

## I STILL HAVEN'T FOUND WHAT I'M LOOKING FOR,<sup>1</sup> BUT I MAY HAVE FOUND SOMETHING ELSE: NON-PHYSICIAN RESEARCHERS AND INCIDENTAL FINDINGS IN MAGNETIC RESONANCE IMAGING

### INTRODUCTION

Brain scans performed on symptomatic patients may serve a diagnostic function, enabling a clinician to locate the cause of a problem.<sup>2</sup> Magnetic resonance imaging (MRI) could help to diagnose a tumor or elucidate the cause of headaches, changes in vision, sensation, or cognition.<sup>3</sup> In stark contrast, brain scans performed on asymptomatic volunteers in a cognition study, for example, may be the source of problems for both the principal investigator and the research participant. Instead of contributing to generalizable data, the scan may reveal a serious problem. These accidental discoveries can have potentially life-changing effects. In one case, a medical student was alerted to an arteriovenous malformation during an fMRI study on memory.<sup>4</sup> After successful surgeries, she was “transformed by this experience as a patient and a student.”<sup>5</sup> In another case, a self-professed “neuro-nerd” eagerly volunteered for an MRI study, curious to see images of his own brain.<sup>6</sup> The opportunity ended up having many far-reaching and serious consequences.<sup>7</sup> The golf-ball sized tumor discovered in a sensitive area of his brain came as a shock to the subject.<sup>8</sup> Disclosure of the discovery caused him to lose his health insurance when he

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1. U2, *I Still Haven't Found What I'm Looking For*, on THE JOSHUA TREE (Universal Island Records 1987).

2. See, e.g., U.S. Nat'l Libr. of Med., MedlinePlus Medical Encyclopedia, Head MRI, at [www.nlm.nih.gov/medlineplus/ency/article/003791.htm](http://www.nlm.nih.gov/medlineplus/ency/article/003791.htm) (last visited May 19, 2009) [hereinafter MedlinePlus, Head MRI]; see also Steven Goldberg, *MRIs and the Perception of Risk*, 33 AM. J.L. & MED. 229, 231 (2007).

3. MedlinePlus, Head MRI, *supra* note 2; see also Goldberg, *supra* note 2, at 231.

4. Eric Racine & Judy Illes, *Neuroethical Responsibilities*, 33 CAN. J. NEUROLOGICAL SCI. 269, 271 (2006); Eric Racine & Judy Illes, *Emerging Ethical Challenges in Advanced Neuroimaging Research: Review, Recommendations and Research Agenda*, J. EMPIRICAL RESEARCH ON HUMAN RESEARCH ETHICS, May 2007, at 1, 3.

5. Racine & Illes, *Neuroethical Responsibilities*, *supra* note 4, at 271.

6. Anonymous, *How Volunteering for an MRI Scan Changed My Life*, 434 NATURE 17, 17 (2005).

7. See *id.*

8. *Id.*

and his wife were expecting their first child.<sup>9</sup> The recommended operation carried a five percent risk of serious complications that could dramatically change his life.<sup>10</sup>

These are just two examples of what could happen if researchers disclose findings. Disclosure is not always pursued.<sup>11</sup> Accidental discoveries place the researcher in what has been termed a “policy vacuum”<sup>12</sup> and within “Pandora’s costly box.”<sup>13</sup> Many difficult questions are raised about how to best handle such discoveries:<sup>14</sup> Does the researcher have an obligation to tell the participant? Could there be liability for alerting the participant to a potential problem that turns out to be nothing at all? Currently, federal policies governing research on human subjects do not provide clear answers to questions surrounding such discoveries.<sup>15</sup>

9. *Id.*

10. The serious complications included the possibility of “hav[ing] to induce a massive stroke of [the] entire left-brain . . . [potentially leaving him] in the horrible position of being unable to communicate with [his] wife, [his] newborn child or [his] students[,]” and ultimately leading to the loss of his job. *Id.*

11. Judy Illes et al., *Discovery and Disclosure of Incidental Findings in Neuroimaging Research*, 20 J. MAGNETIC RESONANCE IMAGING 743, 745-46 (2004) [hereinafter Illes et al., *Discovery and Disclosure*]; Judy Illes et al., *Incidental Findings in Brain Imaging Research*, 311 SCIENCE 783, 783-84 (2006) [hereinafter Illes et al., *Workshop Summary*]. See M.J. Friedrich, *Neuroscience Becomes Image Conscious as Brain Scans Raise Ethical Issues*, 294 JAMA 781, 782 (2005) (discussing variability among research groups when it comes to instituting policies and procedures for handling incidental findings); see also Frances Lawrenz & Suzanne Sobotka, *Empirical Analysis of Current Approaches to Incidental Findings*, 36 J. LAW, MED. & ETHICS 249, 252-55 (2008) (exploring differences in addressing incidental findings among federal documents, professional society and university documents, as well as web-posted consent forms).

12. Erika Check, *Brain-Scan Ethics Come Under the Spotlight*, 433 NATURE 185 (2005) (quoting participant at January 2005 U.S. National Institutes of Health workshop, “Detection and Disclosure of Incidental Findings in Neuroimaging Research”). See NAT’L INST. NEUROLOGICAL DISORDERS & STROKE, DETECTION AND DISCLOSURE OF INCIDENTAL FINDINGS IN NEUROIMAGING RESEARCH, Jan. 6-7, 2005, at [www.ninds.nih.gov/news\\_and\\_events/proceedings/ifexecsummary.htm](http://www.ninds.nih.gov/news_and_events/proceedings/ifexecsummary.htm) (last visited May 19, 2009) [hereinafter PROCEEDINGS ON INCIDENTAL FINDINGS] (meeting summary indicating the need for standards governing the disclosure of incidental findings to research participants).

13. Judy Illes, *‘Pandora’s Box’ of Incidental Findings in Brain Imaging Research*, 2 NATURE CLINICAL PRACTICE NEUROLOGY 60, 60 (2006) (citing Robert I. Grossman & James L. Bernat, *Incidental Research Imaging Findings: Pandora’s Costly Box*, 62 NEUROLOGY 849 (2004)).

