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The Law of Incidental Findings in Human Subjects Research:

Establishing Researchers' Duties

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Technology has outpaced the capacity of researchers performing research on human participants to interpret all data generated and handle those data responsibly. This poses a critical challenge to existing rules governing human subjects research.¹ The technologies used in research to generate images, scans, and data can now produce so much information that there is significant potential for incidental findings (IFs), findings generated in the course of research but beyond the aims of the study.² Neuro-imaging scans may visualize the entire brain and even the entire head; computed tomography (CT) colonography research may visualize the entire torso, from the base of the lungs to the pubis; genetics studies may reveal "extra" and sometimes unwanted information about the family, such as misattributed paternity and undisclosed adoption; and genomic microarray research increasingly involves whole-genome analysis (WGA) revealing an individual's complete genotype, with enormous potential for uncovering unexpected information about an individual's genetics and risks of developing future conditions.

Generating massive amounts of information by sophisticated research technologies raises questions about how this information should be managed. Jack Balkin and others have written about the rise of the surveillance state created by computer technology, producing vast amounts of information about individuals' phone calls, spending habits, and computer searches.³ Yet this is nothing compared to the capacity of genomic microarrays to sequence the three billion base pairs in your genome or full-body magnetic resonance imaging (MRI) to generate a detailed scan of the inside of your entire body. Generating this kind of biomedical information raises a fundamental question: what duties do researchers owe to human subjects in the discovery and management of data generated by research? We focus on a crucial aspect of this issue: how should researchers handle incidental findings of potential clinical or reproductive importance?

Current law and federal regulations offer no direct guidance on how to deal with IFs in research, nor is there adequate professional or institutional guidance.⁴ The problem of IFs in research was little recognized and seldom discussed until recently. Yet studies report that neuroimaging reveals IFs in up to 47 percent of supposedly normal adult control research participants,⁵

though the prevalence of IFs varies with the population examined.⁶ CT colonography reveals extracolonic findings in about half of scans in asymptomatic participant populations.⁷ Genetic family studies are estimated to reveal misattributed paternity in about 10 percent of research participants in the general population, though this percentage is difficult to verify.⁸

Despite the potential to generate IFs during the course of research, researchers, Institutional Review Boards (IRBs), and universities have been conducting research with no agreement that they have any responsibility to address and report IFs. Research currently proceeds with no consensus that researchers have duties to analyze anomalies spotted, secure a clinical consult to verify the existence of these IFs, and offer to disclose verified IFs of likely importance to the research participant. Research protocols may

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Against this background, this article attempts a leap forward. We argue that researchers owe research participants duties that are both ethical and legal obligations: to disclose in the informed consent process the possibility of discovering IFs and the plan for management; to recognize an IF that arises during the course of research; to verify the presence of the IF and evaluate its probable importance, obtaining expert consultation if necessary; and to offer to disclose an IF of likely clinical or reproductive importance to the research participant. These duties should apply even in large-scale human subjects research using genomic microarrays and in reanalysis of archived data sets when the research participant is identifiable.

Our analysis focuses on genetic and genomic research as well as imaging research, two research domains in which IFs are emerging, raising pressing questions of how to handle them. To explore these broad research domains, we examine functional magnetic resonance imaging (fMRI) research, CT colonography research, genetic family studies, and research using genomic microarrays. We examine the problem of IFs across these four research approaches in imaging and genetics/genomic because they span a spectrum of research contexts, research participant populations, and data types. They also pose the potential for banking samples, images, or data for future studies that may themselves yield IFs. Although we focus on these four areas, we generate an analysis that can and should be applied more broadly. We advocate researcher duties that should be applied to any human subjects research generating IFs.

This article first offers background by defining “incidental findings,” illuminating underlying concepts critical to the discussion. Part II traces the ethical and legal theories supporting our finding of an overarching duty on the part of researchers to manage IFs. Part III then specifies researcher duties to manage IFs: to develop a plan for management in the research protocol, discuss the possibility of and management plan for IFs in the informed consent process, as well as address, evaluate, and offer to communicate IFs of likely clinical or reproductive significance to research participants when they arise. We recommend a pathway to be followed in handling IFs in research and unpack the implications — a new vision of researcher duties and research participant rights in the age of powerful research technologies routinely generating IFs. Our recommendations challenge the traditional research/clinical divide, advocating a set of researcher duties based on law and ethics.

I. Incidental Findings: Definition and Underlying Considerations

An incidental finding (IF) is “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.”¹⁰ IFs range from those that have clear clinical significance and reveal conditions that can be treated (*e.g.*, a large bright area on an MRI indicating a life-threatening but operable brain tumor or a genetic mutation known to predispose to a life-threatening disease with a known treatment) to those

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whose clinical meaning is unknown (*e.g.*, a small blip on an MRI or a series of repeating nucleotide sequence information on a gene chip, when the significance of each is unknown).

There are also multiple actors involved in human subjects research relevant to any discussion of IFs: research participants; researchers, including principal investigators and other project personnel; federal regulatory agencies, including the Department of Health and Human Services (DHHS) and the Food and Drug Administration (FDA); institutions, including academic and medical institutions; institutional bodies, including IRBs, data safety monitoring boards (DSMBs), and other ethics-oriented committees; clinical consultants who may be involved if their opinion is solicited on the IF; and funding sources. Care must be taken to avoid confusing these actors when discussing duties arising from research. In this article, we focus on the duties owed by *researchers* to human research participants.¹¹ Ensuring that these duties are fulfilled, however, will inevitably involve IRBs approving and overseeing research, funders setting research budgets allowing resources to address IFs, and others.

We note that IFs will also arise in a range of contexts, including the following: research undertaken by an M.D., Ph.D., or other professional; research conducted in a strictly research setting; and research conducted in a clinical setting, including when the researcher is also the treating physician. Note that for the purposes of this article, we assume the researcher is not wearing two hats, serving as both researcher and treating physician to the research participant; our goal is to analyze researcher duties, though an individual researcher who is also the research participant’s clinician may have both researcher duties and clinician duties. Additional variations in the research scenario arise depending on the research participant population involved; pediatric research raises special concerns,¹² and the federal regulations require further protections for pediatric subjects.¹³ Similarly, adult research participants with diminished capacity may also require additional processes for managing IFs.¹⁴

IFs may seem at first blush a minor or peripheral concern. On closer scrutiny, however, IFs raise fundamental questions. They challenge the traditional line currently drawn between physician duties to patients and researcher duties to human research participants in bioethics and health law.¹⁵ Clinicians owe patients a duty of care, which if breached, exposes clinicians to malpractice liability. Researchers, on the other hand, have until very recently been held to owe research participants few, if any, duties of clinical care enforceable in tort or contract law.¹⁶ This distinction has been grounded in the view that researchers are scientists rather than physicians and therefore do not have the same obligations.¹⁷ Some recent literature suggests, however, that there may be an intermediate researcher duty of care, distinct from that of physicians. Henry Richardson and Leah Belsky, for example, frame this as an ancillary-care obligation grounded on the subject’s vulnerability and entrustment of her well-being to the researcher.¹⁸ In contrast, Alan Milstein suggests that researchers should be held to the same duties of care as physicians.¹⁹ However, entirely collapsing research and clinical duties in this

manner would be problematic, as the relationship between the research participant and researcher is very often *not* that of a patient and physician. The challenge is to reformulate the duties of researchers themselves toward research participants in light of important clinical information that researchers may discover in the form of incidental findings.

