Managing Serious Incidental Findings in Brain-Imaging Research: When Consent for Disclosure is Declined

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Biography
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Publication Details

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Abstract
This paper focuses on the management of serious neuro-imaging incidental findings (NIFs) when a participant declines consent. To prevent severe neurological complications, serious NIFs necessitate immediate clinical referral. When consent for disclosure is explicitly declined, researchers face a significant dilemma in assessing ethical obligations of beneficence relative to the participant’s autonomous choice. Relying on the Belmont principles, I adapt Henry Richardson’s theory of specification to argue that the researcher’s duty of beneficence is shaped by the expressed autonomous choice of the participant. To best avoid such a conflict of principles and norms, researchers should specifically address consent for disclosing serious NIFs as a criterion for study participation.

Keywords
Neuro-imaging incidental findings (NIFs), serious, brain-imaging research, Richardson, informed consent, autonomy, beneficence

Introduction

Brain-imaging research has benefited tremendously from innovations in both functional and structural neuro-imaging technologies. Such technologies have augmented the potential for high-resolution imaging and mapping of intracranial surface structures, brain substructures, and neural correlates with clinical and anatomic precision. The application of neuro-imaging technologies in research has lead to the discovery of novel therapies for treating neurologic and psychiatric diseases. Together with these achievements, scientific and ethical challenges have become evident in the application of neuro-imaging technologies particularly within research. One of such challenges is the ethical dilemma surrounding a researcher’s obligation to disclose [or not disclose] a serious neuro-imaging incidental finding (NIF) when a research participant expressly declines consent for disclosure.

To resolve this conflict of ethical principles and the norms that derive from them, I adopt the ethical tool of specification—a theory of practical reasoning developed by Henry Richardson (1990). I argue that when consent for disclosure of NIFs is declined by
a competent participant, the obligations of beneficence is shaped and specified by the expressed autonomous desire of the participant. The real possibility of detecting serious health-related incidental findings in brain-imaging research engenders a need for careful planning and preparation in the design of brain-imaging studies. To avoid the dilemma of conflicting ethical norms in this context, I propose that researchers specifically address consent for disclosure of clinically urgent NIFs as a criterion for study participation.

**Neuro-Imaging Incidental Findings (NIFs)**

An NIF is defined as a health-related discovery or anomaly in the neuro-imaging scan of a research participant that is not directly relevant to the variables investigated in the research study. NIFs are often identified as unexpected anomalies on a brain scan such as an inflammatory lesion, a vascular malformation, a neoplasm, intracranial aneurysm, cyst, or a host of other potentially symptomatic cerebro-vascular disease-markers (Morris et al. 2009). It is *serious* when it is clinically significant, analytically valid, poses an immediate health or pathological risk of danger, and is actionable. The human brain is such that the existence of anomalous electrical, structural or biochemical variations could indicate adverse conditions like memory loss, paralysis, seizures, neuromuscular diseases, or other potentially serious neurological disorders. As such, detecting, disclosing, and properly managing such anomalies are critical and of great ethical concern within neuro-imaging research. While incidental findings (IFs) in general have been conventionally construed as *incidental* to research, limitations of such descriptions are unquestionable (Parker, 2008). Depicting such findings as *incidental* generates practical challenges about whose health is at stake and whose interests deserve priority (Illes and Chin 2008).

The importance of anticipating and managing serious NIFs in research has been highlighted in empirical studies, government reports, and institutional research guidelines. Proper planning, adequate professional expertise, communication, improved consent practices, and transparency within neuro-imaging research are critical (National Institutes of Health and Stanford University 2005). Likewise, empirical studies underscore the necessity for urgent clinical referral when a serious NIF is confirmed. In one study of 1000 asymptomatic volunteers (between ages 3-83) from a variety of NIH research protocols, 180 cases of NIFs were reported, 18 of which required routine referral, and 11 required urgent referral due to tumors and lesions (Katzman, Dagher, and Patronas 1999). Similarly, a retrospective review of 151 MRI studies on healthy volunteers from previous studies indicated a 6.6% NIF incidence rate requiring clinical referral with 3 cases of clinical urgency (Illes et al. 2004). In addition, Yue and colleagues (1997) reviewed
3672 image scans in a population-based study of asymptomatic elderly individuals and reported 64 cases of NIF with only 9 serious anomalies requiring urgent surgical referral.

