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Stakeholder Opinions And Ethical Perspectives Support Complete Disclosure Of Incidental Findings In MRI Research

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Abstract

How far does a researcher's responsibility extend when an incidental finding is identified? Balancing pertinent ethical principles such as beneficence, respect for persons, and duty to rescue is not always straightforward, particularly in neuroimaging research where empirical data that might help guide decision-making is lacking. We conducted a systematic survey of perceptions and preferences of 396 investigators, research participants and IRB members at our institution. Using the partial entrustment model as described by Richardson, we argue that our data supports universal reading by a neuroradiologist of all research MRI scans for incidental findings and providing full disclosure to all participants.

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Introduction

Neuroimaging researchers can no longer ignore the possibility that they will encounter incidental findings (IF) in the course of conducting clinical studies. This has become a more urgent issue recently, as higher field strength MRI scanners, higher definition monitors and more sophisticated imaging sequences identify IF more often than older, less sensitive imaging equipment and protocols. Dealing with IF is far from straightforward, however. Multiple stakeholders are involved and important ethical principles must be considered (Illes et al., 2006), (Wolfe, Paradise, & Caga-anan, 2008). Indeed, the problem of what to do with IF has been identified by imaging researchers as one of the most important ethical questions in research today (Deslauriers et al., 2010).

In research, an IF can be defined as "a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study" (Wolf, Lawrenz, et al., 2008). IF requiring urgent medical attention are rare, with a published prevalence of approximately 1-2% (Katzman, Dagher, & Patronas, 1999), (Vernooij et al., 2007), (Weber & Knopf, 2004), (Illes et al., 2004), (Gur et al., 2013). With serious findings the diagnosis and intervention options are often clear, and a strong ethical argument grounded in the duty to rescue can be made for providing such results and clinical direction to protect a research participant in imminent danger. More problematic from an ethical standpoint, however, are individuals participating in MRI studies who have IF of unclear medical significance, a number that can be greater than 50% of healthy middle age adults (Wen, Sachdev, Li, Chen, & Anstey, 2009). Most of these findings will have no clinical importance at any time in a person's life. Is the investigator ethically obligated to provide these results back to participants?

While it may not be possible, or even desirable, to always honor all research participant requests, the ethical principle of Respect for Persons suggests that opinions at least be elicited from participants and taken into consideration when feasible. In the only large MRI study evaluating research participant perceptions, Kirschen et al reported a systematic survey of former participants who had a brain MRI scan between several months and 3 years previously (Kirschen, Jaworska, and Illes 2006). Of 105 participants, most were college students or academic faculty (average age 24.5 years), representing several ethnic groups. A majority of these subjects indicated that they participated in the MRI research either for class credit or financial compensation. 59% of respondents expressed a desire to receive IF information from a physician on the research team, and over 90% indicated that they wanted to receive IF information regardless of its clinical significance. Subjects were not specifically asked why they wanted their IF results, therefore motivation for wanting this information is not known.

The Kirschen study is one of the few that characterize research participant perceptions, however other important stakeholders are also involved in the discussion of how to address IF in MRI research (for review see (Wolf, Paradise, & Caga-anan, 2008) and (Illes et al., 2008)). Little empirical data is available that probes the perspectives of all stakeholders involved in neuroimaging research. Such information is necessary to allow development of an approach to IF that satisfies normatively relevant ethical principles but yet does not unduly burden and inhibit the research enterprise. To address this need, we conducted a systematic survey of 3 key stakeholder groups at a single large neuroimaging research center. This work provides the first broad inquiry of key stakeholder opinions and preferences, as well as characterizes the impact of a system of universal IF disclosure to research participants.

Methods

Our questionnaires were completed by investigators working in a system that mandates neuroradiology review of MRI scans and provides reports back to research participants. These activities are accomplished by an institutionally supported structure that provides a neuroradiologist and university based medical director, who is available to answer participant questions and help address any issue concerning IF identified, and therefore requires minimal investigator effort (Shoemaker et al., 2011). Three subject cohorts were studied: former research participants, Institutional Review Board (IRB) members associated with the University of New Mexico (UNM), and investigators who scan at our imaging institution.

Former research participants were identified via review of our imaging center's Collaborative Informatics Neuroimaging Suite (COINS) database. Participants were eligible if they received a single MRI report from a study between three and 18 months previously, were not incarcerated and were 18 years of age or older. Individuals who met inclusion criteria were invited to participate either through an e-mail invitation or via a letter sent to the last known home address. All eligible research participants with known addresses received an e-mail solicitation with a unique link to the survey. IRB Members were identified through publically available lists of current and former members of the five UNM IRB Committees, all of whom received an e-mail invitation to complete the survey. Internal lists of all current and former investigators, including employees and external investigators, were collected for recruitment and sent e-mail invitations.

Three distinct surveys, with overlapping content, were designed to examine the perspectives and experiences of each subject cohort. Surveys were developed through discussion and literature review by an interdisciplinary research team with expertise in bioethics, survey design, IRB administration and neuroimaging research. The final survey versions allowed for both in depth and cross-subject comparisons, drawing on previous queries related to specific IF disclosure issues (Kirschen, Jaworska, & Illes, 2006) as well as adaptations of validated instruments.

