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## A System for Addressing Incidental Findings in Neuroimaging Research

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### Abstract

When healthy subjects undergo brain imaging, incidental findings are not rare. The optimal response to such findings has been the focus of considerable discussion. The current report describes the operations and results of a system that provides review of incidental findings by an appropriate medical professional. A web-based system was created whereby investigators performing brain MRI scans on healthy subjects could refer images with suspected concerns to a board certified radiologist who had a Certificate of Added Qualification in Neuroradiology. The specific details of this system are described. Among 27 scans suspected by an investigator of having a significant finding, all but one were referred by a researcher with a PhD. The most common concerns described by these investigators were for the possible presence of a cyst or of enlarged ventricles. The most common findings reported by the radiologist were Virchow-Robin spaces and cysts. Findings were generally of low clinical significance, with 1 major exception. Identifying the optimal response to incidental findings in neuroimaging research remains a challenge. The current report describes a system for providing expert assistance and so addresses these issues in the setting of suspected incidental findings. To our knowledge the current system is the first to provide a specific means for evaluation of incidental findings in neuroimaging research.

### Keywords

incidental findings; neuroimaging; brain; MRI

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Magnetic resonance imaging (MRI) is an increasingly useful tool for clinical research, with the number of healthy subjects receiving scans for research numbering in the tens of thousands per year. One result is an increase in the frequency with which unexpected, and potentially clinically significant, asymptomatic results have been uncovered (Morris et al., 2009; Seki et al., 2010; Vernooij et al., 2007), with a prevalence in the general population ranging from 2–8 percent (Illes et al., 2002; Illes et al., 2004; Kirschen et al., 2006; Seki et al., 2010; Wolf et al., 2008). Indeed, in one survey of imaging investigators, 82% reported discovering incidental findings in their studies (Illes et al., 2004). Substantial variability exists in the procedures for responding to such findings. This has led to discussions focused on the ethical requirements of clinical investigators who obtain research MRI scans on

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healthy human volunteers. Three vignettes from personal experience (SCC) demonstrate some of the issues:

*Subject A* was scanned as a healthy subject. The graduate student on the project thought she saw an incidental brain lesion, but the Principal Investigator declined to pursue the concern, stating lack of obligation or expertise on such matters. The matter was addressed when the student sought out and received assistance from one of the current authors.

*Subject B* was scanned as a healthy subject. The brain MRI showed several lesions that appeared to be cavernous hemangiomas. When the subject was informed of this and referred to a neurologist for further evaluation, she noted that her brother had the same diagnosis, and that ascertaining her own status on this issue had been her purpose for enrolling in the study.

*Subject C* had a complex medical history but met entry criteria for a study of chronic stroke. Brain MRI disclosed a substantial subdural hematoma, and the subject was referred to a neurosurgeon, who evacuated the hematoma.

Divergent views have been advanced regarding the ethics and obligations of investigators in relation to neuroradiological findings incidentally discovered during research. Suggestions range from having expert review on all research scans on healthy controls (Milstein, 2008) to no reporting of any incidental findings (Royal and Peterson, 2008; Seki et al., 2010). The optimal approach would be one that strikes a balance between reasonable obligations to enrollees without overwhelming the process of research. In this context, several authors have called for universal guidelines for handling incidental findings (Illes et al., 2002; Illes et al., 2004; Kirschen et al., 2006; Seki et al., 2010; Wolf et al., 2008), and in some cases proposed hypothetical protocols for managing incidental findings (Illes et al., 2008; Seki et al., 2010; Wolf et al., 2008). However, to our knowledge, to date there has not been a translation of these suggestions into practice. We report here experience with, and consider the implications of, a system that provides a means for standardized review of selected images acquired in a research context, whereby an MRI scan obtained for research purposes can be submitted for review by physicians with appropriate medical expertise.

## Methods

Investigators at the University of California, Irvine were informed of a service to have a brain MRI scan acquired from a healthy subject interpreted by a neuroradiologist from the Department of Radiology whenever review of the MRI by the investigator generated a concern. This service was supported by General Clinical Research Center (GCRC), now Clinical Translational Sciences Award, funds. The scans had to be acquired in a research study that was approved by the UC Irvine Institutional Review Board. Images were acquired at the University of California, Irvine, using either a 1.5 or a 3 Tesla Phillips scanner. Investigators were informed of the system's existence in two ways. First, the system was described on a link found within the GCRC website; second, the system was actively promulgated to the University of California, Irvine neuroimaging research community via descriptions included at the bottom of lecture announcements from the Neuroimaging Core of the GCRC.