Despite their empirical and clinical significance, there is divergence about managing serious NIFs. The high incidence of false positives, the possibility of triggering burdensome or costly interventions, and the potential for ambiguous findings can complicate disclosure (Royal and Peterson 2008). Consequently, the obligations neuro-imaging researchers owe participants given the overall aims of generalizable knowledge intrinsic to research need to be further specified. Some authors advance a fiduciary relationship requiring certain clinical care and equipoise standards (Weijer and Miller 2003). Others propose an ancillary care framework grounded in partial entrustment (Rangel 2010; Richardson and Belsky 2004). One position underscores the researcher’s obligations as a responsibility with binding professional implications (Miller, Mello, and Joffe 2008). These frameworks, though valuable, only apply when a participant consents to disclosure or when the consent process fails to address serious NIFs. However, when consent is expressly declined, a different kind of ethical assessment is necessitated to specifically address the management of serious NIFs during informed consent.

**Specification**

Richardson’s (1990) notion of specification involves a systematic method of practical reasoning from abstract norms to concrete actionable guides by constantly shaping and substantiating the applicable norms with content. Specification presupposes the existence of a set of ethical norms; it then proceeds to determine how these norms apply in shaping action, particularly when these norms conflict. With respect to research, Richardson proposes a protean research limiting principle and examines its ramifications from a less restrictive and more restrictive perspective. The protean principle states that “it is impermissible to engage in research on human subjects unless the principles of autonomy, beneficence, and justice are adequately satisfied” (301). On this principle, we fruitfully can recast the debate on how both autonomy and beneficence can be specified. Specification articulates the different interpretive options visible in the two ramifications of the protean principle’s notion of adequate satisfaction: “it is impermissible to engage in research on human subjects unless the principles of autonomy, beneficence, and justice are satisfied on balance (less restrictive); it is impermissible to engage in research on human subjects unless we do so in a way that respects their autonomy, proceeds justly, does no (intentional harm), and produces (significant) benefits (more restrictive)” (301).
Practical Considerations

Human subjects’ research is guided by ethical principles (autonomy, beneficence, and justice) outlined in the Belmont Report which provide a basis for assessing obligations. These principles serve as heuristics that offer action-guiding content when specified in the form of norms (Meslin, Sutherland, Lavery, and Till 1995). Since practical reasoning involves a means-end assessment of action-guides in particular contexts, specifying one’s end helps to focus the process of attaining that end. Within research, the obligation of beneficence is shaped and specified by the expressed autonomous choice of the participant. Informed consent formally establishes the relationship between the neuro-imaging researcher and participant. Consent is necessary for disclosing serious NIFs. As such, any action to manage a serious NIF should involve a re-assessment of a participant’s denial of consent in light of the discovered “incidental” abnormality.

The first step in applying specification involves deliberation on the morally relevant facts pertaining to beneficence and autonomy. They include:

- the discovery of a serious NIF;
- the denial of consent for disclosure;
- the possibility of immediate neurological harm and
- the responsibility of the researcher/institution in light of the discovery.

From the protean principle, two norms emerge, one less restrictive, the other, more restrictive.

- less restrictive specification – it is impermissible to disclose serious NIFs to participants unless the requirements of consent are adequately satisfied;
- more restrictive specification – it is impermissible to disclose serious NIFs to participants unless we do so in a way that respects their autonomous choice and maximizes benefits.