One distinction is crucial as a starting point for this discussion: IFs are different from individual research participants' research results, information on the variables under study in pursuit of the study aims. IFs arise in the conduct of research but do not directly relate to the aims of the study. A substantial literature debates the wisdom of returning individual research results to research participants, revealing a rift between a culture of disclosure and one of nondisclosure.²⁰ The debate focuses on whether disclosure should be broad or narrow, perhaps conditioned on the quality of the research information and the potential utility of the information to research participants. Some commentators argue that participants are entitled to information about themselves, especially when they request it.²¹ Others argue that researchers should convey little information, if any, back to the research participant.²² A common argument for the latter position is that researchers are performing research, not clinical care, and thus are not obligated to return information of potential clinical importance; indeed, returning such information may encourage the therapeutic misconception.²³ Further bolstering the argument for silence, some claim that the clinical import of much

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information generated in research is unknown;²⁴ they have insisted that returning this information might cause unnecessary alarm to research participants.²⁵ Indeed, some consent forms either say nothing about the possibility of incidental findings or expressly disclaim responsibility for disclosing them.²⁶

In large-scale research on big datasets (whether those datasets aggregate genomic or imaging data), many commentators argue that researchers cannot track huge numbers of participants, cannot locate them reliably over time,²⁷ and have no budget to report information back to participants, much less offer genetic counseling or follow-up.²⁸ In addition, researchers analyzing archived data may, in fact, be secondary users who did not collect the data and never had direct contact with the research participants, but retrieved the data from a databank or data repository. Indeed, archived data may have been stripped of individual research participant identifiers, making it difficult to return information to participants at all.²⁹ Arguably such anonymization means that analysis of the data is no longer human subjects research governed by the federal regulations on such research anyway.³⁰

Federal authorities have begun developing statements on returning individual research results in the context of genomic research. These statements vary, but recognize that there are circumstances in which researchers should offer individual research results to research participants.³¹ Because it can be difficult to distinguish research results from IFs in large-scale genomic "discovery" research whose research aims are open-ended (*e.g.*, to look for phenotype-genotype correlations), some of these statements may have implications for IFs. Discussion of IFs discovered in archival genetic and genomic research has already begun,³² though the implications of IFs for data repositories — such as the National Institutes of Health (NIH) repository for genome-wide association studies (GWAS)³³ or a public repository for fMRI studies³⁴ — have yet to be fully addressed. Indeed, both HHS and the Office for Human

Research Protections (OHRP) have taken the position that research on archived data that has been anonymized is exempt from regulation by the Common Rule.³⁵

As a financial matter, an IF discovered during the course of research can increase the cost and burden to the research enterprise and institutions supporting medical research. Any increase in researchers' responsibilities in terms of verifying and offering to disclose an IF may inhibit research by increasing the cost of the research itself. Institutions, IRBs, and researchers will have to determine how to handle these additional costs, particularly whether they will be included in the research budget or expressly excluded. Striking the right balance between necessary management of IFs and containment of research costs will be important.

Some recent case law suggests that a legal trend may be emerging toward recognizing an obligation on the part of a researcher to provide a research participant with information acquired from a study, when that information has clinical implications for the participant.³⁶ Courts have not yet resolved whether there is a researcher duty to share research information.³⁷ However, a recent article notes that "researchers should expect that research participants will begin to assert their right of access."³⁸ For the purposes of this article, we make a distinction between (1) researcher obligations to recognize, analyze, and offer to disclose IFs, and (2) researcher duties to supply research data to an individual research participant at the participant's request. The Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule gives individuals a right of access to "protected health information" which may include research data under some circumstances;³⁹ both NIH and NHGRI have issued guidance regarding the extent of this right of access in research.⁴⁰ Any researcher within a "covered entity"⁴¹

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may be subject to the Privacy Rule unless an exemption applies.⁴² However, those rules speak to researcher duties when a research participant initiates a request for information generated in research. We address something distinct in this paper — researcher obligations to manage IFs apart from any research participant request.

In the next section we articulate the ethical and legal bases for researcher duties to plan for, address, evaluate, and ultimately offer to communicate certain IFs to research participants.

II. Grounding Researcher Duties: Ethical and Legal Sources

As we discuss below, the research ethics literature has begun to urge that researchers may owe more to participants than existing policies provide. This ethical discourse has been complemented by increased attention in the law to participants' rights and researcher duties.

⁴³ Below, we set forth the ethical and legal foundations of researcher duties to manage IFs.

A. Sources of Ethical Duties

We argue that researchers have an ethical duty to manage IFs based on the convergence of a number of important ethical concepts. Other papers in this symposium focus on the ethics arguments, so we touch on them only briefly here in order to move on to law. The ethics literature that directly discusses IFs in research is still relatively sparse.⁴⁴ There appears to be a shared sense that researchers do shoulder an ethical duty to manage IFs, though the reasons for this position diverge. This duty is based partly on the need to address IFs in order to preserve the scientific integrity of a study;⁴⁵ if supposedly "normal controls" are actually not "normal," for example, treating them as such may confound the data. Thus, Robert Grossman and James Bernat discuss the need to address findings that "may actually confound the results of the scientific study."⁴⁶ Judy Illes et al. also discuss preserving the integrity of the study as only one reason for a duty to address and manage IFs.⁴⁷ They base that duty additionally on broader

ethical concepts of reciprocity, concern for research participants' welfare, and respect for participants' autonomy.

