 percent required a routine referral and four percent required urgent referral.⁸ Although there were more findings in older subjects, all referrals of older subjects were routine, whereas 75 percent of the findings in younger subjects (although only four in number) were considered urgent.⁹ The study concluded that standards are needed to guide investigators in managing and communicating incidental findings, but did not propose standards other than addressing in the consent form the possibility of incidental findings.¹⁰

Another study revealed even more disturbing data.

Indeed, recent studies reveal an extraordinary number of incidental findings in neurological research. One such study characterized the frequency and severity of incidental findings in brain MRI and fMRI of 151 adult volunteers. The results revealed incidental findings in 47 percent of the total number of scans examined, 6.6 percent of which required follow-up.

There, the investigators identified the prevalence of incidental neuroradiologic abnormalities in adults with past occupational exposure to lead.¹¹ Incidental findings were detected in 84 percent of the subjects; 30 percent of whom required no referral, 51 percent required routine referral, 17 percent required urgent referral, and 1.5 percent required immediate referral.¹² Again, a greater number of incidental findings were identified in the older population.¹³ The investigators concluded that such findings underscored the need for radiologists to evaluate the anatomic images generated by research studies, particularly those from older subjects.¹⁴

Evaluating different procedures for managing incidental findings in brain research studies, one researcher found extraordinary variability in procedures to detect and disclose incidental findings to subjects. The variables included whether or not a neuroradiologist was involved and the competency and training level of the research staff.¹⁵ In this study, investigators detected incidental findings in 82 percent of the subject population.¹⁶ With respect to the qualifications of the staff primarily responsible for imaging, 41 percent of the staff were students and 21 percent were post-doctoral or professional personnel. Only 38 percent of the protocols required that radiologists conduct scans.¹⁷ Only 53 percent of the protocols involved procedures for managing and disclosing incidental findings to the subjects.¹⁸ All other protocols proceeded on an ad hoc basis.¹⁹

IRBs required neuroradiologist involvement in only 22 percent of the research protocols.²⁰ Of those that did not require a neuroradiologist, scans were consistently read 13 percent of the time, upon suspicious findings 69 percent of the time, and never read 18 percent of the time.²¹

The problem, of course, is money. As one commentator admitted, “Current procedures for handling incidental findings may be adequate...because more stringent procedures would be ‘difficult to implement in terms of both practicality and costs.’”²² The consequence of requiring researchers to budget for managing incidental findings, according to another commentator, is “in the present financial climate...that half as much research gets done, and that has, in my mind, a much greater impact on society and the health of society than the very, very low incidence of incidental findings which are actually correct and an even lower incidence where there is something you could have done.”²³

Leaving aside the question of whether the study from my case files above is ethical — and in my view it clearly is not²⁴ — the foreseeability of such incidental findings raises several questions for the IRB and for the design and budgeting of the research protocol. These include the following:

1. Must a board-certified or board-eligible radiologist review the MRI scans to look for any abnormality?
2. Must the MRI scanning be conducted in accordance with standard medical practice for reviewing the clinical status of the whole brain even if

the PI is concerned with only one portion of the brain captured in one MRI sequence?

3. Must the informed consent document disclose the potential that incidental findings of abnormalities might be revealed, and what consequences might follow if they are?
4. If any abnormalities are incidentally revealed, must the subjects be promptly informed by a physician capable of explaining the significance of the findings and the alternatives available?

Perhaps not surprisingly, I would answer each of these questions with an emphatic “yes” because of the researcher’s duty to protect human subjects. More-

created between researchers and their human subjects; and (3) government regulations can also create duties on the part of researchers toward human subjects out of which “special relationships” can arise.²⁷ The court held that “[a] ‘special relationship’ exists in circumstances where such experiments are conducted,” based upon the consent form, the relationship between researcher and research subject, federal regulations governing human subjects research, and the Nuremberg Code.²⁸

With respect to the informed consent document, the court found that the representations in the document create a bilateral contract between the parties, hold-

In one example, a former neuroanatomy teacher, soon-to-be father and professed “neuro-nerd,” volunteered for an MRI of his brain which revealed a golf-ball sized tumor. The diagnosis came just before he applied for additional insurance for his family, which was subsequently denied as a result of the incidental finding. He now says that he “should have thought about the consequences of volunteering more thoroughly.”

over, I would submit that if the failure to take any of the above actions results in the exacerbation of disease or injury that was or should have been revealed by the MRI, then the PI and the members of the research enterprise should face substantial liability. The basis for such liability lies in the special relationship between researcher and human subject.

Once the research subject or the guardian for a minor subject signs the informed consent document, a fiduciary relationship is formed between the PI and the research subject. The very nature of scientific research on human subjects creates special relationships out of which fiduciary duties arise, similar to the physician/patient relationship. The fiduciary relationship is formed not only by the informed consent agreement between the parties, but also by the trust the subject necessarily places in the researcher. In the context of human subjects research, a special relationship is created between the human subject and those responsible for the design, approval, and implementation of the experiment because the latter have a duty to protect human subjects both under the Common Rule²⁵ and common law.