The 67-question research participant survey focused on levels of perceived anxiety, health literacy and the impact of receiving their MRI report. Modifications of three validated

instruments were incorporated in this participant survey. This included The Health Anxiety Inventory, which is based on self-assessment of 18 questions (i.e.,"I think I have a serious illness" or "I never worry about my health") generating a composite Health Anxiety Score (Salkovskis, Rimes, Warwick, & Clark, 2002). The second validated instrument used was Spielberger's Test Anxiety Inventory which was modified to specifically reflect anxiety related to receiving an MRI scan report, based on 11 questions rated on a scale from 0 to 100 (Spielberger et al., 1980). Finally, a modified Brief Health Literacy Tool was included which required research participants to self-assess their level of health literacy based on 4 questions regarding ability to understand general health information (Chew, Bradley, & Boyko, 2004); this generated a health literacy composite score. Participant survey data were analyzed alongside existing MRI report information, including severity of finding and recommendation for follow up, gathered from the initial identification process described above.

The 35-question IRB member survey assessed attitudes on the importance of addressing IF in the IRB review process and the relative perception of participant benefit or harm. The 45-question investigator survey queried concerns regarding the research burden of performing IF review and reporting all results to research participants. The survey included questions about the logistics of the reporting process and investigator perceptions of research participant's literacy and anxiety levels. Many survey questions were similar across stakeholder groups to allow intergroup comparisons. All three surveys collected demographic information and utilized a variety of question types (multiple choice, open text and analogue sliders ranging from 1-100).

All surveys were available to stakeholders online (completed remotely or on-site upon request) through the use of the COINS self-assessment feature, a software developed at our imaging center that allows secure data collection and storage (Bockholt et al., 2010).

Statistical methods

One-sample binary variables were analyzed using exact binomial confidence intervals. Two-way tables of categorical variables were analyzed using Fisher Exact tests (including situations with larger than 2X2 tables). Group comparisons on continuous variables were performed using one-way ANOVA with Tukey post hoc comparisons, except in cases where there were outliers or large numbers of tied values (e.g. many values of "100"). When ANOVA was not appropriate for group comparisons on continuous variables then Mann-Whitney-Wilcoxon or Kruskal-Wallis tests were employed, as appropriate, with exact p-values calculated; post hoc comparisons were performed in this case using exact Mann-Whitney-Wilcoxon tests (when there were more than two groups). Correlation between continuous variables was assessed using Spearman's rho, because in all cases distributional problems were present. Statistical significance was taken as two-sided p-value < 0.05. Summary statistics for continuous variables were reported as Median [Lower Quartile = Q_1, Upper Quartile = Q_3] due to skewness in the data. All calculations were performed in SAS ver. 9.3.

Results

Subject Demographics

396 individuals completed surveys. Stakeholder characteristics are summarized in Table 1. Additional specific characteristics are as follows. *Former research participants*: n=196, included the following racial percentages American Indian (2.1%), Asian (1%), Native Hawaiian or Pacific Islander (.5%), African American (3.1%), White (77.5%) and the remaining preferred not to answer (15.7%). *Investigators*: n=150, research positions included research staff (60%), Co-Investigators (9%) and Principal Investigators (21%) and of all investigators 62% had direct interaction with participants. *IRB Members*: n=50, length of IRB membership was quantified as those serving less than 5 years (62%) and those serving for more than 5 years (32%).

Evaluating Research MRI Scans

Several questions were asked regarding evaluating and reporting IF. When asked whether the ethical approach is to report IF regardless of cost, the vast majority of all stakeholders agreed. The median for all groups for this question was greater than 90 on a scale from 1 (strongly disagree) to 100 (strongly agree) [Q_1:79, Q_3:100].

When asked slightly differently, whether the time and money required to report IF was worth it even if only a small number of research participants medically benefited, there was also consistency among stakeholders. The median response was 79.4 [Q_1:50, Q_3:95.5] for investigators, IRB members and research participants, with no significant difference between groups. Some stakeholders completing the surveys took advantage of an opportunity to expand on their answers with written comments; examples of these comments are in Table 2A.

Investigators acknowledged that research participants are likely to want to know about IF on their scans (median 87.1 [Q_1:70, Q_3:99.3]), and indeed research participants expressed the position that having their MRI scan reviewed for incidental findings and getting a report of this radiology review is a benefit of study participation (yes-89.5%).

Incidental Finding Disclosure

Several questions highlighted more specific stakeholder opinions regarding evaluating and reporting MRI scan results. 73% of investigators and 57% IRB members expressed the position that all MRI scans should receive neuroradiology review, not just those where an MRI technician observed unusual scan findings, or scans performed on high risk populations. Less consensus was noted regarding what information should be provided back to the individual participants. Only 27.2% of investigators and IRB members stated that all results should be provided to participants, which is significantly lower than the 78% of research participants who wanted all scan findings to be communicated ($p<.0001$). When queried about specific examples, 88.8% of participants stated they would want to know if their MRI was normal or had no findings, 86.7% if there was a treatable condition such as a brain tumor, and 84.2% would want to know even if the MRI scan showed an untreatable condition such as an incurable brain tumor.