Relying on the ethical duty of reciprocity⁴⁸ suggests that researchers “incur obligations to help or benefit [research participants] in part because [researchers] have received or will receive assistance from [those participants].”⁴⁹ This duty to benefit research participants is part of a broader researcher duty of beneficence to secure participants' well-being by maximizing benefits and minimizing harms.⁵⁰ Reciprocity has most recently been discussed in human subjects research as a component of justice: reciprocity in this context refers to “what people deserve as a function of what they have contributed to an enterprise or society.”⁵¹

Support for a duty to manage IFs can also be grounded in concern for research participants' welfare.⁵² Grossman and Bernat argue that “[w]hen an important abnormality is present, the subject trusts that the research team will observe it.”⁵³ Some might argue that this trust and expectation is based on the therapeutic misconception,⁵⁴ but other commentators offer arguments that complement those of Grossman and Bernat. Richardson and Belsky similarly focus on trust, arguing that because research participants entrust aspects of their well-being to researchers, those researchers have a duty to manage IFs as part of their ancillary-care obligations.⁵⁵ Richardson and Belsky develop a model of partial entrustment based on the elements of discretion and vulnerability in research: research participants authorize researchers “to employ significant personal judgment in deciding how to act on the behalf of [the participants],” thus conferring discretion, and how researchers exercise that discretion will affect the participants' well-being, because of their vulnerability.⁵⁶ How researchers choose to manage IFs specifically can greatly affect the well-being of participants, particularly when a life-threatening but treatable finding is discovered. Richardson and Belsky state, for example, that fMRI researchers “generally have a responsibility to do diagnostic readings of brain scans and to follow up appropriately”; they contend that objections to this demand on researchers' time are overcome by the fact that some IFs may be highly significant and may even require urgent clinical referral.⁵⁷

A third justification is based on the respect for research participants' autonomy.⁵⁸ This principle is commonly understood as “respect for persons” and incorporates the ethical conviction that “individuals should be treated as autonomous agents.”⁵⁹ Such respect suggests that research participants have a “presumptive entitlement” to information about themselves.⁶⁰ Respect for persons includes a respect for participants' self-determination and consequent need for information relevant to their health and well-being: “[i]t would be disrespectful to treat research volunteers as conduits for generating scientific data without giving due consideration to their interest in receiving information about themselves derived from their participation in research.”⁶¹

These justifications together suggest that a duty to manage IFs does exist. More broadly, they suggest that the research enterprise indeed owes more to research participants than it currently provides.

B. Sources of Legal Duties

We argue that, in keeping with their ethical duties, researchers have a legal obligation to offer findings of likely clinical or reproductive significance to research participants. From this obligation arises the following duties: (1) a duty to develop a management plan for IFs in the research protocol; (2) a duty to discuss the possibility of IFs during the informed consent process and reveal how IFs will be managed; (3) a duty to address IFs in data; (4) a duty to verify the presence of an IF and assess whether the IF has probable clinical or reproductive significance; and (5) a duty to offer to disclose IFs of likely clinical or reproductive significance to the research participant.

This section will discuss legal theories regarding researcher duties. We emphasize that the fear of legal liability should not drive the evolution of duties regarding IFs; this is a multidisciplinary problem that requires collaborative scientific, medical, ethics, and legal analysis. But law is certainly relevant. Researchers, IRBs, institutions sponsoring research (such as universities), research funders (such as NIH), and those overseeing research (such as OHRP) should address the problem of IFs now, rather than awaiting litigation or explicit regulation.

The law germane to IFs derives from two main sources: administrative and regulatory law (including the federal DHHS Common Rule and its FDA variant⁶² governing human subjects research) and the

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law emerging in litigated cases. Federal administrative actions (*e.g.*, by OHRP) are primarily directed at research institutions and arise from the federal regulations on human subjects research. However, injured research participants are increasingly trying to impose liability on researchers, research institutions, and even IRBs and IRB members as defendants.⁶³

Duties Under Federal Research Regulations—While neither the Common Rule nor the FDA regulations explicitly addresses IFs, several of their provisions are relevant to the management of IFs and are discussed below.⁶⁴ The duties enumerated in the regulations are enforced by federal agencies against a research institution for violation. Plaintiff-research participants have also attempted to enforce the regulations through various theories (as discussed further below), but these attempts have so far largely failed.

The federal research regulations have several requirements that suggest how IFs should be addressed in the research protocol. The IRB reviewing a proposed research protocol must “determine that [r]isks to subjects are minimized.”⁶⁵ Whenever individuals participate in genetic, genomic, or imaging research, they risk discovery of an IF. Finding out about an IF may impose psychological burden, the financial burden of follow-up assessment, and risk of bad sequelae from the follow-up tests. Moreover, not all IFs will turn out to be genuine findings; some will be false-positives. This adds to the risk for research participants. Yet

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there is also a risk that researchers will fail to notice an IF of high clinical importance, and research participants will thus lose a chance to avoid or ameliorate serious clinical consequences. This is the risk of a false-negative. The regulatory duty to minimize all of these risks suggests the obligation to create a solid plan to address IFs in the course of research.

That plan will need to include means of verifying IFs and then offering them to research participants in a way that minimizes the psychological burden. In order to minimize psychological harm and ensure that participants understand the significance of the information presented, the OHRP *IRB Guidebook* states that investigators conducting genetics research should provide genetic counseling when any genetic information, explicitly including the possibility of IFs, is given to research participants;⁶⁶ these considerations are also important in the imaging context. Thus, minimizing risk may require that, if the research protocol calls for IFs to be offered to participants, there be adequate provisions to avert harm to participants

from that disclosure. In addition, an IRB shall also determine that “[r]isks to subjects are reasonable in relation to anticipated benefits, if any, to subjects.”⁶⁷ The reality is that IFs both pose risks and may offer benefits, information that may even prove life-saving in some cases. Researchers and IRBs seeking to fulfill the regulatory mandate to seek a reasonable balance of risks and benefits will need to consider what kinds of IFs the study is likely to produce and how they can best be managed to minimize harms while realizing any benefits.

The regulations also have several provisions that can be interpreted to require the disclosure of the risks and benefits of IFs in the informed consent process. The regulations provide that in obtaining the research participant’s informed consent, “[a] description of any reasonably foreseeable risks or discomforts to the subject” and “[a] description of any benefits to the subject or to others which may reasonably be expected from the research” must be provided to the subject.⁶⁸

The regulations require additional elements of informed consent in appropriate studies, including “[a] statement that the particular treatment or procedure may involve risks to the subject...which are currently unforeseeable;...[a]ny additional costs to the subject that may result from participation in the research;...[and a] statement that significant new findings developed during the course of the research which may relate to the subject’s willingness to continue participation will be provided to the subject.”⁶⁹ All three of these additional elements speak to IFs, requiring researchers to address the unexpected risk of facing an IF, the ensuing costs of pursuing clinical follow-up, and the fact that discovering a clinically significant IF may mean that the research participant will no longer wish to participate in the research but instead want to focus on clinical assessment of the IF. IRBs are also permitted by the regulations to require that additional information be given to subjects when in the IRB’s judgment this information would be protective of the rights or welfare of the subjects.⁷⁰ This catch-all also invites the IRB to consider requiring the investigator to address IFs in the consent process.