Neuroradiological consultation was provided through a secure link off the GCRC website. Access was restricted to persons with a University of California, Irvine online ID and password. Website instructions prompted investigators to provide contact information for the investigator, subject age and gender, and the concern to be addressed. Instructions made clear the need to avoid transmitting any identifying information about the subject.

Instructions then prompted the investigator to upload available anatomical MRI images, which consisted of a T1-weighted high resolution scan. Images could be in either ANALYZE format, in which case both image and header files were uploaded in unison, or DICOM format, in which case all slice images were uploaded in a single zipped folder. After the upload was completed, an e-mail was sent to the investigator confirming receipt of the request and images. ANALYZE images, if submitted, were converted to DICOM image format.

A unique, anonymous ID number was assigned to the request, then a .txt extension was appended to each file to prevent auto-execution of fraudulent files. Images were then scanned with antivirus software. DicomWorks (<http://dicom.online.fr/>) was used to anonymize images in a HIPAA-compliant manner, then subject age and gender were added to the DICOM header.

Finally, images were securely transmitted to the Picture Archiving and Communication System (PACS) computer in the Department of Radiology at the UC Irvine Medical Center using eFilm ([www.efilm.com/](http://www.efilm.com/)). Information on the concern to be addressed was inserted into a Microsoft Access database that was made available to the radiologist.

After images were uploaded to the PACS computer, an e-mail was sent to the appropriate official in the Department of Radiology, with notification of the new consultation request. This notification also provided an account to be used to pay for the radiology fees. These fees were covered by the GCRC so that the investigators were not billed. An additional e-mail was sent to the investigator, with an update on the status of the consultation request.

Each scan was reviewed by a faculty member of the Department of Radiology who was board certified in Radiology, and who had a Certificate of Added Qualification in Neuroradiology. The radiologist reported findings and, at his/her own judgment, adding possible recommendations for referral as appropriate. A hard copy of the report was sent to the GCRC, which then forwarded results to the investigator, with an MD on the study team (SCC) available to answer any further questions raised by the report. Subsequent action was at the discretion of the investigator.

## Results

### Characteristics of investigators requesting radiological consultation

A total of 27 scans were submitted over a 63 month period, during which time an estimated 5,000 brain MRI scans were obtained overall for research purposes at this university. The cost of each MRI interpretation was \$50, a rate defined through negotiation with the Dept. Radiology upon establishing this service. Approximately 25 labs had access to the system. The submitted scans originated from multiple departments: 17 from the Department of Neurobiology & Behavior, 7 from Cognitive Science, 1 from Family Medicine, 1 from Neurology, and 1 from Pediatrics. All but one (96.3%) of the submissions came from groups whose principal investigator was a PhD; with one request coming from a group led by an MD. Three researchers accounted for 19 (70.4%) of the requests; two of these focus on issues related to aging.

### Concerns described by MRI investigators

Among the 27 subjects who were scanned, gender was equally distributed, with 14 (51.9%) being female and 13 (48.1%) being male. The age of subjects ranged from 18 to 90 years, with mean ( $\pm$  SD) of  $38 \pm 24$  years. The specific concern described by investigators in their request was a cerebrospinal fluid cyst (29.6 %), enlarged ventricles (22.2 %), focal atrophy (11.1 %), or stroke (7.4 %). Requests that occurred once (3.7%) included concern for

aneurysm, detached blood vessels, enlarged frontal sinus, hypodensity, pituitary gland abnormalities, sinus polyp, subdural hematoma, unidentified bright spots, and unidentified dark spots (Table).

### Radiologist findings and recommendations

The time between request for review and review of the scan was  $8.1 \pm 8.5$  days, with a range of 0 to 37 days. The most common findings were Virchow-Robin spaces (25.9 %), dorsal midline cystic cavity (11.1 %), arachnoid cyst (7.4 %), atrophy (7.4 %), congenital ventricular asymmetry (7.4 %), and venous angioma (7.4 %). Findings that occurred once included enlarged ventricles, falx calcification, hydrocephalus, hyperostosis of inner table of bilateral frontal bones, maxillary sinus polyps, and sphenoid sinus cyst. In 22.2 percent of scans, there was no abnormality noted (Table). Note that none of these findings varied significantly in relation to age.