There was a significant difference between investigators and participants on how best to provide incidental finding information to research participants (p<.0001). Participants largely preferred either a letter (40.8%) or a letter and a phone call (22.5%), while investigators felt the method of communication depended on the severity of the finding (56.5%). If incidental finding information was provided by a person, another point of disagreement between stakeholders was who that person should be (p<.0001). Participants preferred to hear the report from a physician on the research team (34.6%) or someone with whom they have had significant previous contact (32.5%), whereas investigators and IRB members agreed that a team physician should convey the results when possible (32% and 42.8% respectively) but showed little support for a familiar research team member reporting findings to participants (6.8% and 11.9% respectively). Some stakeholders chose to further elaborate on their answers to questions regarding incidental finding disclosure, and representative comments are in Table 2B.

Harm

Our surveys queried about several types of harm that might result from reviewing scans and reporting incidental findings to participants. Time burden to researchers was not a major concern expressed by our investigators overall with a low median of 20.3 [Q_1:6, Q_3:51] on a scale from 0 to 100, however there were differences between subgroups of investigators. When comparing PIs with research staff, PIs reported significantly less burden than research staff (PI median=11.0 [Q_1:4, Q_3:30] and research staff median=26.5 [Q_1:5, Q_3:50], p<.018). Similarly, investigators with and without direct participant interaction were compared; the burden to research was described to be less by investigators having direct participant contact (median=12 [Q_1:4, Q_3:49]) than those investigators without direct participant contact (median=28 [Q_1:6.5, Q_3:50], p<.047). Cost burden was judged to be lower by PIs (median=20 [Q_1:6.5, Q_3:50]) than research staff (median=50 [Q_1:11.5, Q_3:51], p<.06).

Harm to research participants may also be a concern. However, the majority of IRB members and investigators feel it is unlikely that reporting IF to participants will cause them harm (IRB median is 24.1 [Q_1:10, Q_3:36.3] and investigator median is 15.2 [Q_1:5, Q_3:35]). There was an observed significant difference between principal investigators and research staff (principal investigator median 11.4 [Q_1:5, Q_3:23] and research staff median 19.1 [Q_1:10, Q_3:35.8]), but no difference based on amount of participant interaction, nor between IRB members and investigators. Only 2.5% of research participants felt that reporting IF results could cause harm to them.

Anxiety was specifically addressed in our surveys. This included general anxiety about one's own health as well as anxiety related to receiving an MRI report. 49% of investigators and 55.6% of IRB members agreed that causing some mild amount of anxiety as part of providing incidental finding reports was acceptable. Select stakeholder comments further characterizes both IRB member and investigator concerns regarding potential emotional and financial harm in Table 2C.

In a related series of questions, former research participants were asked to rate the anxiety they personally experienced as part of receiving their incidental finding report. This was quantified using the MRI Report Anxiety Score, which was rated as very low overall on the

scale from 0-100 (median=8.6 [Q_1:3.3, Q_3:22.2]) and was not related to insurance status (p<.47). There was a significant relationship between anxiety and the severity of the incidental finding identified (p<.001), indicating that if an incidental finding requiring medical follow up was identified, there was greater participant anxiety. The participant MRI Report Anxiety Score also significantly correlated with a measure of general medical anxiety, the Health Anxiety Score (Rho=.20, p=.01, see Figure 1A).

Following up IF can be an added burden to research participants. 18% (n=36) of our research participants had received an MRI report that indicated they should follow up an IF with their primary care physician. 9% (n=17) of participants actually sought further medical evaluation as a result of an IF that was identified, and 4 of these 17 incurred additional costs as a result. However, of the 17 who sought a medical evaluation, only 10 participants actually received a recommendation for clinical follow up, while the remaining 7 received an MRI report that specifically stated no clinical follow up was necessary. Thus, 28% of subjects did not see their doctor when asked to do so, and 2.7% saw a doctor despite a recommendation that it was not necessary.

Health Literacy

A significant disparity was noted between investigator and IRB member estimates of participant health literacy levels as compared to research participant self-reports. Participants consistently report significantly higher health literacy skills (p<.0001, Figure 2A), ability to understand research consent forms (p<.0001, Figure 2B) and radiology cover letters and MRI reports (p<.0001, Figure 2C). Despite these significant stakeholder differences, similarities were found across the qualitative statements provided by all subjects on the topic of participant literacy and research document readability (See Table 2D).

The self-reported level of health literacy of research participants also showed a significant correlation with MRI Report Anxiety (Rho=−.229, p<.002, Figure 1B) demonstrating that higher health literacy was related to lower anxiety associated with receiving an MRI report. Baseline Health Anxiety was also related to self-reported health literacy (Rho=−.1555, p<.044, Figure 1C) suggesting that higher literacy is related to lower baseline anxiety. Finally, there was a positive relationship between high judgments of participant health literacy and a preference for investigators returning all MRI incidental finding reports back to research participants (p<.001).