Importantly, the regulations forbid exculpatory language in the informed consent process, whether oral or written.⁷¹ This is language “through which the subject or the representative is made to waive or appear to waive any of the subject’s legal rights, or appears to release the investigator, the sponsor, the institution or its agents from liability or negligence.”⁷² This would seem to raise questions about consent forms that disclaim any researcher or institutional responsibility for managing IFs and include language claiming to immunize researchers or their institution from any legal consequences or liability for failing to warn research participants of IFs with serious clinical implications.

Thus, all of these regulatory provisions seem a source of responsibilities devolving both on researchers and IRBs. Note that both the Common Rule and the FDA regulations regarding human subjects research articulate procedures for non-compliance, including investigation of the research institution and suspension of research.⁷³ OHRP’s enforcement of the Common Rule begins with a letter of inquiry to officials at the research institution and may lead to telephone interviews of institutional personnel or on-site visits. Eventual outcomes of the process include required corrective actions, withdrawal of institutional assurance approval, or for the most egregious cases, suspension or government-wide debarment of the institution or the investigator.⁷⁴

Although research participants have attempted to bring claims to enforce violations of the regulations, to date no court has held that either the Common Rule or the FDA regulations provide participants with the right to bring a private cause of action and recover

Grimes and *Blaz* suggest that researchers indeed have legally cognizable duties towards research participants, although the scope of these duties is not yet well-defined. Of these two cases, *Grimes* is the more important for analysis of IFs because

the court found a special relationship giving rise to a duty even though the risks of lead-paint exposure were not directly caused by the research or the research institution.

damages.⁷⁵ An early federal district court decision left open the question of whether a private cause of action arises out of the Common Rule.⁷⁶ However, later attempts by research participants to assert that violation of the Common Rule gives rise to a private cause of action have been rejected by federal district courts.⁷⁷ The Supreme Court has likewise indicated that the Food, Drug, and Cosmetic Act (FDCA) regulations do not confer a private right of action.⁷⁸

Research participants have also attempted to enforce the Common Rule and the FDA regulations via the Civil Rights Act, 42 U.S.C. § 1983, but these cases have been unsuccessful as well.⁷⁹ The Civil Rights Act provides for a civil action for deprivation of rights “secured by the Constitution and laws.”⁸⁰ *Wright v. Fred Hutchinson Cancer Research Center* rejected a § 1983 claim brought under the federal regulations, relying on earlier rulings that the FDCA does not create or imply a private right of action. The court reasoned that regulations promulgated by an agency cannot give rise to a private cause of action if the authorizing statute does not confer that right.⁸¹ Another case, *Robertson v. McGee*, acknowledged that federal regulations might confer a right, but found that neither the Common Rule nor FDA regulations provided for a cause of action, holding that “§ 1983 cannot be used to create a right of action where one does not exist.”⁸² The *Wright* court cited in particular the existence of regulatory enforcement mechanisms, either by OHRP or the FDA, to deny the existence of an individual cause of action.⁸³ According to the court, Congress had “contemplated, but ultimately rejected, a statutory mechanism for the compensation of individuals and their families for injuries resulting from their participation in human subjects research.”⁸⁴

In other unsuccessful claims, research participants have asserted third-party beneficiary status arising out of contract or argued violation of ethical principles articulated in the *Belmont Report*. In *Wright*, research participants attempted to assert that they were the third-party beneficiaries of the assurance agreement that the research institution would abide by the federal regulatory requirements on human subjects research and present research to an IRB for approval.⁸⁵ The court rejected this argument because there was no language in the assurance agreement that provided research participants with an actionable right. More recently, in *Washington University v. Catalona*, research participants brought an action arguing that Washington University did not abide by the ethical principles of the *Belmont Report* and thus violated its assurance to DHHS.⁸⁶ The court found that the research participants were neither parties to, nor third-party beneficiaries of, a government contract (*i.e.*, the assurance agreement) and therefore had no private cause of action to enforce the terms of the contract,⁸⁷ a holding that was affirmed by the 8th Circuit.⁸⁸

Duties Under State Common Law—Research subjects have also claimed that researchers have duties arising under state common law doctrines grounded in tort, property, or contract.⁸⁹

To bring a tort action in negligence, a court must recognize a relationship between the parties that creates a duty of care; the physician-patient relationship is one such special relationship, and breach of consequent duties gives rise to a medical malpractice action.⁹⁰ When there is no existing relationship, courts will apply an ordinary negligence standard, meaning a failure to use reasonable care under the circumstances. The existence of a particular researcher duty of care toward a participant depends on a court recognizing a special relationship between them that imposes a standard of care higher than an ordinary negligence standard.⁹¹ One state court recognized this type of relationship when the researchers had entered

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into informed consent agreements with the families, agreed to share results with them, and interacted with the families throughout the research project.⁹² The court found that when such a special relationship existed and there was a violation of the federal regulations regarding informed consent agreements, the research participants could sue in state court for negligence.⁹³ The court also found researcher duties to be consistent with international ethics statements such as the Nuremberg Code.⁹⁴

When there is an existing doctor-patient relationship and patients are also research subjects, courts may treat these cases as a type of medical malpractice.⁹⁵ For example, *Moore v. Regents of the University of California* recognized that plaintiff could bring an action for breach of the physician's fiduciary duty of care when Moore's doctor had removed his spleen and taken bodily samples for non-therapeutic use in deriving a cell line. The court did not address the injuries to Moore as a form of human subjects research performed without consent because the doctor-patient relationship already existed.⁹⁶

Courts that do not recognize research cases as falling under the umbrella of medical malpractice apply an ordinary negligence standard rather than finding a special researcher duty of care.⁹⁷ However, this approach has been criticized. Under the ordinary negligence standard, "investigators in sophisticated clinical studies would owe their subjects nothing more than the same ordinary prudence that any citizen owes his fellow citizens — a standard quite likely too lenient."⁹⁸