14. See *id.*; see also Illes et al., *Workshop Summary*, *supra* note 11, at 784.

15. See 45 C.F.R. §§ 46.101 – 46.409 (2008); see Jennifer J. Kulynych, *The Regulation of MR Neuroimaging Research: Disentangling the Gordian Knot*, 33 AM. J.L. & MED. 295, 314 (2007); see also Henry S. Richardson, *Incidental Findings and Ancillary-Care Obligations*, 36 J.L., MED. & ETHICS 256, 256 (2008) (stating that “the Common Rule that has shaped medical research ethics . . . is largely silent about what needs to be done in response to researchers’ positive obligations.”).

This comment will explore the current status of incidental findings in MRI research. Part I will provide MRI research basics. Part II will introduce the concept of incidental findings within the scope of MRI research. Part III will discuss the limitations in policies and regulations and the resulting variety of institutional approaches. Part IV will advocate for research participant protections and propose a new approach to funding this endeavor without sacrificing the research enterprise.

#### PART I: MAGNETIC RESONANCE IMAGING

The roots of MRI date back to then-cutting edge research of the 1930s which characterized magnetic properties of atoms.<sup>16</sup> This concept was applied to molecules and eventually to tissues in a procedure known as nuclear magnetic resonance.<sup>17</sup> In conjunction with echoplanar imaging, which enables imaging of slices of the brain, this technology became modern-day MRI.<sup>18</sup> In the early 1980s, the name was formally changed from nuclear magnetic resonance to magnetic resonance imaging to allay public fears and remove any negative connotation associated with nuclear materials.<sup>19</sup> In the most basic sense, MRI translates the changes observed when cells transition from aligning with a magnetic field to returning to “pre-magnetized states” into images.<sup>20</sup> Various tissue types respond differently to the magnetic field.<sup>21</sup> Likewise, fMRI uses a magnetic field to detect changes in blood oxygen levels which accompany brain activity.<sup>22</sup> Specific areas of the brain use more oxygen than others to perform certain tasks.<sup>23</sup> Under

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16. Goldberg, *supra* note 2, at 230. For an excellent summary of the history of MRI within the context of other imaging types, see Stacey A. Tovino, *Imaging Body Structure and Mapping Brain Function: A Historical Approach*, 33 AM. J.L. & MED. 193 (2007); Laura Stephens Khoshbin & Shahram Khoshbin, *Imaging the Mind, Minding the Image: An Historical Introduction to Brain Imaging and the Law*, 33 AM. J.L. & MED. 171 (2007).

17. Goldberg, *supra* note 2, at 230.

18. Khoshbin & Khoshbin, *supra* note 16, at 180.

19. *Id.*; see also Goldberg, *supra* note 2, at 231-33.

20. Joseph H. Baskin et al., *Is a Picture Worth a Thousand Words? Neuroimaging in the Courtroom*, 33 AM. J.L. & MED. 239, 248 (2007); see also Laurence R. Trancredi & Jonathan D. Brodie, *The Brain and Behavior: Limitations in the Legal Use of Functional Magnetic Resonance Imaging*, 33 AM. J.L. & MED. 271, 274 (2007).

21. Baskin et al., *supra* note 20, at 248; see also Trancredi & Brodie, *supra* note 20, at 277 (discussing how the presence of oxyhemoglobin and deoxyhemoglobin in tissues affects the magnetic field).

22. Khoshbin & Khoshbin, *supra* note 16, at 180.

23. See Marcus E. Raichle, *Behind the Scenes of Functional Brain Imaging: A Historical and Physiological Perspective*, 95 PROCEEDINGS OF THE NAT'L ACAD. OF SCI. 765, 765 (1998) (noting that brain activity is characterized by changes in local blood flow, which is accompanied by changes in oxygen consumption); Khoshbin & Khoshbin, *supra* note 16, at 180 (“The underlying principle here is that neurons, when activated, convert oxyhemoglobin to

this premise, researchers have set out to link areas of the brain activated with various cognitive tasks and emotions.<sup>24</sup> Researchers will tackle more and more complex brain functions and emotions,<sup>25</sup> armed with improved technology—stronger magnets and combined imaging techniques.<sup>26</sup> Better images, in turn, may enable researchers to see more detail and ultimately increase the number of accidental discoveries in MRI research.<sup>27</sup>

#### A. *The MRI Research Participant Experience*

For the research participant, MRI is non-invasive and usually harmless.<sup>28</sup> No long-term adverse effects have occurred from MRI scanning.<sup>29</sup> Before the procedure, participants are screened for metal—due to the use of strong magnets, people with metal implants are ineligible for the procedure.<sup>30</sup> The participant then lies flat on her back with her head resting on a helmet-like coil.<sup>31</sup> Next, the participant is moved into the bore of the scanner with the lower body remaining outside of the scanner.<sup>32</sup> During the scan, all others must remain outside of the room.<sup>33</sup> Participants must lie motionless for the duration of the scan and will hear loud buzzing and clicking noises.<sup>34</sup>

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deoxyhemoglobin as they utilize oxygen, which can be detected by MRI to indicate an increase in neuronal activity when compared to surrounding tissues.”) (internal citation omitted).

24. Goldberg, *supra* note 2, at 231; Baskin et al., *supra* note 20, at 254-257, 264-66 (discussing research efforts to localize brain areas responsible for cognitive functions and development, lying, antisocial behavior, and psychopathy).

25. See, e.g., Tina Hesman Saey, *In the Brain, Justice Is Served from Many Parts: Imaging Study Reveals Variation in Brain Activity Depending on the Severity of Punishment a Person Decides*, SCIENCE NEWS WEB EDITION, Dec. 10, 2008, at [www.sciencenews.org/view/generic/id/39239/title/In\\_the\\_brain\\_justice\\_is\\_served\\_from\\_many\\_parts](http://www.sciencenews.org/view/generic/id/39239/title/In_the_brain_justice_is_served_from_many_parts) (last visited May 19, 2009) (describing a recent study using fMRI that indicated that emotion plays a role in making legal determinations regarding the punishment that an individual should receive).