In *Grimes v. Kennedy Krieger Institute*,²⁶ the highest court of Maryland held, in the context of a human subject experiment, that (1) informed consent documents create “special relationships” giving rise to duties; (2) such “special relationships” are normally

ing that informed consent imposes obligations and confers consideration on both researcher and subject. The court further reasoned that

[r]esearchers cannot ever be permitted to completely immunize themselves by reliance on consents, especially when the information...is incomplete in a material respect. A researcher’s duty is not created by, or extinguished by, the consent of a research subject or IRB approval. The duty to a vulnerable research subject is independent of consent....²⁹

The court went on to describe the nature of the “special relationship”:

A special relationship giving rise to duties, the breach of which might constitute negligence, might also arise because, generally, the investigators are in a better position to anticipate, discover, and understand the potential risks to the health of their subjects. Practical inequalities exist between researchers, who have superior knowledge, and participants....

This duty requires the protection of the research subjects from unreasonable harm and requires the researcher to completely and promptly inform the subjects of potential hazards existing from time to time because of the profound trust that participants place in investigators, institutions, and the research enterprise as a whole to

protect them from harm. Faced with seemingly knowledgeable and prestigious investigators engaged in a noble pursuit, participants may simply assume that research is socially important or of benefit to them individually; they may not be aware that participation could be harmful to their interests.³⁰

A fiduciary duty requires not simply ordinary care but the highest standard of care imposed by law.³¹ This duty is imposed because of the trust that human subjects will naturally have in the researcher. The word “fiduciary” itself comes from the Latin *fides* meaning “faith.”

Both the seriousness and probability of harm contribute to a duty to prevent it.³² In the Illes et al. study previously described, incidental findings were identified in 47 percent of the healthy subjects.³³ Of the younger participants who had findings, 75 percent of them required urgent referral.³⁴ Of the entire population of subjects, urgent referral was necessary in four percent of the subjects.³⁵

Given these data, and the requirement of a high degree of care in any fiduciary relationship, how

that a radiologist read every research scan.³⁸ Many institutions, however, still use what is referred to as the “Good Samaritan approach,” in which they tell the subject in the informed consent process that their scans are not of clinical quality and are not being interpreted by medically qualified personnel; if by chance, however, the researchers stumble upon a finding, they will inform the subject.³⁹ Such an approach invites litigation and ignores the duties owed to the subject in human research. After all, it is the participant in a nontherapeutic research study who is the Good Samaritan, and that status entitles the subject to the highest standard of care the researcher can offer.

The same logic demands that the MRI research procedure be performed in accordance with at least the standards according to which MRIs are routinely conducted clinically. Again, the American College of Radiology has established protocols for the sequencing of MRI images, as does virtually every hospital in its Policy and Procedure Manual governing such diagnostic tests. Performing an MRI in a manner contrary to these protocols would be contrary to the required standard of care,⁴⁰ even when the MRI was not indicated by any medical condition.

Thus, even in those research studies in which the PI is looking only at a specific area of the brain such as the hypothalamus and believes one sequence of MRI images is adequate for the limited purpose of the research, the full sequence of MRI images is required. No radiologist would take a limited sequence of images because the referring neurologist advised he or she was only concerned about one area of the

brain. Such conduct would surely be contrary to the hospital’s protocol requiring a full sequence of images and, thus, below the requisite standard of care. No less a standard would be required of the radiologist in the research enterprise.

If brain research using MRI is to be performed, and if the results of such procedure may have some consequence to the subject, the PI must disclose and discuss this information with the subject or his or her guardian during the informed consent process, because it may be material to the decision of whether or not to participate in the research.⁴¹ Some subjects, wisely or unwisely, may choose not to participate in such circumstances. That is their right. Others may be concerned about the potential effects of learning such information, such as whether it might impact their ability to obtain insurance or participate in certain activities. Incidental findings may impose a substantial psycho-

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then could the research enterprise ever justify having unqualified personnel review the MRI scans? Unqualified personnel will predictably miss important incidental findings. Virtually every hospital requires that, if an MRI is performed, it be read by a qualified radiologist who is certified in radiology or diagnostic radiology by the American Board of Radiology.³⁶ This is the standard of care in medical malpractice actions as well. If the MRI images reveal an abnormality that a reasonably careful radiologist would detect, then it would be a hollow defense to claim that the researchers or their assistants had neither the training nor the expertise to properly interpret the data.

The National Institutes of Health approaches the issue by giving full clinical brain scans to every subject participating in its intramural neuroimaging studies.³⁷ Many research institutions currently require, consistent with the standard of care proposed here,

logical and financial burden on the human subject. In one example, a former neuroanatomy teacher, soon-to-be father and professed “neuro-nerd,” volunteered

available at <<http://www.fmri.org/fmri.htm>> (last visited February 20, 2008).