At least one court has distinguished research from clinical care and imposed a researcher standard of care on a researcher with no clinical relationship to the research participant. This case hinged on the court's reading of an existing state statute regarding the standard of care for informed consent related to health care treatment.⁹⁹ Although the court did not address the general relationship between researchers and research participants, they found that "the degree of required disclosure of risks is higher than in the nontherapeutic context" under the North Carolina statute.¹⁰⁰ In this case, *Whitlock v. Duke University*, plaintiff took part in experimental simulated deep dives as part of research on high-pressure nervous syndrome, but suffered organic brain damage.¹⁰¹ Finding that the state statute did not apply, the court turned to the federal regulations to help determine the standard for informed consent in the non-therapeutic research context, holding that informed consent should be consistent with the federal regulations requiring "[a] description of any reasonably foreseeable risks to the subject."¹⁰² The court ultimately held that there was no breach of the researcher duty to inform the research participant of reasonably foreseeable risks because evidence in the case indicated that organic brain damage was "not a risk to be reasonably expected."¹⁰³ The Fourth Circuit Court of Appeals affirmed.¹⁰⁴

Two courts have recognized a special relationship between researchers and research participants in the absence of a physician-patient relationship.¹⁰⁵ *Grimes v. Kennedy Krieger Institute*, which discussed researcher duties extensively, has drawn more attention as well as controversy. *Grimes* involved research on lead-paint abatement in homes rented to families with young children; the researchers at Kennedy Krieger Institute (KKI) analyzed blood lead levels of the children in order to determine the effectiveness of varying degrees of abatement.¹⁰⁶ The research participant plaintiffs were children found by the study to have elevated blood-lead levels; they claimed that KKI had failed to warn them of the lead-paint hazards that it knew or should have known existed in the plaintiffs' homes.¹⁰⁷ The Maryland Court of Appeals held that "the very nature of nontherapeutic research on human subjects can, and normally will, create special relationships out of which duties arise."¹⁰⁸ *Grimes* stated that

researchers are generally in a better position to “anticipate, discover, and understand the potential risks to the health” of research participants¹⁰⁹ and found a duty arising out of researchers’ superior knowledge, given that participants are “often poorly placed to protect themselves from risk.”¹¹⁰ The court held that informed consent requirements under the federal regulations create a duty of care arising out of that relationship, a breach of which was actionable under state law.¹¹¹ The court looked to the Nuremberg Code for further support, finding that it “speaks strongly to the existence of special relationships imposing ethical duties” on researchers.¹¹² The court thus vacated the lower court decision and remanded the case.¹¹³

Prior to *Grimes*, a federal trial court in Illinois also found a special relationship between researcher and research participant. *Blaz v. Michael Reese Hospital*

Informed by the discussed cases in the clinical context that recognize that a physician may have a duty to transmit information to a patient that will or could avert future harm, it is arguable that these core elements are present in the case of IFs with serious clinical implications. Like the health care professional, the researcher has knowledge of foreseeable harm. The researcher is also in a position to convey that information to the participant and avert or lessen possible harm.

*Foundation*¹¹⁴ involved patients at Michael Reese Hospital Foundation treated with x-ray therapy for benign conditions from 1930 to 1960, including plaintiff Joel Blaz.¹¹⁵ The hospital set up a follow-up program in 1974 to gather data and conduct research on the patients subjected to the x-ray therapy.¹¹⁶ The program contacted Blaz in 1975 to notify him that he was at increased risk of developing thyroid tumors because of the treatment and again in 1976, giving similar information and inviting him to return to the hospital for evaluation and treatment at his own expense, which he declined.¹¹⁷ In 1981, Dr. Schneider (the physician in charge of the follow-up program) sent a letter and a questionnaire, which Blaz received but did not return.¹¹⁸ The letter stated that the purpose of the questionnaire was to “investigate the long term health implications” and “determine the possible associated risks” of the childhood radiation treatments that Blaz and others had undergone.¹¹⁹ The letter did not disclose the fact that the hospital had discovered strong evidence of a connection between the treatment and tumor development.¹²⁰

In 1987 Blaz was diagnosed with a neural tumor.¹²¹ In 1996 Blaz sued the hospital and Dr. Schneider, alleging that they failed to notify him of their findings that he might be at greater risk of neural tumors in a way that might have permitted their earlier detection and removal or other treatment.¹²² The court stated that “[a] duty to warn exists when there is ‘unequal knowledge and the defendant possessed of such knowledge, knows or should know that harm might occur if no warning is given.’”¹²³ The court held that Dr. Schneider’s position researching the effects of treatments and contacting patients who were previously subjected to them created a special relationship under state law that conferred a duty, even absent a physician-patient relationship.¹²⁴ The court found negligence based on the general criteria established by the Illinois Supreme Court:¹²⁵ (1) whether the harm was “reasonably foreseeable,”¹²⁶ (2) the likelihood of the injury, (3) the magnitude of the burden of guarding against the injury, and (4) the consequences of placing that burden upon the defendant.¹²⁷

Grimes and *Blaz* suggest that researchers indeed have legally cognizable duties towards research participants, although the scope of these duties is not yet well-defined. Of these two cases, *Grimes* is the more important for analysis of IFs because the court found a special relationship giving rise to a duty even though the risks of lead-paint exposure were not directly caused by the research or the research institution.¹²⁸ Courts would seem most inclined to impose a legal duty when researchers could have prevented a serious harm to a research participant by disclosing information. Jennifer Kulynych recognizes the possible implications of this holding (especially the court’s criticisms of the KKI researchers for failure to warn

promptly) for neuroimaging research: researchers would have to anticipate “comparable disclosure issues that might arise in an imaging protocol, should researchers detect a potentially harmful medical condition of which the subject is unaware.”¹²⁹ These concerns can also be extended to the other research domains in which researchers encounter IFs.

Thus, the Common Rule has been used to show a relationship between the researcher and the research participant triggering certain duties recognized under state law.¹³⁰ For example, the *Grimes* court stated that, while there were genuine disputes of material fact to be examined on remand, the duty of informed consent within the federal regulations creates a relationship and therefore, a duty of care as a matter of Maryland state law.¹³¹ In *Vodopest v. McGregor*, the court stated that the federal regulations are “strong evidence that a medical researcher should not be allowed to conduct research on human beings without being held to the normal duty of care,” implying the existence of a relationship imposing a duty of care.¹³² Thus far, the use of the Common Rule to show a researcher duty of care has focused on issues of informed consent,¹³³ but the logic could certainly be extended to other provisions of the Common Rule. Moreover, the regulations have also been read in conjunction with other important declarations of research obligations, such as the Nuremberg Code and the Declaration of Helsinki, which address researchers’ obligations beyond obtaining informed consent, and thus would similarly ground broader duties.¹³⁴