26. Khoshbin & Khoshbin, *supra* note 16, at 180-81.

27. John H. Stone, *Incidentalomas — Clinical Correlation and Translational Science Required*, 354 NEW ENG. J. MED. 2748, 2749 (2006).

28. MedlinePlus, *Head MRI*, *supra* note 2; Jennifer Kulynych, *Legal and Ethical Issues in Neuroimaging Research: Human Subjects Protection, Medical Privacy, and the Public Communication of Research Results*, 50 BRAIN & COGNITION 345, 351 (2002).

29. MedlinePlus, *Head MRI*, *supra* note 2.

30. *Id.* No metal objects are allowed in the room. People with metallic implants, such as artificial joints, heart valves, or brain aneurysm clips, will not be eligible. *Id.*; see also University Institutional Review Board, *Informed Consent Document for Research*, Oct. 30, 2007 (on file with author) [hereinafter *University Consent*].

31. MedlinePlus, *Head MRI*, *supra* note 2.

32. *Id.*; *University Consent*, *supra* note 30.

33. See MedlinePlus, *Head MRI*, *supra* note 2; see also *University Consent*, *supra* note 30. Those operating the scanner usually watch from an adjoining room, maintaining contact with the participant through an intercom system. MedlinePlus, *Head MRI*, *supra* note 2.

34. *University Consent*, *supra* note 30.

Researchers may take two types of scans: anatomical or functional.<sup>35</sup> An anatomical scan will show brain structures. Researchers wishing to observe brain function will also take fMRI scans while the participant performs certain mental tasks.<sup>36</sup> Depending on the type of study, the scanner may also have equipment for presenting visual or auditory stimuli.<sup>37</sup> Participants may be asked to respond to the stimuli using a hand controller.<sup>38</sup> Eye movement may be monitored with an eye tracking device.<sup>39</sup> The fMRI scans generated during these tasks show areas of activation hypothetically related to the tasks performed.<sup>40</sup> However, there is some debate as to whether observable activity within specific areas of the brain can be reasonably tied to these tasks; for example, the observed areas of activation may in fact be caused by sensations associated with participating in the scan.<sup>41</sup>

fMRI research may be classified as having “minimal risk” to subjects.<sup>42</sup> Minimal risk means risk in which “the probability and magnitude of harm or discomfort . . . are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.”<sup>43</sup> During a scan, the risks include

potentially acute discomfort and psychological distress from lying prone in the confined gantry of the MRI scanner, acoustic noise, which in some scanning procedures may cause hearing loss without the use of ear protection, and the possibility of serious physical injury if the subject and the nearby environment are not properly screened for metal implants or objects.<sup>44</sup>

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35. *Id.*

36. *Id.*

37. *See id.*

38. *See id.*

39. University Consent, *supra* note 30.

40. *See* Trancredi & Brodie, *supra* note 20, at 280.

41. *See id.*; *see also* Baskin et al., *supra* note 20, at 249.

42. Kulynych, *supra* note 28, at 351.

43. 45 C.F.R. § 46.102(i) (2006).

44. Kulynych, *supra* note 28, at 351-52 (internal citations omitted). “[A]dverse consequences may be infrequent, but they can and do occur, as evidenced by the recent tragic death of a young patient struck by a metal canister during a routine MRI scan.” *Id.* at 352 (internal citations omitted).

B. *The Future of Functional Magnetic Resonance Imaging Research*

In its second decade of existence, use of fMRI has thrived.<sup>45</sup> It is estimated that approximately 30,000 research participants have been included in fMRI studies between 1991 and 2001.<sup>46</sup> This brain imaging technique represents one of the more recent developments of ever-evolving attempts to look inside the brain.<sup>47</sup> Science will continue to build upon it.<sup>48</sup> The 2007 Symposium Issue of the *American Journal of Law & Medicine* was dedicated to legal and ethical issues in brain imaging.<sup>49</sup> Like methods such as phrenology, Positron Emission Tomography (PET), and Single-Photon Emission Computed Tomography (SPECT) before, fMRI also raises important legal and ethical questions regarding which conclusions can be properly drawn from the techniques.<sup>50</sup> Many of these questions are framed in the *American Journal of Law & Medicine* Symposium Issue: Can measured brain activity provide evidence of complex mental functions such as bias or feelings of guilt?<sup>51</sup> What is the proper role of brain imaging in demonstrating incapacity through brain structure and deterioration?<sup>52</sup> Might imaging provide insight to subjective experiences such as the perception of pain?<sup>53</sup> Researchers look to MRI and fMRI to provide answers to such questions and further understand the brain. The resulting increase in the number of studies involving these types of scans will likely increase the chance of encountering accidental discoveries like those previously described in the Introduction.<sup>54</sup>

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45. Friedrich, *supra* note 11, at 781; see Judy Illes et al., *Ethical and Practical Considerations in Managing Incidental Findings in Functional Magnetic Resonance Imaging*, 50 *BRAIN & COGNITION* 358, 364 (2002) [hereinafter Illes et al., *Ethical and Practical Considerations*] (identifying approximately 3,500 fMRI studies published between 1991 and 2001).

46. *Id.*

47. See generally Tovino, *supra* note 16 (describing the history of neuroimaging).

48. See Khoshbin & Khoshbin, *supra* note 16, at 180-81 (explaining upcoming advances in neuroimaging techniques).

49. See generally George J. Annas, *Foreword: Imagining a New Era of Neuroimaging, Neuroethics, and Neurolaw*, 33 *AM. J. L. & MED.* 163 (2007).

50. See Tovino, *supra* note 16, at 215-228.

51. Khoshbin & Khoshbin, *supra* note 16, at 186-87; Baskin et al., *supra* note 20, at 264-69.

52. Baskin et al., *supra* note 20, at 250-54 (discussing how brain imaging can be used to demonstrate incapacity and deterioration).

53. Adam J. Kolber, *Pain Detection and the Privacy of Subjective Experience*, 33 *AM. J.L. & MED.* 433, 433-34, 447-49 (2007).