3. *Id.*
4. J. Illes et al., “Discovery and Disclosure of Incidental Find-

Though current research ethics do not require the investigator to treat the anomaly, it is worth asking whether researchers should have some obligation to notify the mother of the incidental finding and then help her address it therapeutically. We are forced to face the broader question: what does medicine owe to the person who volunteers his or her body for medicine’s progress?

for an MRI of his brain which revealed a golf-ball sized tumor. The diagnosis came just before he applied for additional insurance for his family, which was subsequently denied as a result of the incidental finding.⁴² He now says that he “should have thought about the consequences of volunteering more thoroughly.”⁴³

Finally, if abnormalities are found, the subject must be promptly informed of those critical findings so as to decide whether to seek whatever treatment is required. This means that the researchers must have a way to contact the subject and a physician who understands the import of the findings and the available treatment alternatives.⁴⁴ In a study such as the one from my case files, in which the poor and uninsured are the likely recruits, more difficult issues may arise. Suppose the MRI reveals in the brain of an eight-year-old a tumor easily removable, but certain to kill if it is not removed. The child’s single mother tells the physician that she has no insurance, no regular doctor, and no idea of what she can do to help her child. Though current research ethics do not require the investigator to treat the anomaly, it is worth asking whether researchers should have some obligation to notify the mother of the incidental finding and then help her address it therapeutically. We are forced to face the broader question: what does medicine owe to the person who volunteers his or her body for medicine’s progress?

Acknowledgment

This publication was made possible by National Human Genome Research Institute (NHGRI) grant # R01 HG003178 (PI, S. M. Wolf; Co-Is, J. P. Kahn, F. Lawrenz, C. A. Nelson). Its contents are solely the responsibility of the author and do not necessarily represent the official views of NHGRI.

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5. J. Illes et al., “Ethical Consideration of Incidental Findings on Adult Brain MRI in Research,” *Neurology* 62, no. 6 (2004): 888-890.
6. *Id.*
7. *Id.*
8. *Id.*
9. *Id.*
10. *Id.*
11. See Alphas et al., *supra* note 1, at 1-7.
12. *Id.*
13. *Id.*
14. *Id.*
15. See Illes et al., *supra* note 4.
16. *Id.*
17. *Id.*
18. *Id.*, at 745.
19. *Id.*
20. *Id.*
21. *Id.*
22. *Id.*, at 746.
23. K. Ross, “When Volunteers Are Not Healthy,” *EMBO Reports* 6, no. 12 (2005): 1116-1119, at 1118, available at <<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1369211>> (last visited February 20, 2008) (quoting Alan Evans, neuroimaging researcher from McGill University, Montreal, Canada); see also Illes et al., *supra* note 5, at 890 (“[W]e must balance the benefit of involving medical personnel trained to read scans and interact with participants against the legal risk and financial burden of clinician assessment of all participant MRIs and the workload challenges associated with sheer volume.”).
24. The study exposed children to greater than minimal risk with no benefit and induced participation for money not altruism. 45 C.F.R. 46 (2007).
26. 366 Md. 29 (2001).
27. *Id.*, at 113.
28. *Id.*, at 89, 91-100, 103.
29. *Id.*, at 101.
30. *Id.*, at 101-102 (citing in part National Bioethics Advisory Commission, *Ethical and Policy Issues in Research Involving Human Participants*, 2001, available at <<http://bioethics.georgetown.edu/nbac/human/overvol1.pdf>> [last visited February 20, 2008]).
31. See, e.g., *Lambert v. Park*, 597 F.2d 2369 (10th Cir. 1979); *Perna v. Pirozzi*, 92 N.J. 444 (1983).
32. *Id.* (citing *Faya v. Almaraz*, 620 A.2d 327, 333 [Md. 1993]).
33. See Illes et al., *supra* note 5.
34. *Id.*

35. *Id.*
36. See generally, American College of Radiology, "Accreditation Programs," available at <<http://www.acr.org/accreditation.aspx>> (last visited February 20, 2008).
37. See Ross, *supra* note 23, at 4 (citing E. Check, "Brain-Scan Ethics Come Under the Spotlight," *Nature* 433, no. 7030 (2005): 185).
38. *Id.* (citing Illes et al., *supra* note 4).
39. *Id.*
40. See, e.g., *Simpson v. Sisters of Charity of Providence in Oregon*, 588 P.2d 4 (Or. 1978).
41. 45 C.F.R. § 46.116 (2007).
42. *Id.*
43. See Ross, *supra* note 23.
44. See, e.g., *Stanley v. McCarver*, 92 P.3d 849 (Ariz. 2004); *Vucinich v. Ross*, 893 So. 2d 690 (Fla. Dist. Ct. App. 5th Dist. 2005).