The presumption from beneficence is to maximize benefits and minimize risks. When consent for disclosure is expressly denied, the obligation of beneficence becomes even more difficult. Beneficence does not simply override the duty to respect a participant’s autonomous choice. Moreover, beneficence cannot be coercive with the objective of maximizing the health benefit of the participant. A denial of consent practically limits the scope of beneficence. Since serious NIFs are detected in the form of unexpected anomalies—lesions, aneurysms, vascular defects, etc., managing them can be significant. The human brain is such that the existence of anomalous electrical, structural, and/or biochemical variations could be indicative of critical neurological conditions needing immediate referral. As a result, overlooking such anomalies (doing nothing) cannot be adequate. The nature and integrity of brain-imaging research, demands a higher ethical
standard: using a brain scan from a supposedly healthy volunteer discovered to have a tumor or intracranial malformation is, at the very least, problematic (Illes and Chin 2008). As a matter of fact, discovering a serious NIF shifts the priority from research participation to an urgent need for clinical care, at least for the given participant. While it is impermissible to foist disclosure of serious NIFs on participants, doing nothing is ethically untenable. A refusal of disclosure during initial consent is inadequate to satisfy the requirements for managing significant and serious NIFs. Though re-consenting in light of an actual (not potential or statistic) finding may be practically and logistically difficult, it is necessary to pursue immediate clinical referral. A refusal of consent at this point severely jeopardizes the participant’s continued participation in the study.

Implications for Consent

Addressing the disclosure and management strategy for potential NIFs during informed consent must be an essential provision and requirement for conducting brain-imaging research. While the nature, incidence, sensitivity, and severity of NIFs may vary across brain-imaging research settings, their clinical significance, utility, and actionability tend to fall within three major categories of classification requiring immediate/urgent referral, routine referral, and/or no referral. The meanings and implications of these categories should be explained and subjects should provide individual consent/non-consent (perhaps in the form of checkboxes or initials) to be informed about NIFs that require an action plan for each of these categories. One reason for this is that, general consent to be informed about NIFs may not specifically address clinical considerations of action plan that require urgent, routine, or no referral.

It is important to note that the potential for discovering serious NIFs in brain-imaging research demands a careful assessment of suitability for study participation based on participants’ disposition for consent. If the consent process adequately educates participants on the nature, empirical incidence, and significance of NIFs, and clearly specifies areas of individual consent/non-consent for disclosure of such findings, a legitimate refusal of consent for disclosure, should be grounds for study exclusion. Obviously, this position is practically difficult given concerns about scientific validity and social value. The nature and integrity of neuro-imaging research nonetheless calls for a rigorous consent process. Likewise, the possibility of a serious adverse event looms large if a serious NIF is not managed immediately.

Participants as such, should be given an option on the consent form to voluntarily opt out of participating in the study, if they do not wish to consent to disclosure for
serious NIFs or be contacted in the future, if a serious NIF is found. This determination is clearly distinct from categorically excluding participants from the study based on a perceived potential for a serious NIF. This latter situation should be discouraged since it violates the ethical principle justice which operationalizes fairness and equality in the selection of participants and the distribution of burdens.

**Conclusion & Recommendations**

At minimum, a serious NIF detected in brain-imaging research deserves medical attention. It ultimately changes the context of research for the given participant. The informed consent process should explicitly and adequately address the incidence/potential for serious NIFs, invite constructive discussions from participants, discuss the real possibility of re-contacting participants, and map out any clinical follow-up plan for serious NIFs. In sum, a proactive and preparatory strategy for managing NIFs is certainly preferred to a reactive one.

I recommend that consent documents address different consent levels for NIFs (using initials or checkboxes, for example) with varying degrees of clinical referral need:

- For NIFs that require no clinical referral (have low indication of risk), consent for disclosure may not be required;
- For NIFs that require routine referral, requirements for consent for disclosure should be based on individual assessments of severity by a competent clinician;
- For NIFs that require urgent and immediate referral (high risk of harm), consent must be required for participation in the study. If this box is not initialed or checked, participation in the study should be prevented.
References