54. See Introduction, *supra*.

## PART II: INCIDENTAL FINDINGS

Incidental findings are broadly defined as an unexpected discovery either outside the area of interest (in the clinical context)<sup>55</sup> or unrelated to the original purpose of the inquiry (in the research context).<sup>56</sup> Studies document incidental findings in a variety of settings.<sup>57</sup> This comment will focus only on the unique issues surrounding incidental findings in MRI neuroimaging studies performed by non-physician researchers. In this context, the definition of incidental findings is limited to any finding unrelated to the original purpose of the scan.<sup>58</sup> While much of the research performed examines brain function through fMRI, the studies usually also include a series of anatomical scans.<sup>59</sup> Incidental findings in MRI research most likely stem from the structural images of the brain (e.g., tumors); however, there is potential for functional images to generate incidental findings as well. Researchers note that it is “premature to attempt to identify incidental findings” in fMRI.<sup>60</sup>

## A. Incidence

Estimates of how often one may expect to encounter incidental findings vary. In 1999, the first study looking for incidental findings in healthy or asymptomatic volunteers was conducted.<sup>61</sup> The researchers retrospectively analyzed the brain MRI scans previously obtained from healthy controls in other experiments.<sup>62</sup> Most of the 1,000 scans were normal; 18% of scans

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55. Roberto Iezzi et al., *Extravascular Incidental Findings at Multislice CT Angiography of the Abdominal Aorta and Lower Extremity Arteries: A Retrospective Review Study*, 32 *ABDOMINAL IMAGING* 489, 489 (2007).

56. Illes et al., *Workshop Summary*, *supra* note 11, at 783.

57. See, e.g., Brian Van Ness, *Genomic Research and Incidental Findings*, 36 *J.L., MED. & ETHICS* 292, 293-94 (2008) (incidental findings in genomic research may include the “discovery of misattributed paternity” or gene variations which might carry risk for disease such as BRCA1); Mikael Hellström et al., *Extracolonic and Incidental Findings on CT Colonography (Virtual Colonoscopy)*, 182 *AM. J. ROENTGENOLOGY* 631, 631 (2002) (reporting twenty-three percent of CT colonography scans reviewed potentially showed clinically significant findings in the organs surrounding the colon); Jeffrey Mueller et al., *Cardiac CT Angiography After Coronary Bypass Surgery: Prevalence of Incidental Findings*, 189 *AM. J. ROENTGENOLOGY* 414 *passim* (2007) (retrospective review of cardiac CT scans found previously unnoticed anomalies in the lungs and abdomen).

58. Illes et al., *Workshop Summary*, *supra* note 11, at 783.

59. University Consent, *supra* note 30.

60. Illes et al., *Workshop Summary*, *supra* note 11, at 784.

61. Gregory L. Katzman et al., *Incidental Findings on Brain Magnetic Resonance Imaging From 1000 Asymptomatic Volunteers*, 281 *JAMA* 36, 36 (1999).

62. *Id.* at 36-37.

were determined to be anomalous.<sup>63</sup> The anomalous scans were classified further by apparent need for follow-up:<sup>64</sup> 15.1% required no follow-up; 1.8% required routine referral; 1.1% required urgent referral; none were classified as requiring immediate care.<sup>65</sup> Subsequent studies confirm incidental findings in healthy volunteers; however, the incidence ranges from 5% to 47%.<sup>66</sup>

Incidental findings are not limited to any specific age, race, or gender.<sup>67</sup> One study reported incidental findings in 13% of the sixty healthy volunteers ages 10 to 21,<sup>68</sup> though none of these discoveries amounted to anything of clinical significance.<sup>69</sup> In contrast, another study found that incidental findings among the youngest portion of the study group (mean age 25.5 years) more often required urgent referral (three of the four incidental findings)<sup>70</sup> compared to the older portion (mean age 75.5 years) in which none of the scans required more than routine referral.<sup>71</sup>

One limitation of these analyses is the retrospective use of scans from other studies.<sup>72</sup> The original studies from which the scans were obtained are not uniform; they differ in sample size, population, strength of MRI scan, and type of scan viewed.<sup>73</sup> This variance makes it difficult to reconcile the

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63. *Id.* at 37.

64. *Id.* Examples of incidental findings requiring no follow-up included sinusitis and normal age-related changes. Incidental findings requiring routine referral included possible demyelinating disease and pineal cysts. Incidental findings requiring urgent follow up included low-grade tumors and aneurysm. *Id.*

65. *Id.*

66. A 2004 study by Judy Illes et al. reviewed 151 MRI scans and found an overall prevalence of 47% containing incidental findings. Judy Illes et al., *Ethical Consideration of Incidental Findings on Adult Brain MRI in Research*, 62 *NEUROLOGY* 888-89 (2004). A 2007 study by Meike W. Vernooij et al. reviewed 2000 scans and determined incidental findings had a prevalence of 7.2%. Meike W. Vernooij et al., *Incidental Findings on Brain MRI in the General Population*, 357 *NEW ENG. J. MED.* 1821, 1821-23 (2007).

67. See, e.g., Surya N. Gupta & Brook Belay, *Intracranial Incidental Findings on Brain MR Images in a Pediatric Neurology Practice: A Retrospective Study*, 264 *J. NEUROLOGICAL SCI.* 34, 35 (2007).

68. Sanjiv Kumra et al., *Ethical and Practical Considerations in the Management of Incidental Findings in Pediatric MRI Studies*, 45:8 *J. AM. ACAD. CHILD ADOLESCENT PSYCHIATRY* 1000, 1002 (2006).

69. *Id.* at 1002-03.

70. Illes et al., *supra* note 66, at 889.

71. *Id.*

72. See ANN ASCHENGRAU & GEORGE R. SEAGE III, *ESSENTIALS OF EPIDEMIOLOGY IN PUBLIC HEALTH* 263 (2d ed. 2008) (discussing bias as an issue that comes up in retrospective review of scans).