Discussion

We report the first objective, systematic study of the impact on key stakeholders at a single site of an IRB mandated radiology review for IF in MRI research. We found areas of consensus as well as disagreement among IRB members, investigators and research participants. Major findings are that while there was agreement that research MRI scans should be reviewed for IF, most research participants wanted all results reported back to them, while IRB members and investigators preferred providing only those reports with clear clinical significance. Investigators rated their burden in providing IF review and participant reporting to be low. We did not find evidence of high levels of predicted harm in the process of IF reporting by investigators or research participants. Similarly, research

participants' self-assessed anxiety related to actually receiving an IF report was also low. Of the anxiety that was present, significant correlations were identified between MRI report anxiety and health literacy, as well as between MRI report anxiety and baseline levels of health anxiety. However, these correlations explained little of the data variance, possibly because anxiety was generally very low. Finally, although IRB members and investigators perceived that research participants had low health literacy and ability to understand research consents and an MRI report and cover letter, research participants felt the opposite and rated their understanding to be high in all three categories. Taken together, these and other findings provide objective evidence of actual concerns and mistaken assumptions among key stakeholders regarding issues of importance to IF in MRI research, and offer insight into possible approaches to mitigating harm and maximizing the benefit associated with providing MRI reports to research participants.

Despite the high prevalence of IF in clinical neuroimaging research, there is no consensus or national standard to guide investigators in providing feedback to research participants. General guidelines have been suggested (Illes et al., 2008), but without specific published national standards, it is not surprising that various approaches are expressed in the literature. Current suggestions for dealing with IF range from providing a full clinical scan and reading with any research study (Milstein, 2008), to having a neuroradiologist review only those scans where something unusual is noted by a member of the research team even if the team is composed of non-medically trained persons (Cramer et al., 2011), to not reading any scans because of concerns of causing greater harm than benefit (Royal & Peterson, 2008). Thus, participants volunteering for similar studies can be treated very differently depending on the preference or other contextual features (i.e., budget, access to radiologists, available staff or institutional requirements) of a particular investigator or institution.

Central to discussing IF reporting is confronting the issue of harm. Searching for and reporting IF has been hypothesized to potentially harm research participants by causing needless anxiety, possibly leading to risky (and potentially unnecessary) preventative surgery or lifestyle changes, or at the very least, time consuming clinical appointments required to further evaluate an IF of unclear significance (Royal and Peterson 2008). Misunderstanding the inherent limitations of a research scan may provide a false sense of security (Kirschen et al., 2006), or when an IF is identified, disclosing this may impact one's ability to obtain health or life insurance. Indeed, the risk of harm is more than simply theoretical, with at least one published case of an individual who was unable to obtain life insurance after disclosing results of his research scan which unexpectedly identified a brain tumor (Anonymous, 2005).

Our study investigated several aspects of potential harm. Of the 196 research participants completing our questionnaire, 33 did not have health insurance at the time of the research scan, two of whom stated they were concerned that their research MRI scan might adversely affect their ability to obtain insurance at a later date. Fourteen of our research participants who were uninsured at the time of their research MRI scan subsequently did try to obtain health insurance and one person noted having had difficulty getting it as a result of the findings on the MRI scan. This experience highlights that health insurance can be a real issue for some research participants. In the US, even with the Affordable Care Act

prohibiting health insurance discrimination against those with pre-existing conditions, it is not clear how disclosing an incidentally identified brain abnormality to a health provider or an employer might affect the process of obtaining employment, insurance, or how this disclosure might affect the cost of coverage. The recently published report from the Presidential Commission for the Study of Bioethical Issues suggests that accessible and affordable healthcare is a requirement of justice, and a necessary component for appropriately addressing IF (chapter 3, recommendation #5, (Presidential Commission for the Study of Bioethical Issues, Washington, DC, 2013). There may still be challenges reaching this goal in the United States. Also, although our study did not specifically address obtaining life insurance, this may be affected as well by IF disclosure (Anonymous, 2005), which at present would not be protected under the Affordable Care Act. Thus, although the risk of adversely affecting insurability may be low depending on the population studied, reporting IF can result in significant adverse consequences for the individual. We agree with suggestions noted in prior reports that the insurability risk should be discussed and assessed for participant understanding during the consenting process when MRI scans are reviewed for IF.

Our study also addressed anxiety as a possible harm of IF reporting. Based on our MRI Report Anxiety Scale, most research participants rated the level of anxiety generated by receiving their MRI report as very low (median less than 10 on the scale from 0-100), although there were outliers who indicated higher anxiety. Anxiety associated with receiving an MRI report was higher when incidental findings of greater medical concern were identified, and in subjects who were generally more concerned about their health to begin with (Figure 1), however there was no relationship to the participant's medical insurance status.