Of the 27 requests, the radiologist added a specific recommendation for referral to the MRI interpretation in two instances. In one case where the initial concern was enlarged ventricles, urgent referral was recommended, and was pursued (Table). In a second case with the same initial concern, the radiologist noted that the findings likely represented a normal variant and suggested a follow-up MRI in several months.

### Discussion

With a prevalence of 2–8 percent (Illes et al., 2002; Illes et al., 2004; Kirschen et al., 2006; Seki et al., 2010; Wolf et al., 2008), incidental findings are not uncommonly encountered when healthy human subjects undergo a brain MRI scan. Although asymptomatic and often unimportant, incidental findings can be of potential clinical significance in at least some instances. The current report describes the operations and results of a system that provides review of incidental findings by an appropriate medical professional. Among 27 scans suspected by a research investigator of having a significant finding, the most common concerns expressed were for the presence of a possible cyst or of enlarged ventricles. The most common findings reported by the neuroradiologist were Virchow-Robin spaces and cysts. Findings were generally of low clinical significance, as expected (Katzman et al., 1999). The most serious finding was a single case in which hydrocephalus was described. Although several protocols for the management of incidental findings have been suggested in the past (Illes et al., 2008; Seki et al., 2010; Wolf et al., 2008), to our knowledge the current system is the first to provide a specific means for evaluation of incidental findings in neuroimaging research.

Vigorous debate has surrounded the ethical requirements that accompany scanning the brain of healthy subjects for research purposes. Importantly, given the non-trivial prevalence of incidental findings, the likely question is when, not if, such findings will be encountered. On the one hand, great attention to each scan has been proposed. A *de facto* maximum standard of including an expert on the research team for clinical review of these incidental findings (Illes et al., 2008) and the more rigorous *de jure* maximum standard of having an expert review all research scans on healthy controls in pursuit of incidental findings (Milstein, 2008) have been suggested. Others have noted that any incidental findings identified should be shared with the research subject (Illes et al., 2008; Seki et al., 2010; Vernooij et al., 2007). In support of these views is the fact that, regardless of the language in consent forms, many subjects participate in imaging research with the expectation that if an incidental lesion is present, it will be identified and reported to the subject.

A number of concerns exist on the other side of the debate. In particular, requiring expert review of all research scans makes this a form of medical screening, which in most cases is

not the goal of the research. Medical screening with MRI is generally of unproven medical utility, as the rate of false positive findings may be prohibitively large in the healthy population (Seki et al., 2010) and the vast majority of asymptomatic findings are ultimately of limited clinical importance (Ilmoniemi et al., 1997). Note that the system described herein is not intended to serve as a means to expand screening, but instead to serve as a mechanism to access professional input when this is deemed necessary by a concerned research investigator.

Other concerns exist regarding the suggestion to require expert review of all research MRI scans. Noting to enrollees that all research scans will undergo formal clinical review might serve as an inducement to enrollment, as with *Subject B* (see Introduction). Disclosure of low-significance incidental findings to subjects might generate undue anxiety (Wolf et al., 2008). Also, some have noted that requiring expert review of all research scans is unrealistic (Wolf et al., 2008) and often not feasible (Royal and Peterson, 2008), such as in relation to the financial burden this would impose. Indeed, requiring formal clinical assessment of every scan obtained for research purposes could seriously hamper the pace of brain research. Furthermore, research-based MRIs are usually not optimized for clinical diagnosis (Illes et al., 2002; Illes et al., 2004; Kirschen et al., 2006; Royal and Peterson, 2008; Seki et al., 2010; Wolf et al., 2008). For example, in the current case, only a single anatomical pulse sequence was acquired, in contrast to the multiple pulse sequences typically acquired during a clinical MRI session. In the most extreme stance, exhaustive reporting requirements for potential incidental findings might therefore imply a need to acquire multiple pulse sequences not directly related to the research question under investigation. In light of these concerns, some have suggested that incidental findings should never be reported given the overall clinical risk-benefit analysis (Royal and Peterson, 2008; Seki et al., 2010).