73. See Trancredi & Brodie, *supra* note 20, at 280-83 (discussing reliability and reproducibility of fMRI results); see also Baskin et al., *supra* note 20, at 249 (discussing limitations inherent in comparing scans from different scanners).



data to pinpoint an exact incidence in the general population beyond revealing some likelihood of discovering a brain anomaly in healthy volunteers. Further,

[t]here are limits to the 'objectivity' of neuroimaging. Brain imaging is the product of a complex set of techniques, subjective decisions, technical choices, and informed interpretations. Scientists, technicians, and clinicians decide the level of detail they will use to scan the brain. They must determine what types of imaging should be ordered, how thick or thin the slices should be, the degree of clarity, the difference in contrast between types of tissue, and how the signal should be filtered from background noise.<sup>74</sup>

Thus, the researchers will likely optimize certain aspects of the scans to serve their research purposes. These settings may be incongruent with ideal settings for diagnostic purposes in a clinical setting.

#### B. *The Problem of False Positives*

Equally worrisome are the incidental findings that turn out to be unimportant. These numbers may be directly related to the size and inclusion criteria for the study population and type and strength of scan.<sup>75</sup> While the early detection of serious problems can improve outcomes, false positives present a serious burden both in clinical and research settings. One doctor noted the incidental discovery of a renal mass "ruined the patient's peace of mind and diverted [the] focus from the otherwise clear path to health."<sup>76</sup> The possible presence of brain anomalies is countered by the occurrence of false positives which may trigger a "cascade effect"—riskier, more expensive, stressful tests are performed only to discover there is no problem.<sup>77</sup> A researcher noted that follow-up on asymptomatic tumors is both expensive and stressful.<sup>78</sup> For example, once a suspect mass is found, annual MRI scans are usually performed for two to three years to assess growth and monitor changes.<sup>79</sup> "If this were done for all persons incidentally found to have meningiomas, many MRI examinations would be performed in otherwise healthy asymptomatic persons"<sup>80</sup> at a substantial cost. Similarly, it can be very distressing to receive news of an incidental finding. "[T]he provision of a diagnosis of a structural anomaly without

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74. Baskin et al., *supra* note 20, at 249.

75. See Mueller et al., *supra* note 57, at 416-18 (discussing how incidence is affected by different study variables).

76. Stone, *supra* note 27, at 2748.

77. Goldberg, *supra* note 2, at 236 (internal citations omitted).

78. Vernooij et al., *supra* note 66, at 1826.

79. *Id.*

80. *Id.*

some type of immediate intervention or treatment resulting in resolution of the problem [is] problematic because the disclosure [may] generate[] anxiety . . . .”<sup>81</sup>

As brain imaging technology improves, scans will likely detect increasingly precise and smaller-sized findings.<sup>82</sup> At what point do the findings become significant enough to warrant disclosure?<sup>83</sup> With the continuing improvement of scanning technologies and their increased use in research settings, researchers will encounter more incidental findings and must determine when they warrant disclosure based on factors such as size and organ involved.<sup>84</sup>

Perhaps more persuasive than incidence studies is a recent survey of researcher experiences. When asked whether they had encountered incidental findings in their studies, eighty-two percent of researchers responded that they had.<sup>85</sup> Incidental findings are a very real possibility confronting non-physician researchers using MRI regardless of the type of research or the sample used. The findings may require urgent care or nothing at all; however, researchers must be cognizant of this possibility and aware of the implications.

### PART III: APPROACHES TO INCIDENTAL FINDINGS

#### A. *Regulations and Obligations*

Regulations for MRI research come from many sources, though together remain “insufficient in some respects and inefficiently duplicative in others.”<sup>86</sup> Most applicable to the participant experience is the U.S. Department of Health and Human Services’ Common Rule.<sup>87</sup> These regulations aim to protect research participants by setting standards for obtaining informed consent and institutional self-governance through Institutional Review Boards (IRB).<sup>88</sup> The IRB is charged with ensuring research protocols do not overlook the best interests of the participants in research endeavors.<sup>89</sup> The Common Rule applies to all federally funded research, but its reach is “extended considerably in practice” through

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81. Kumra et al., *supra* note 68, at 1003.

82. Stone, *supra* note 27, at 2748-49.

83. See *id.* at 2748.

84. See *id.* at 2748-49.

85. See Illes et al., *Discovery and Disclosure*, *supra* note 11, at 744 (surveying authors of peer-reviewed MRI studies in U.S. and abroad from 1999-2001).

86. Kulynych, *supra* note 15, at 296.

87. See generally 45 C.F.R. §§ 46.101 – 46.409 (2008).

88. *Id.*

89. *Id.*

voluntary application.<sup>90</sup> Further, state laws and institutional policies may impose additional regulations over and above these federal regulations.<sup>91</sup>

In the context of incidental findings, the Common Rule “is largely silent about what needs to be done in response to researchers’ positive obligations.”<sup>92</sup> Instead, researcher obligations with respect to incidental findings may be derived from other sources such as contracts, general beneficence, or professional responsibility.<sup>93</sup> It is established that informed consent documents can bind researchers to the obligations therein.<sup>94</sup> The question remains whether, absent specific language addressing incidental findings in the informed consent document, the researcher has any resulting duty. While the philosophical underpinnings of potential researcher duties are well beyond the scope of this comment, some duties are recognized, stemming from the principle of general beneficence and the special relationship between researcher and participant.<sup>95</sup> Institutions choosing to address incidental findings do so without elucidating the source of the duty.

#### B. Institutional Approaches

In the absence of explicit regulatory requirements for incidental findings, some research institutions have begun to implement their own policies.<sup>96</sup> While some research protocols incorporate these unexpected discoveries,

90. BARRY R. FURROW ET AL., *BIOETHICS: HEALTH CARE LAW AND ETHICS* 420 (6th ed. 2008).

91. Kulynych, *supra* note 28, at 351. For example, New York has enacted state regulations which essentially extend federal IRB and informed consent requirements to all research that might not otherwise be subject to federal regulations. Similarly, the California Protection of Human Subjects in Medical Experimentation Act creates the Experimental subject’s bill of rights which also extends to protect participants in experiments not covered by federal law. *Id.* at 349; N.Y. PUB. HEALTH LAW §§2441-2446 (McKinney 2007); CAL. HEALTH & SAFETY CODE §§ 24171-24179.5 (West 2007).