Of particular interest was the relationship between anxiety associated with receiving one's MRI report and estimated levels of health literacy. As might be expected, participants with only a high school education had lower health literacy estimates based on the modified Brief Health Literacy Screening Tool than those with a higher level of education. Although health literacy did not predict motivation for participating in research studies, higher health literacy did correlate with an increased preference for investigators returning all MRI incidental finding reports back to research participants, and with reduced anxiety related to receiving an MRI report. While more participants with poor health literacy would be needed to better understand this relationship, this finding does raise the important question of whether anxiety associated with getting an MRI report could be further reduced by ensuring that information is adequately understood in participants with poor health literacy. This could be achieved by such measures as creating better communication tools or taking extra time when relaying MRI information to individuals with low health literacy. Therefore it appears that researchers conducting MRI research might consider including a valid measure of health literacy as part of their standard research protocol. Importantly, there was a discrepancy between what research participants reported to be their own high level of understanding of MRI reports and research consents, compared to investigators and IRB members who were concerned that research participants would not fully understand these documents (see Figure 2). Further work may help clarify how best to assess a participant's level of health literacy so that communication can be tailored appropriately.

Our data suggests that receiving an MRI report actually causes very little anxiety. Any harm resulting from this might be further reduced by identifying which individuals are at risk of excess anxiety based on 1) severity of the MRI findings, 2) participant's level of health literacy and 3) participant's anxiety about personal health issues in general. Pre-emptively identifying who is at greatest risk of adverse anxiety could potentially allow individualizing approaches to providing MRI results that might help mitigate this potential, albeit rare, harm.

We found conflicting views regarding which IF reports should be returned to research participants. Most investigators (research staff as well as principal investigators) stated that all scans should undergo professional neuroradiology review, but when asked specifically which reports should be provided to research participants, only 27% supported the position that all reports should be returned independent of their clinical value. This represents a fundamental difference in opinion than that of research participants, 78% of whom express wanting to receive complete reports. The source of resistance to returning radiology reviews is not clear. Investigators rated burden of the IF review system as low, therefore it seems unlikely that cost or time was a reason for not providing IF to research participants. Perhaps more likely, resistance may arise out of concerns regarding poor participant health literacy (Figure 2 indicates investigators largely assume research participants are unlikely to understand the MRI report), or concerns about causing needless worry (see also qualitative comments). Both of these concerns may be misplaced, however. In contrast to investigator assumptions about them, research participants rated their own ability to understand MRI reports as quite high, and showed generally low anxiety associated with receiving an MRI report (Figures 1 and 2). The preference of investigators to withhold MRI reports from research participants who want them suggests that some investigators may harbor paternalistic attitudes regarding the types of research generated information that participants "need" to know about, and see themselves as the primary decision-makers about those judgments. Given how participants in our study describe themselves and what they see to be benefits, such attitudes are difficult to reconcile with the objective data obtained in this study.

In clinical medicine, the role of paternalism began to change several decades ago. Until the latter part of the 20th century, physicians commonly focused on therapy and patient reassurance, even if this required hiding the full truth (such as not telling a patient they have an incurable disease, or that their cancer has returned so as not to destroy patient hope (Rosner, 2004). The rise of patient rights in the 1960's leading to the Patient Bill of Rights in 1973 stipulated that patients have a right to complete, accurate and understandable information from their health providers. Patient autonomy is now highly valued (Katz, 1984), and it is expected that all pertinent information be provided to patients to allow making personal health decisions consistent with their own value system and set of circumstances. This is not an obligation to provide ALL information – clearly such a "data dump" of important as well as extraneous information can impede understanding and appropriate decision making. There are exceptions to this duty, such as certain cultural contexts, when patients have limited capacity due to age or illness, or in emergent medical situations where there is no time for discussion. But in general it is expected that patients,

with physician support, make their own personal healthcare decisions regardless of whether the physician see them as coherent (Epstein, Fiscella, Lesser, & Stange, 2010).

However research is not clinical medicine, and obligations of investigators to research participants are certainly different than those of physicians toward patients. As stated in the Kennedy vs Krieger opinion: "...scientific research on human subjects can, and normally will, create special relationships out of which duties arise." (Grimes vs Kennedy Krieger, http://www.courts.state.md.us/opinions/coa/2001/128a00.pdf. See Glantz 2002). Miller and colleagues specified that position further when they proposed that the investigator/participant relationship is bound within the principles of beneficence and professionalism (Miller, Mello, & Joffe, 2008). In other words, researchers are obligated to actively prevent harm and benefit participants which will at times require the effacement of their own preferences and self-interest.

How far does an investigator's obligation extend when incidental findings are encountered? Henry Richardson argues the parameters of this obligation are defined through a fundamental relationship of *partial entrustment* that exists between investigators and research participants ((Richardson & Belsky, 2004), (Richardson 2012)). This relationship is an integral component of clinical research and arises from the participant's waiver of privacy rights that must occur for research to proceed. Waiving these rights automatically transfers fiduciary responsibility over study information to the researcher, which includes an obligation to provide some degree of ancillary care if study information discloses a need for medical care. In the Partial Entrustment Model (PEM), the *scope* of waived privacy rights defines whether an ancillary care obligation exists, and the *strength* of the researcher/participant relationship defines how much ancillary care is required.