Beyond using the federal regulations, cases have presented causes of action based on the failure to warn, or breach of a duty to warn, which may be relevant to researcher duties to communicate IFs to research participants. There have not been many cases in the research context raising claims of duty to warn, so it is informative to examine this theory in the clinical context. *Pate v. Threlkel* involved a doctor who knew that his female patient was afflicted with a genetically transferable disease, medullary thyroid carcinoma.¹³⁵ The suit was brought by the patient’s daughter against the doctor for failure to warn the mother of the disease and of the risks to her children of inheriting the disease. The plaintiff argued that had her mother been told of the genetic condition, she would have tested her children, discovered that the plaintiff was afflicted, and taken preventative action.¹³⁶ The Florida Supreme Court found that when the prevailing standard of care imposed a duty on a physician to warn a patient of a genetically transferable disease, that duty extended to third parties who clearly stood to benefit from that information.¹³⁷ However, the duty was limited to warning the patient of the disease, and that patient was then in the position to inform relevant third parties.¹³⁸ Wrongful life and wrongful birth cases raise similar issues, as when the New Jersey Supreme court found actionable a pediatrician’s failure to warn parents of their first child’s cystic fibrosis diagnosis early enough to prevent the birth of a second child affected by the disease.¹³⁹

Some of the more controversial physician duty-to-warn cases have found a duty to warn third parties of possible physical harm inflicted by the patient.¹⁴⁰ Perhaps the most famous duty-to-warn case is *Tarasoff v. Regents of the University of California*, in which the court imposed a duty on the therapist to disclose grave potential harm, though the victim was a third-party to the therapist-patient relationship, and such disclosure required the therapist to violate a duty of confidentiality toward the patient.¹⁴¹ Note, however, that controversy over duties to warn third parties are not relevant to the core IF case in which the question is the researchers duty to warn the research participant him- or herself. While it is possible to imagine an IF case, especially regarding a genetic or genomic IF, in which a relative tries to sue for failure to warn the relative, we are focusing here on the simpler duties of a researcher to warn the research participant.

Informed by the above cases in the clinical context that recognize that a physician may have a duty to transmit information to a patient that will or could avert future harm, it is arguable that these core elements are present in the case of IFs with serious clinical implications. Like the

health care professional, the researcher has knowledge of foreseeable harm. The researcher is also in a position to convey that information to the participant and avert or lessen possible harm.

Many state courts allow recovery for “loss of a chance,” especially in medical contexts.¹⁴² Commonly the doctrine is applied in medical malpractice cases, but can be applied more broadly.¹⁴³ A number of courts have used the doctrine to allow recovery for “failure to protect a person from a pre-existing condition.”¹⁴⁴ In these scenarios, the defendant has not created the underlying risk, but has failed to use due care to identify and alert the plaintiff to the risk. For example, “[w]here a physician is negligent in diagnosing a disease, and the resulting delay reduces the plaintiff’s chance of survival . . . , a strong argument can be made that the physician should be responsible for the value of the chance that the plaintiff lost, so long as the initial act of the physician was itself negligent.”¹⁴⁵ The loss of a chance doctrine is relevant to IFs because researcher failure to offer to disclose a clinically significant IF may cause a research participant to lose an opportunity for effective treatment and so may reduce the participant’s chance of cure or survival.

There has been little discussion of the loss of a chance doctrine in the research context. It has been mentioned with relation to research participants who forego therapeutic options that might have been more effective and enroll in a study to receive therapy that produces no therapeutic benefit.¹⁴⁶ The doctrine has also been mentioned when individuals who believe that they were “wrongfully denied enrollment [in a research study] might sue, claiming a lost opportunity for recovery, improvement in health status, or participation in the endeavor of scientific advancement.”¹⁴⁷ Recently, however, an article discussing the U.K. Biobank (UKB) raised the issue of a possible duty of disclosure by UKB if a participant is found to have a

To the extent that the discovery of an IF may lead the participant to seek medical follow-up, the possibility of discovering IFs and their leading to costs for the participant should be disclosed. Assuming that the researchers themselves do not plan to fund medical follow-up evaluation and treatment for an IF, they should disclose this in the informed consent process.

mutation or a genetic disorder, when treatment could be sought or changes made to lifestyle.¹⁴⁸ As with IFs, here the breach of a “duty to provide information” would increase the risk of disability or premature death as a result of the genetic disease.¹⁴⁹ Recognizing a breach would acknowledge that the research participant “‘lost his chance’ to pursue diagnosis and treatment.”¹⁵⁰

Research participants have also made claims under property law doctrines, though these have been largely unsuccessful.¹⁵¹ These cases claim a property right not only to biologic samples, but also to the results of research using those samples. In *Greenberg v. Miami Children’s Hospital Research Institute*, the plaintiffs attempted to use a state statute regarding DNA analysis to support their claim that “persons who contribute body tissue for researchers to use in genetic analysis do not relinquish ownership of the results of the analysis.”¹⁵² The court found that the statute was inapplicable since the statute provided penalties only for disclosure of confidential genetic information without consent or lack of informed consent for the testing, rather than granting any right in the results.¹⁵³ In *Ande v. Rock*, researchers conducted a cystic fibrosis study on samples from newborns and did not inform parents of a newborn who tested positive of the results.¹⁵⁴ The parents claimed a property right to these test results and argued that if this information had been disclosed, they could have avoided harm in two ways: they would have been able to accept treatment for their child to lessen the severity and progression of her disease, and they would have chosen not to have a second child who was also diagnosed with cystic fibrosis.¹⁵⁵ None of their claims to this information succeeded.¹⁵⁶

While these property claims have not been successful, E. Haavi Morreim writes that with increased public emphasis on privacy in health care, “[i]t is at least plausible that personal genetic information and other products of research may give rise to stronger property rights both within and outside the context of research.”¹⁵⁷ Because IFs are a product of research as well, and may convey information of even greater clinical or reproductive significance than research results themselves, recognition of property rights to information generated in research would strengthen research participants’ claims to IFs.

Research participants have also attempted to bring contract claims against researchers, though courts have generally been reluctant to find binding contractual obligations in the research setting.¹⁵⁸ However, some courts have applied a contract analysis to the informed consent form between researcher and participant,¹⁵⁹ particularly to any exculpatory provision contained in the consent form.¹⁶⁰ A contract analysis has implications for how IFs are managed. It suggests that researchers take on whatever obligations to manage IFs are articulated in the consent process and that research participants may hold the researchers accountable for failure to meet those obligations. Case law also casts doubt on the viability of exculpatory clauses attempting to relieve the researcher of responsibility for managing IFs.

In *Grimes*, the Maryland Court of Appeals found that KKI made express representations creating a binding contract with the research participants.¹⁶¹ KKI had expressly promised in its consent form to “collect lead dust samples from appellants’ homes, analyze the samples, discuss the results with appellants, and discuss steps that could be taken, which could reduce exposure to lead; and collect blood samples from children in the household and provide appellants with the results of the blood tests.”¹⁶² The court reasoned that because the informed consent process specifically informed the research participants that in return for providing samples they would receive the results of blood tests it created a contract in the research context.¹⁶³

The inability to identify exactly what IF will arise is not critical; identifying the potential to generate IFs regardless of their exact type or implications will ground researcher duties to disclose this possibility during the disclosure of risks and benefits of the research.