92. Richardson, *supra* note 15, at 256.

93. Franklin G. Miller et al., *Incidental Findings in Human Subjects Research: What Do Investigators Owe Research Participants?*, 36 J.L., MED. & ETHICS 271, 272 (2008).

94. *Id.* See *Grimes v. Kennedy Krieger Institute, Inc.*, 782 A.2d 807, 858 (Md. 2001) (holding, in part, “that informed consent agreements in nontherapeutic research projects, under certain circumstances can constitute contracts; and that, under certain circumstances, such research agreements can, as a matter of law, constitute ‘special relationships’ giving rise to duties, out of the breach of which negligence actions may arise.”); see also Alan C. Milstein, *Research Malpractice and the Issue of Incidental Findings*, 36 J.L., MED. & ETHICS 356, 358 (2008).

95. Miller et al., *supra* note 93, at 272; *Grimes*, 782 A.2d at 858; Milstein, *supra* note 94, at 358-59; Richardson, *supra* note 15, at 256-57.

96. Illes et al., *Discovery and Disclosure*, *supra* note 11, at 745 (revealing “substantial procedural variability across research units for . . . detecting and communicating abnormal findings to [subjects]”).

there is no regulation of their uniform disposal.<sup>97</sup> In fact, there is no requirement for researchers to address them at all.<sup>98</sup> Further, “there appears to be little guidance available on what researchers should do” when confronted with incidental findings.<sup>99</sup>

A team lead by Judy Illes examined fMRI research protocols in a 2004 study.<sup>100</sup> The authors surveyed researchers who had published peer-reviewed fMRI research studies between 1991 and 2002.<sup>101</sup> The responding cohort consisted of seventy-four investigators from the United States and abroad who conduct structural or functional MRI studies.<sup>102</sup> A majority of the investigators conduct fewer than 500 scans per year (seventy-one percent) with the remaining twenty-nine percent conducting 500 or more scans in a year.<sup>103</sup> Eighty-two percent of the respondents reported having knowledge of incidental findings in their research, such as tumors, cysts, and malformations.<sup>104</sup> Once incidental findings were discovered, there was much variation in protocols for handling incidental findings.

53% (28/53) reported that they have standardized procedures in place for handling incidental findings and communicating with research participants in whom findings [were] discovered. All others proceed on an ad hoc, case-by-case basis. Neuroradiologist involvement is an IRB requirement for 22% (11/49) of laboratories reporting on this question. In laboratories in which neuroradiologist involvement is not required by the IRB, scans are nonetheless always read 13% (5/38) of the time, upon suspicious finding 69% (26/38) of the time, and not at all 18% (7/38) of the time.<sup>105</sup>

The study also revealed differences in “lag time”—the time between receiving the scan and review by a neuroradiologist—and how neuroradiologists are compensated for this review.<sup>106</sup>

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97. Moira A. Keane, *Institutional Review Board Approaches to the Incidental Findings Problem*, 36 J.L., MED. & ETHICS 352, 352 (2008).

98. See *id.* (noting IRBs are not regulated with respect to ethical guidelines and regulations).

99. Lawrenz & Sobotka, *supra* note 11, at 249.

100. Illes et al., *Discovery and Disclosure*, *supra* note 11, at 743.

101. *Id.*

102. *Id.* at 744. The survey was conducted via email and had an 11% response rate (81 out of 717). Eighty-one investigators accessed the survey, 74 of which responded to at least some of the survey. Fifty-eight percent of the respondents were from the United States (fifteen/twenty-six). Other countries included France, Japan, Italy, The Netherlands, Scotland, United Kingdom, and Sweden and represented the remaining forty-two percent (eleven/twenty-six). *Id.*

103. *Id.*

104. *Id.* at 744-45. The survey did not specifically ask respondents to report what the incidental findings were, but some included the information in a comments section. *Id.*

105. Illes et al., *Discovery and Disclosure*, *supra* note 11, at 745.

106. *Id.*

A more recent study by Frances Lawrenz and Suzanne Sobotka examined guidance documents found online for handling incidental findings (IFs).<sup>107</sup> Overall they conclude

- “Very few documents address IFs . . . .”
- “Terms used to describe IFs are not consistent across documents.”
- “Very few say to not disclose IFs . . . .”
- “Very few documents recommend checking with a clinical consultant to evaluate whether an IF of concern appears present before disclosing it.”<sup>108</sup>

### C. Recommendations

In an effort to reach a consensus in handling incidental findings in MRI research, professionals from a variety of backgrounds convened to discuss the present issues.<sup>109</sup> The group was guided by the belief that “[a]ny future official recommendations on incidental findings should promote trust in research without unduly encumbering the scientific process.”<sup>110</sup> All agreed that incidental findings must be anticipated, that institutions have protocols in place for incidental findings, and that these protocols are clearly communicated to volunteers through informed consent.<sup>111</sup> Other recommendations include:

- “[I]nclusion of a professional competent to interpret a neuroimaging scan for clinically significant findings.”
- “[T]he [participant] or surrogate is first in line for disclosure of an incidental finding. Communication with the [participant] or surrogate should be done by a qualified member of the research team: the Principal Investigator (PI), a neuroradiologists or physician.”
- “The development of a database of incidental findings and an atlas of different types of incidental findings would be a valuable scientific resource.”<sup>112</sup>

## PART IV: SUGGESTIONS

Given the current landscape and these recommendations, ignoring the possibility of incidental findings in MRI research is not a viable option. Beyond the minimum requirement of addressing incidental findings, there is

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107. Lawrenz & Sobotka, *supra* note 11, at 249-250.

108. *Id.* at 254-55.

109. PROCEEDINGS ON INCIDENTAL FINDINGS, *supra* note 12.

110. Illes et al., *Workshop Summary*, *supra* note 11, at 783.

111. *Id.* at 783-84; see also *supra* Part III for support from ethical guidelines.