Using the PEM as a guide, we believe our data supports the position that universal and fully professional radiology review of all research MRI scans should occur and in addition, results should be provided to participants. This is because of several shared properties of most human MRI research studies. First, most studies include at least one readable structural sequence which may provide information of potential medical importance to the research participant. This meets the PEM scope requirement. Secondly, although the strength of the investigator/participant relationship is highly contextual, three of the five factors necessary to assess this requirement as articulated by Richardson are present in essentially all MRI studies as follows:

- Participant vulnerability (if incidental finding information was not provided, how bad would this be for the participant?) – the immediacy of vulnerability depends on the finding. In some cases a research MRI discloses a finding that requires immediate medical action or encourages important lifestyle changes. More commonly, however, a participant's structural image is normal, or has a finding of unclear significance; this is critical information that can substantially improve the medical interpretation of any future clinical MRI scans that may be needed. Even a single structural sequence offers useful baseline information. Because approximately 6.6 million people undergo a clinical brain MRI scan annually in the US, there is a reasonable chance that a research subject would be among this

number at some point in their life (Report, 2010). This represents a large number of people who could potentially benefit from having a “baseline” for comparison when they need an MRI scan for medical reasons. Such an opportunity to help should not be minimized.

- Dependence on researchers (do participants have other options for getting this information?) - a structural MRI as part of a research study provides unique and personal information that is likely not otherwise available to most healthy research participants. It is not surprising that our surveyed research participants placed a high value on this information, with most wanting their MRI report regardless of what it showed.
- Cost (time and money required to be spent by the research team to provide this information) - In our system of MRI review, investigator and institution costs are minimized and a clinical neurologist is provided to assist participants with questions about their MRI reports.

The other strength factors to be evaluated as part of the PEM include participant burden and strength of the researcher/participant relationship. Optimizing this relationship can be achieved by meeting the clearly strong preferences for a broadened transparency regarding findings expressed by subjects in our study. This emphasizes the position that respect for persons be considered a longitudinal obligation throughout research participation and not just at the point of consent. These strength factors vary considerably based on study design, but may also favor providing incidental finding information to participants depending on circumstances. Therefore with our data suggesting low researcher burden, low participant harm, a strong participant desire to receive the MRI information, and a reasonable potential for benefit now or at some point in the future, it seems reasonable to review all research MRI scans for incidental findings and provide the MRI report to all participants.

Context is important. Many research environments do not currently have access to ancillary support such as neuroradiology review and medical director assistance. In such circumstances, providing a neuroradiological review of research scans may take time and money away from research activity. Ideally NIH would support such costs to research (Nelson, 2008). However the present NIH funding environment is highly competitive and many NIH grant budgets are cut, as was the one supporting this manuscript. What should be required of researchers in these straitened circumstances?

While investigators are not obligated to look for incidental findings (Presidential Report Recommendation #14 pages 91-93) it is unavoidable in MRI research, whether just by the person running the scanner, or by those involved in data analysis. This “unofficial” review is done by people of varying levels of expertise and experience, leading to inherent inconsistencies in quality of review as well as threshold for communicating information to research subjects. A more consistent and helpful review can be obtained by engaging a neuroradiologist to read all scans. This enhances justice by providing the same quality review to all subjects regardless of who is running the scanner or which research team is conducting the study, and also increases the possibility of beneficence to individuals who receive a professional reading of their MRI scan. However neuroradiologists are not always

available or affordable in proportion to the research budget. Because research promotes social good, the cost of providing any ancillary care (such as addressing incidental findings in MRI research) is a morally relevant concern (Richardson, 2012 p 163) which must be balanced against the overall research budget. When engaging a neuroradiologist may not be financially feasible, rather than lose the potential social benefits that research may provide, it seems appropriate to allow research to proceed without mandating formal neuroradiology review. Satisfying the principle of justice in such instances may be possible by identifying the most qualified team member to systematically review all study scans, ensuring that at a minimum, all scans receive the same quality of reading with the same threshold for communicating results to subjects.

A related issue is whether the opinion of someone who is not a neuroradiologist (or perhaps a closely qualified clinician such as a general radiologist or a neurologist) be provided to research subjects? For example, should an MRI technologist, or a medically untrained research assistant who happens to be running the research scan, tell the subject their scan "looks fine" or provide a written report commenting on their scan results?

The danger in providing scan information either in person or in written form by someone other than a qualified physician is that it invites therapeutic misconception. Commenting on a scan is a clinical activity. A research subject's implicit understanding is that the person providing the information is qualified to do so. This was shown by Kirschen (2006) who found that even in their primarily college educated cohort, a majority said they expected their scan to identify any abnormalities that existed, despite knowing that their scan would likely *not* be reviewed by a physician. Physicians who read scans as part of their professional responsibility are trained differently than non-clinician researchers or MRI technologists, but this might not always be clear to research subjects. Confusing the expertise of a clinical physician with that of a researcher may be particularly easy to do if the researcher is addressed as "doctor" (the difference between PhD and MD may not be obvious to all non-medical people). Furthermore, in addition to the risk of causing therapeutic misconception for research participants, a similar misconception may occur among treating physicians which limits beneficence. For example, when faced with a research scan reading, the clinician must not only understand the limits of what a research scan can provide (different than a clinical scan), but also the limits of the person providing the opinion. While one can generally assume a certain level of expertise by a board certified radiologist or neurologist, it is impossible to gauge the expertise of someone without similar professional licensure. Therefore because of the high likelihood of therapeutic misconception, and the very low possibility of any beneficence, it is difficult to argue for providing any clinical MRI information such as commenting about incidental findings unless vetted through a qualified radiologist or neurologist. A different issue occurs when whoever runs the MRI scanner identifies a large and obviously abnormal brain lesion as part of doing their job. This is typically reported to a research team member who notifies a physician out of a general duty to rescue, and is not the same as providing a dedicated review of the MRI scan looking for abnormalities of potential medical significance.