If experience comes to suggest high utility for a system such as this, a number of issues might require addressing in the future. Some investigators at our university used this system more than others, a complex issue that likely reflects divergent investigator views on the need for and value of such a neuroimaging consult system. One future focus might therefore explore how to modify the system to increase subscription among a higher fraction of investigators. Another future direction might be to provide support for imaging modalities beyond brain MRI. Possibly, a centralized university service, or even commercial structure, might be implemented to provide this service more broadly, including for sites that lack the needed expertise. To be fair, such a suggestion raises the issue of the cost of this system, which was covered by an NIH grant in the current experience but might ultimately increase the cost of research scanning. Also, the approach used with a system such as this might vary in relation to the study population, for example, the optimal approach to the issue of incidental findings might vary when studying children of those with neurofibromatosis I vs. healthy subjects in their ninth decade vs. healthy teenagers. If such a service to investigators does expand over time, issues such as if and how to describe it in consent forms would require clarification. The current service was available only to academicians, but a similar service might extend access to MRI technicians, who regularly see a large volume of scans. Finally, potential legal implications might arise, for example, for diagnosing a false positive or for failing to diagnose a true positive.

The approach underlying the system in its current form is a centrist one, neither ignoring all incidental findings outright nor requiring that each research scan receives the attention of a radiologist. The aim is a balance--having expert review available but not required. This approach is only useful to the extent that an incidental lesion is apparent to an investigator performing MRI research, and in this regard is concordant with the minimum ethical standard advocated by Illes et al (Illes et al., 2002). Strengths of the current approach are its HIPAA compliance, ease of use, and reliance on physicians with subspecialty expertise.

Weaknesses include a focus on brain MRI scans, though a service could easily be expanded to other scan types, and a turnaround of approximately one week, though this could be shortened as necessary. Less than 1% of brain MRI scans performed at our university were referred to this service during its five years of operation, though incidental findings are found with much greater frequency (Illes et al., 2002; Illes et al., 2004; Kirschen et al., 2006; Seki et al., 2010; Wolf et al., 2008). This difference might reflect many factors, such as variation in local interest in this service, or use of more elaborate MRI protocols with multiple pulse sequences in some prior studies of incidental findings.

Identifying the optimal response to incidental findings in neuroimaging research remains a challenge. We believe that the current system is a useful step towards defining a balanced response to such findings: if *Subject A* (see Introduction) is scanned today at the University of California, Irvine, the Principal Investigator now has a simple option available to access clinical neuroradiology expertise. Analyses and recommendations for management of incidental findings (Illes et al., 2006) have noted that researchers “should anticipate the possibility of identifying incidental findings” and highlight the need for a “plan to verify and evaluate a suspected incidental finding” (Wolf et al., 2008). The current report describes a system for providing expert assistance and so addresses these issues in the setting of suspected incidental findings.

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Table

Concern described by investigator	Radiologist findings and recommendations
Aneurysm (n=1)	No abnormality (n=1)
Cerebrospinal fluid cyst (n=8)	Arachnoid cyst (n=1) Dorsal midline cystic cavity (n=3) No abnormality (n=2) Virchow-Robin space (n=2)
Detached blood vessels (n=1)	No abnormality (n=1)
Enlarged ventricles (n=6)	Atrophy (n=1) Congenital ventricular asymmetry (n=2) Enlarged ventricles (n=1) Hydrocephalus (n=1)** Likely no abnormality, though possible hydrocephalus (n=1)*
Focal atrophy (n=3)	Atrophy (n=1) No abnormality (n=1) Arachnoid cyst (n=1)
Hypodensities (n=1)	Virchow-Robin space/venous angioma (n=1)
Large frontal sinus (n=1)	Virchow-Robin space (n=1)
Pituitary gland abnormality (n=1)	Sphenoid sinus cyst (n=1)
Sinus polyp (n=1)	Maxillary sinus polyp (n=1)
Stroke (n=2)	Virchow-Robin space (n=2)
Subdural hematoma (n=1)	Hyperostosis of inner table of bilateral frontal bones (n=1)
Unidentified bright spot (n=1)	Falx calcification/venous angioma (n=1)
Unidentified dark spot (n=1)	Virchow-Robin space (n=1)

Investigators from diverse backgrounds expressed concerns about brain MRI scans acquired in healthy subjects in a research context. Each scan was reviewed by a neuroradiologist who reported findings and, when appropriate, added a recommendation regarding referral.

\*\* Urgent referral recommended by radiologist.

\* Non-urgent referral recommended by radiologist.