112. PROCEEDINGS ON INCIDENTAL FINDINGS, *supra* note 12.

"no single approach . . . [instead] a range of morally acceptable options exist."<sup>113</sup> Any option that is pursued must strike a balance between promoting both participant welfare and the research endeavor.<sup>114</sup> Institutions and the collective group of researchers conducting these types of studies might consider three options to achieve this balance. First, the informed consent process for MRI studies should be revised to explicitly address incidental findings in a way that is easily understood by participants. Next, given truly informed consent, participants should be able to opt out of receiving any diagnostic tipoff regarding health. Finally, given the unpredictable nature of how incidental findings could impact any one study, alternate sources of funding should be created that will relieve the potential burden on institutions of allocating money for expensive follow-up with participants. Each of these suggestions will be advocated below.

How researchers handle incidental findings may differ significantly from what the participants believe, regardless of the informed consent language.<sup>115</sup> One survey demonstrates that participants may believe, despite informed consent language to the contrary, that they will be notified if non-physician researchers discover a potential anomaly.<sup>116</sup> In this study, volunteers received survey invitations via email subsequent to participating in neuroimaging studies in one of two different environments: a medical setting (adjacent to a medical center) and non-medical setting (adjacent to a university psychology building).<sup>117</sup> More than half of the 105 participants (51% or 40/78 from the medical setting and 63% or 17/27 in the non-medical setting) responded they expected brain abnormalities to be detected if present, even though a majority of participants acknowledged physicians would not be reviewing the scans.<sup>118</sup> Almost all of the participants said they would want to know if researchers found abnormalities of any significance level.<sup>119</sup> Despite the small sample size and potentially biasing consent language in both settings,<sup>120</sup> this study suggests that volunteers may not

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113. Judy Illes & Vivian Nora Chin, *Bridging Philosophical and Practical Implications of Incidental Findings in Brain Research*, 36 J.L., MED. & ETHICS 298, 303 (2008).

114. *Id.*

115. See Matthew P. Kirschen et al., *Subjects' Expectations in Neuroimaging Research*, 23 J. MAGNETIC RESONANCE IMAGING 205 (2006).

116. *Id.* at 206.

117. *Id.*

118. *Id.* at 207.

119. *Id.*

120. Kirschen et al., *supra* note 115, at 206-07. Medical setting consent language: "The investigators for this project are not trained to perform radiological diagnosis, and the scans performed in this study are not optimized to find abnormalities. The investigators and [name of institution] are not responsible for failure to find existing abnormalities in your MRI scans. However, on occasion the investigator may notice a finding on an MRI scan that seems abnormal. When this occurs, a neuroradiologist will be consulted as to whether the finding

understand the consent forms.<sup>121</sup> The cohort, comprised mostly of students and academics, still believed existing abnormalities would be discovered.<sup>122</sup> This implicates therapeutic misconception, potentially leaving participants with a false sense of confidence from their participation.<sup>123</sup> Almost none of the participants entered the initial MRI study for diagnostic purposes; however, most left assuming they had no existing brain abnormalities.<sup>124</sup>

Given the unique status of using medical devices in non-therapeutic research, investigators must make absolutely sure the participants understand what benefits to expect.<sup>125</sup> Institutions receiving federal research funding must file an assurance "it will comply with the requirements set forth in [the Code of Federal Regulations] policy."<sup>126</sup> The general requirements for informed consent state the researcher must "obtain[] the legally effective informed consent of the subject . . . under circumstances that provide the prospective subject . . . sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence."<sup>127</sup> The form must be in "language understandable to the subject."<sup>128</sup> The rest of the section spells out the minimum basic elements of informed consent: purpose, description of risks, and benefits reasonably expected.<sup>129</sup> The United States Department of Health and Human Services website provides additional guidance for interpreting the federal regulations:

It is up to the IRB to determine in a particular instance whether some or all of the . . . additional elements must be included as part of the informed consent process for a particular study. The IRB should make this determination based on the nature of the research and its knowledge of the local research context. If the IRB determines that additional elements are appropriate to the research study, this additional information should be

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merits further investigation, in which case the investigator will contact you." *Id.* at 206. Non-medical consent language stated, "[t]his study is part of a research protocol, and is not intended to provide a comprehensive clinical MRI examination of the brain. If, however, a potential abnormality is identified on your MRI scan, you will be immediately notified and your scan will be forwarded to your family physician." *Id.*

121. *Id.* at 207-08.

122. *Id.* at 207. This literate and educated group should arguably have the best comprehension of consent language.

123. *Id.* at 208.

124. *Id.* at 207. Motivations for volunteering for MRI studies include: financial compensation or course credit (sixty-two percent); contribute to scientific knowledge (twenty-one percent); favor to experimenter (sixteen percent); and health concern (one percent). *Id.* at tbl.1.

125. 45 C.F.R. § 46.116 (2008).

126. 45 C.F.R. § 46.103(a) (2008).

127. 45 C.F.R. § 46.116 (2008).

128. 45 C.F.R. § 46.116 (2008).

129. 45 C.F.R. § 46.116(a) (2008).

considered just as essential as the eight basic elements of informed consent described in the HHS regulations at 45 CFR 46.116(a).<sup>130</sup>

Incidental findings raise a difficult to understand concept. Given the increased potential for misunderstanding, additional precautions should be taken. The Common Rule enables an IRB to require additional information to the consent which would “meaningfully add to the protection of the rights and welfare of subjects.”<sup>131</sup> It should be inferred from these studies that the potential existence of brain abnormalities and knowledge about the institution’s policies for handling incidental findings absolutely contribute to “circumstances that provide the prospective subject . . . sufficient opportunity to consider whether or not to participate . . . .”<sup>132</sup> The false sense of confidence is certainly an effect upon health that comes directly from participating in the research and may ultimately prevent some from seeking future medical treatment. While incidental findings do not always present a particularly serious risk in MRI research, they do present a known risk in terms of incidence and volunteer misconception.<sup>133</sup>