As noted by Richardson (2012, p 165), there is no simple calculus that can decide the extent of ancillary care obligations. There are likely research situations with no realistic

opportunity to provide neuroradiology review, in which the research is ethically justified based on a researcher's duty to advance generalizable knowledge, ultimately benefitting society. However changes in technology make this position less common. When costs are distributed among multiple studies, the short time required to read and generate MRI reports on the large number of normal studies can balance out the smaller number of abnormal scans that require more time for interpretation and discussion with participants. The dramatic expansion and ease of use of secure "cloud" based shared data systems facilitates reading scans remotely (as is done in our system), which presents an opportunity for smaller research centers to form collaborations for incidental finding review. Also, our data shows that many participants prefer to hear about an incidental finding first from a familiar member of the research team, which can be followed by a phone call from a clinician/ medical director who can be off-site. Thus the needed expertise to assist participants can be provided remotely. Furthermore, although the health system in the US is undergoing changes, most people can access medical care (indeed, the Presidential Report states that universal access is a basic principle of justice as fairness). In our institution we provide ancillary care in what Richardson calls a "facilitated referral" where, with participant permission, we provide assistance in directing participants to appropriate health insurance resources if needed, scheduling appointments with appropriate medical specialists and providing a copy of the structural MRI scan and radiology review to consulting physicians when asked to do so. In this way our institution eases the transition from research participant to clinical patient. Without participant access to health care this type of facilitated referral would not be possible.

Therefore it may become difficult to argue *against* universal reading of research MRI scans and providing results to individual participants. Mitigating harm further should be done during the consenting process to ensure that therapeutic misconception is avoided, and that risks are understood regarding potential for an identified incidental finding affecting insurance eligibility or causing other unforeseen consequences. Also, at the time of incidental finding disclosure it may be helpful to specifically tailor delivery of information for those with a medically serious finding, with a high baseline level of anxiety, or for those with low health literacy. Finally, we and others have shown that a large number of IF will be of uncertain clinical significance no matter what imaging sequences are used, whether it is a single structural scan or a full clinical study. For this reason it seems essential that participants have an a priori understanding of the nature and limitations of knowledge produced by an MRI scan done for research purposes.

There are several limitations to the generalizability of this study. This was a retrospective study and participant anxiety may have tempered with time, or experiential details could have been forgotten. However by asking research participants to reflect back some months in time may provide a more enduring representation of feelings regarding the issues discussed. Also, perhaps the most significant limitation is that the single site of our study limits opinions to those stakeholders who have been working within our system of mandated radiology review. Performing similar survey research in locations with other approaches to radiology review will provide a more complete picture of opinions and preferences. In addition, this is a self-report survey, thus opinions reflect research participants' self-

assessments, which may provide different data in some areas probed. For example, we asked research participants to rate their health literacy based on a standard self-assessment tool rather than test it directly. Similarly, if our questions regarding anxiety had been asked of family members we may have obtained a different view of how anxious the participant appeared when the radiology feedback was initially received. Finally, there were a number of areas not addressed within the parameters of our study such as assessing more specifically the economic impact of IF follow up or determining the impact of our IF system on local primary health care providers. We also did not evaluate attitudes of reading radiologists who were in the unfamiliar position of having to assume all research participants were healthy because they had no access to clinical information to help guide their readings. Despite these limitations, the broad representation of almost 400 IRB members, investigators and former research participants provides a reasonable characterization of the opinions of those surveyed, and the impact of radiology review on these stakeholders.

In summary, we provide the first empirical data characterizing the opinions of IRB members, investigators and former research participants at a single site regarding incidental findings in MRI research. Future studies obtaining data from stakeholders at other types of neuroimaging centers will help further characterize important ethical and practical issues regarding optimal incidental findings disclosure in neuroimaging research. This will be essential data to provide appropriate guidance for investigators and IRBs.