Contract doctrines have also been applied to exculpatory language within an informed consent document. *Vodopest v. MacGregor* involved the enforceability of a preinjury release form signed by the plaintiff research participant.¹⁶⁴ The research examined the use of a breathing technique to alleviate altitude sickness and required that participants trek up a mountain.¹⁶⁵ When the plaintiff began to feel sick on the trek, the researcher encouraged her to continue climbing anyway.¹⁶⁶ The participant later charged the researcher with a “failure to recognize signs and symptoms of the very thing that she was doing research on.”¹⁶⁷ The court held that, insofar as the researcher attempted to use the form to release herself as a researcher from liability for negligent acts performed in furtherance of medical research, enforcing the agreement would violate public policy.¹⁶⁸ The court wrote that “the public’s interest in the safety of human subjects and the public’s interest in the integrity of legitimate and necessary research militate against allowing researchers to negligently conduct research with impunity.”¹⁶⁹ This holding is consistent with the federal regulations’ prohibition of exculpatory language in informed consent forms.¹⁷⁰

Taken together, all of the legal approaches discussed above provide a number of bases for finding researcher legal duties in handling IFs. In the next section, we introduce the core duties of researchers regarding management of IFs that seem to flow from these legal underpinnings as well as applicable ethics standards.

III. Researchers' Duties

We argue that researchers shoulder affirmative duties to manage IFs, consisting of five core responsibilities: (1) to plan for IFs in the research protocol; (2) discuss the possibility of IFs with research participants during the informed consent process; (3) responsibly address IFs that arise; (4) evaluate IFs (*i.e.*, to verify their presence and determine their level of potential importance, seeking expert consultation as needed); and (5) in some cases offer to disclose IFs to research participants. The scope of these duties will be discussed below, in the order in which they would arise chronologically in the research process.

We note at the outset that researchers may resist any duty to manage IFs, arguing that research imposes on researchers no duty of clinical care; addressing IFs may cause research participants to mistake research for clinical care, an instance of the therapeutic misconception; offering to disclose any IFs will pose psychological, health, and privacy risks for research participants; and duties to manage IFs will impose insupportable costs on researchers. However, we argue that these objections are overcome by emerging trends in both ethics and law, which have begun to recognize that research participants may be entitled to more than researchers — and indeed, the existing research enterprise — currently provide them. We suggest that participants are entitled to information regarding IFs of likely clinical or reproductive significance based on the federal regulations pertaining to human subjects research, as well as common law theories such as tort negligence and the duty to warn, the loss of a chance doctrine, and contract law.

A. Duty to Plan for IFs, Develop a Pathway to Handle Them, and Implement the Plan

Researchers should plan in their study protocol for the possibility of obtaining IFs in the course of research. Planning includes creating a process for verifying IFs, evaluating their likely clinical or reproductive importance, and potentially offering to disclose them to the research participant. Researchers should tell potential research participants in the informed consent process and forms that IFs may be found, when that is the case. Researchers should also inform potential participants of the process by which IFs will be evaluated and the circumstances under which IFs will be offered to participants. IRBs should review the study protocol to ensure that an acceptable process for managing IFs is in place and review the informed consent plan and forms to make sure that potential participants will be made aware of both the possibility of IFs and whether and when this information will be offered to them.

These duties to plan for IFs and create a pathway to handle them in the research protocol and the ultimate duty to offer to disclose findings of likely importance to subjects flow from the researcher's duty to minimize risks to research participants, as required ethically and legally by the federal regulations. These risks include health dangers resulting from the failure to disclose IFs of likely clinical or reproductive significance and the risk of reporting false-positives in identification of IFs to subjects. This duty is also supported by common law tort theories of a researcher duty of care arising from the expertise of the researcher, as seen in both *Grimes* and *Blaz*, since the researcher is in a better position than the research participant to identify and address IFs.

Before researchers offer to disclose certain IFs to their research participants, they have a duty to verify and evaluate those IFs. The researcher must confirm the existence of an IF, determine whether the IF has likely clinical or reproductive significance and whether the level of significance warrants offering the IF to the research participant, and consult a clinical expert, if necessary, to make these determinations.

B. Duty to Discuss Incidental Findings in the Informed Consent Process

Once the proposed research protocol is approved by the IRB, researchers shoulder a duty to disclose the possibility of IFs to potential research participants in the informed consent process. One of the primary vehicles of human subjects protection provided in the federal regulations is the informed consent process and forms. As such, the regulations articulate requirements for informed consent that are relevant to the management of IFs.

The federal regulations require that the risks and benefits of the research be disclosed to potential research participants in the informed consent process.¹⁷¹ This includes a description of “any reasonably foreseeable risks or discomforts to the subject,” “any benefits to the subject or to others which may be reasonably expected from the research,” and when appropriate, a statement that the procedure “may involve risks to the subject...which are currently unforeseeable.”¹⁷² IFs may be viewed either as risks or as anticipated benefits of research, depending on the individual preferences and values of research participants.¹⁷³ This subjective perception of IFs supports a duty to address in the informed consent process the possibility of IFs; disclosure of the risks and potential benefits of IFs will allow research participants to determine for themselves whether these risks and benefits affect their decision to participate in the research.

Whether a particular finding is harmful or beneficial may depend on the participant’s individual values, as well as the availability of intervention. The possibility of psychological harms in research was early recognized in the *Belmont Report*,¹⁷⁴ but has more recently been extensively discussed in relation to disclosure in genetic research.¹⁷⁵ For IFs, the psychological harms are due to the information itself, such as a serious medical condition that has not manifested and was previously undetected.¹⁷⁶ Such discoveries may also confer therapeutic benefit or benefit in life planning, but when the information is unexpected or alarming or when there is no intervention available, the disclosure of the finding could be psychologically distressing.¹⁷⁷

IFs may also pose social and economic burdens. Insofar as genetic information is recognized as presenting risks of stigmatization, this would be true of IFs of genetic research. In addition, concerns regarding adverse effects on employability and insurability due to genetic information have been discussed in legal and bioethics literature.¹⁷⁸ Similar effects on insurability have been pointed out in fMRI research as well.¹⁷⁹ As with psychological risks, social and economic risks were also recognized in the *Belmont Report* and the *IRB Guidebook*.¹⁸⁰ Thus, they should all be disclosed to potential subjects. How these risks will be managed should also be disclosed.