The incidental finding language cited in the volunteer expectation study was out of context of the entire form; however, one institution placed the incidental finding language at the end of the “Description of the discomforts, inconveniences, and/or risks that can be reasonably expected as a result of participation in this study” section.<sup>134</sup> Moving the incidental finding language to a separate section may prevent confusion. One study has explored different methods for improving volunteer comprehension in informed consent research.<sup>135</sup> Results were inconclusive for the effect of multimedia and enhanced consent forms such as touch-screen interactive forms and PowerPoint presentations.<sup>136</sup> Some results suggest volunteer understanding may be improved by having a research team member or neutral educator spend time explaining the consent form.<sup>137</sup> Overall, these

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130. OFFICE FOR HUMAN RESEARCH PROTECTIONS (OHRP), HHS, OHRP INFORMED CONSENT FREQUENTLY ASKED QUESTIONS, at [www.hhs.gov/ohrp/informconsfaq.html](http://www.hhs.gov/ohrp/informconsfaq.html) (last visited May 19, 2009).

131. 45 C.F.R. § 46.109(b) (2008) (“An IRB shall require that information given to subjects as part of informed consent is in accordance with § 46.116. The IRB may require that information, in addition to that specifically mentioned in § 46.116, be given to the subjects when in the IRB’s judgment the information would meaningfully add to the protection of the rights and welfare of subjects.”).

132. 45 C.F.R. § 46.116 (2008).

133. See Kirschen et al., *supra* note 115.

134. University Consent, *supra* note 30.

135. James Flory & Ezekiel Emanuel, *Interventions to Improve Research Participants’ Understanding in Informed Consent for Research: A Systematic Review*, 292 JAMA 1593, 1593-94 (2004).

136. *Id.* at 1595 tbl.1.

137. *Id.* at 1599.



are relatively low-cost and easily implemented options to ensure consent is truly informed which should be further investigated.

Participants at the National Institute for Health discussed the possibility of consent forms that give volunteers the opportunity to opt-out of receiving any health information generated from their participation in the research.<sup>138</sup> To the extent it puts researchers in an “ethical conundrum” when faced with seemingly obvious life threatening findings, it must be reconciled with respect for volunteer autonomy.<sup>139</sup> If the volunteer chooses not to find out about potential health problems, the other questions surrounding incidental findings need not be addressed. A survey about the expectations and attitudes of volunteers prior to participating in research after providing a full picture of the risks and benefits tied to disclosing incidental findings could help focus options for dealing with those volunteers who still wish to be informed.

While some have changed their positions on this matter,<sup>140</sup> option consent forms should be implemented, thus removing the burden of unwanted information from volunteers’ minds and removing any difficulty a researcher may have in deciding whether or not to disclose information. In addition to an explicit description of the current protocol for handling incidental findings,<sup>141</sup> volunteers could benefit from learning of the prevalence of incidental findings, the risks involved with disclosure, the possible outcomes, and the likely outcomes. Also, volunteers should know that the scans are not likely optimized for diagnosis. The Workshop participants agreed it would be an unfair burden to require research labs take additional clinical-grade scans for the purpose of potential diagnosis.<sup>142</sup>

Finally, alternate sources of funding should be considered to cover costs associated with participant follow-up. While changing research protocols to include the potential for incidental findings will certainly increase costs, one important concern is which costs the researcher should cover beyond notification. Referral is considered an absolute minimum, but the question remains whether it is sufficient to refer a participant who has no means to pay for necessary follow-up.<sup>143</sup>

The potential for incidental findings is shared by all researchers conducting MRI studies. Therefore, to relieve burdensome costs associated

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138. Illes et al., *Workshop Summary*, *supra* note 11, at 784.

139. *Id.* (noting respect for participant “autonomy is difficult to reconcile with a Good Samaritan ethos.”).

140. Illes & Chin, *supra* note 113, at 303.

141. See discussion *supra* Part III.

142. Illes et al., *Workshop Summary*, *supra* note 11, at 784.

143. Illes & Chin, *supra* note 113, at 303-04.

with volunteer follow-up, one option might be to create a centralized source of funding. Analogous to IOLTA accounts,<sup>144</sup> money received for qualified research could be held in trust, with interest allocated to a centralized pool which would fund necessary participant follow-up costs. Qualified research might include neuroimaging studies in which researchers have protocols in place for reviewing scans and notifying participants of incidental findings. This would both relieve researchers of the dilemma posed by under- and uninsured volunteers who potentially need urgent follow-up care and minimize budget increases for handling incidental findings.

#### CONCLUSION

The increased prominence of MRI in research settings means that an increasing number of researchers will be faced with incidental findings. Incidental findings place both researchers and participants in a difficult situation, introducing potentially urgent medical conditions to otherwise unrelated research. To continue MRI research, protocols should anticipate incidental findings and recognize the unique problems surrounding their discovery. This possibility may necessitate heightened attention in the informed consent process. Once the potential for incidental findings is properly explained in the consent, participants should have the option to not be informed. Finally, the increased costs relating to volunteer follow-up should not be shouldered by individual institutions. Given the nature of incidental findings, institutions should look for ways to share costs through pooled participant follow-up funds. This will help ensure that the scientific pursuit is not sidelined for a potentially medically significant incidental finding.

HOLLI KUBICKI\*

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144. IOLTA.ORG, What is IOLTA?, at [www.iolta.org/grants/](http://www.iolta.org/grants/) (last visited May 19, 2009). IOLTA stands for Interest on Lawyers Trust Accounts. "Without taxing the public, and at no cost to lawyers or their clients, interest from lawyer trust accounts is pooled to provide civil legal aid to the poor and support improvements to the justice system." *Id.*

\* J.D./M.P.H. candidate, Saint Louis University, January 2010; B.S., Cognitive Studies, Psychology emphasizing Neuroscience, *cum laude*, Vanderbilt University, 2001. I would like to thank the Executive Board and Staff of the *Saint Louis University Journal of Health Law & Policy* and all others who graciously agreed to read earlier drafts.