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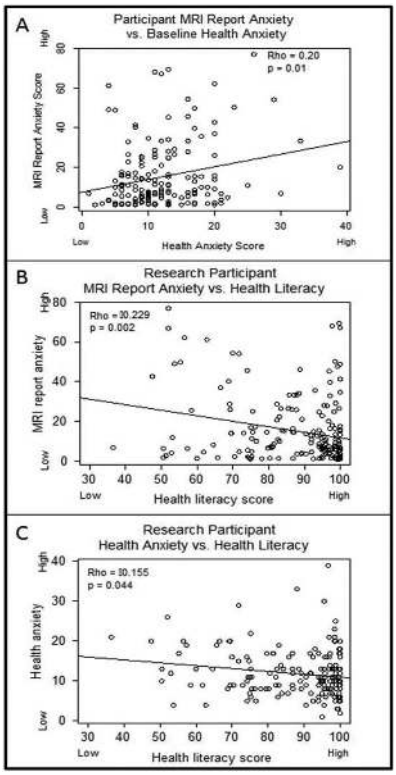

Figure 1.

Plotted distributions of research participant MRI report anxiety, participant health anxiety and participant health literacy, all composite scores based on standard measures of test anxiety, health anxiety and health literacy respectively.

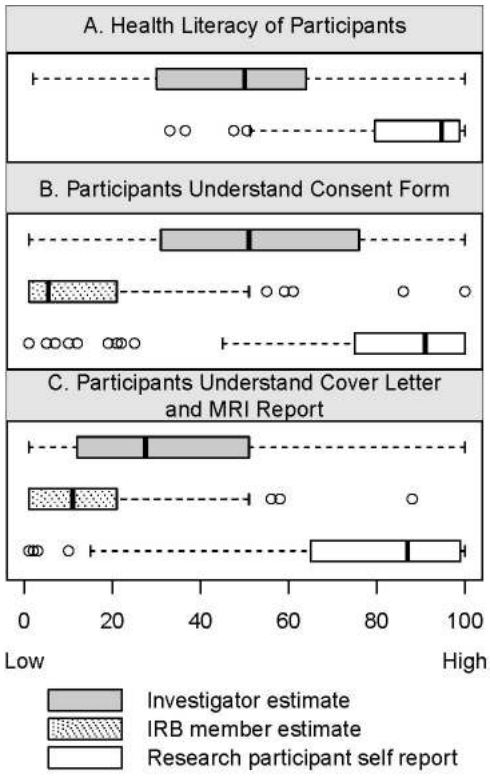

Figure 2.

Box-plot comparisons based on a series of analogue questions from 1-100 comparing investigator and IRB member estimate to research participant self-report reveal significant differences in perception of the health literacy ability of participants and participant ability to understand both consent forms and the radiology cover letter and MRI report.

TABLE 1

Demographics

Description of demographics for investigators, IRB members and research participants, listing cross-group general characteristics related to age, gender and education.

	Investigator (n=150)	IRB Member (n=50)	Research Participant (n=196)
Age - mean (range)	32 (20-66)	51 (32-78)	38 (18-88)
Gender			
Male	58 (40%)	17 (39%)	94 (49%)
Female	83 (58%)	26 (59%)	95 (50%)
Education			
High school	0 (0%)	0 (0%)	17 (9%)
Some college	13 (9%)	1 (2%)	66 (35%)
Bachelors	50 (35%)	2 (4%)	46 (24%)
Some Grad school	0 (0%)	1 (2%)	17 (9%)
Masters	25 (17%)	8 (18%)	37 (20%)
Doctorate	53 (37%)	33 (74%)	6 (3%)

TABLE 2

Representative Stakeholder Comments

Qualitative data taken from representative stakeholder comments across investigators, IRB members and research participants highlight the main themes disclosed from both open comment boxes and specific responses following survey questions. Select quotations are ordered thematically and correspond to quantitative survey questions where noted in the text.

A. Researcher Obligated to Report Incidental Findings

- *Research Participants*

"I think it would be morally wrong for a researcher to not tell a participant about a serious medical problem, even if it was unrelated to the study."

- *IRB Members*

"Cost does not come before ethics."

- *Investigators*

"The cost and time are secondary to the ethics of affording participants every benefit we are able to."

B. Reporting Incidental Findings Supports Participant Autonomy

- *Research Participants*

"I do little medical treatment but want a lot of information so I can make my best, well informed decisions."

"I would definitely want to know if there was any issue so that I could begin whatever medical process I would need."

- *IRB Members*

"The reporting of information about a research participant is consistent with the notion of autonomy. The information permits an individual to act upon new information generated by their participation in a study that is personally relevant."

C. IRB Members and Investigators Concerned About Causing Harm

- *IRB Members*

"The risk would be that telling participants about incidental findings could cause them distress and not lead to any benefits."

"Conveying them to the participant may just cause undue stress in a situation of lack of knowledge of what the findings might mean."

- *Investigators*

"When there is a finding, this mostly just produces anxiety on the participants."

"Often participants become concerned over findings that are benign, because they don't understand what they mean."

D. Concerns Regarding Participant Understanding of MRI Reports and Consent Forms

- *Research Participants*

"I didn't understand what the MRI results were and wish I could have talked to someone about the results."

- *IRB Members*

"Consent forms with all of the regulatory requirements and legalese are too complicated for even highly educated to really understand let alone an average New Mexican with a 5th grade reading level."

- *Investigators*

"In general I feel most participants do not fully understand the disclosures provided to them."