Some may argue that this conception of the risks of research is broader than the federal regulations because it implicates non-physical risks beyond risks directly caused by the research procedure. However, discovering IFs is a direct product of the research process. And non-physical risks are already taken into account in IRB evaluation of proposed protocols, from the moment, for example, when researchers apply for expedited review of their protocol; the regulations look to whether research procedures would be damaging to the subjects’ financial standing, employability, insurability, reputation, or be stigmatizing.¹⁸¹ This recognition in the federal regulations of the importance of these non-physical risks supports an obligation to disclose to potential research participants the possibility of finding IFs. At the very least, IRBs are authorized by the federal regulations to require researchers to offer information to research participants regarding certain risks “when in the IRB’s judgment the information would meaningfully add to the protection of the rights and welfare of subjects.”¹⁸² This requirement must be balanced against the well-recognized right, particularly relevant in genetics, for participants to refuse information about them discovered during the course of research.¹⁸³

Researchers may argue that as long as they disclose during the informed consent process that they will not pay attention to or evaluate IFs, they should be

The pathway for handling IFs, including expert consultation when needed, should be explained in the informed consent process. Researchers should clarify for participants the level of review that IFs will receive, so that participants do not mistakenly rely on the belief that more work-up will be provided than the research protocol actually calls for.

absolved from duties to address, evaluate, and offer to disclose IFs. This is one possible strategy for limiting the expectations of research participants regarding IFs. However, we argue that such agreements are a violation of researchers' ethical and legal duties. Researchers should not be able to use the informed consent process to "contract out" of their ethical obligations: they should not be able to avoid the management and disclosure of IFs in research, no more than they could ask individuals to participate in research with an unreasonable balance of risks and benefits.

In addition, because the use of exculpatory language is prohibited when it serves to release researchers or their institution from liability for negligence,¹⁸⁴ language indicating that researchers will not be held responsible for IFs may be in violation of the regulations.¹⁸⁵ When an IF is of clear health significance to the research participant, language in the consent form purportedly releasing the researcher from liability for failure to disclose the IF may not protect the researcher. If the information could have been relayed to the research participant to avoid a serious health danger, the court may find it negligent not to have offered that information.¹⁸⁶

The federal regulations require researchers to disclose any additional costs to the research participant "that may result from participation in the research."¹⁸⁷ To the extent that the discovery of an IF may lead the participant to seek medical follow-up, the possibility of discovering IFs and their leading to costs for the participant should be disclosed. Assuming that the researchers themselves do not plan to fund medical follow-up evaluation and treatment for an IF, they should disclose this in the informed consent process. This information may be particularly important for those research participants who have no health insurance.

Finally, the federal regulations require that, when appropriate, the informed consent form should include "[a] statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject."¹⁸⁸ IFs may indeed be "significant new findings" affecting a participant's willingness to continue. This supports a researcher duty to disclose in the consent process the possibility of IFs. Legal theories supporting this duty include contract law. The consent form may be found to create a contract with the participant that requires the communication of information resulting from or discovered during the research that has health implications, as in *Grimes*. Also arising under contract claims may be the issue of exculpatory language; a state court may find exculpatory language that is prohibited under the federal regulations to evidence a state law breach of contract. State law requirements may also support the need to address IFs in the informed consent process. Recall that *Whitlock v. Duke*, interpreting a state statute, found that informed consent required a description of all "reasonably foreseeable risks" during the informed consent process in the non-therapeutic research context.¹⁸⁹ The inability to identify exactly what IF will arise is not critical; identifying the potential to generate IFs regardless of their exact type or implications will ground researcher duties to disclose this possibility during the disclosure of risks and benefits of the research.

C. Duty to Address Incidental Findings as They Arise

The duty to disclose IFs of potential clinical or reproductive significance implies a duty to exercise the care of a researcher with the training of the researcher in question in order to recognize and address IFs as they arise in research. This is based on the existence of a special relationship between the researcher and research participant, in which the researcher is privy

The researcher's duty to handle IFs culminates in a duty to offer to disclose based on ethical and legal considerations including the duty to warn and the loss of a chance doctrine. While the federal regulations do not explicitly refer to IFs, as discussed above, general considerations of research ethics — respect for persons, minimizing risks, and providing a reasonable relationship between risks and anticipated benefits — help determine the standard for the duty to disclose IFs.

to information about the participant based on their interaction. This duty was demonstrated in *Grimes* and in *Blaz*. This is not a duty to hunt for IFs or collect more information or different information than the research protocol actually requires; this would exceed the scope of the research design in a manner that is overly burdensome and costly to the researchers. The researcher should adequately analyze the information gathered during the regular course of research. For example, an fMRI researcher whose protocol calls for scans that are not optimized for clinical diagnosis would not be compelled to procure scans that are so optimized. Some institutions do have this type of policy,¹⁹⁰ but in some research, obtaining a clinical-grade scan may actually expose the participants to more physical risk. (As seen in *Blaz*, a heightened dose of radiation, while producing a clearer image, may confer increased future risk.)

More importantly, such efforts begin to resemble clinical care or screening rather than research. We agree with Jay Katz that the distinction between research and clinical care is an important one.¹⁹¹ We argue only that researchers have more duties with respect to IFs than have been recognized, not that researchers should undertake the full duties of clinicians.

While researchers should not be required to actively search for IFs, they should not blind themselves to the existence of IFs in their collected research data. For example, a CT colonography researcher should not exclude from her field of view all areas beyond the borders of the colon in the hope of avoiding extracolonic findings. Such information is intrinsic to the research modality — a researcher who collects this information is not then free to disregard portions in order to evade possible responsibilities to the research participant. To allow this would be to reduce participants to mere means to pursue the researcher's ends and would disregard obligations of respect for persons and reciprocity.¹⁹²

As part of fulfilling the duty to address IFs, researchers should be charged with knowing if IFs may be discovered in their research. In some research domains, the existence and prevalence of IFs is already beginning to be reported in the literature.¹⁹³ Researchers should be alert to this literature, the likelihood of discovering IFs in their research population, and the kinds of IFs likely to emerge, so that they may plan their research protocol to address IFs.

D. Duty to Verify Incidental Findings and Assess Likely Clinical or Reproductive Significance

Before researchers offer to disclose certain IFs to their research participants, they have a duty to verify and evaluate those IFs. The researcher must confirm the existence of an IF, determine whether the IF has likely clinical or reproductive significance and whether the level of significance warrants offering the IF to the research participant, and consult a clinical expert, if necessary, to make these determinations.

The duty to evaluate stems from the ethical principles of minimizing risk to research participants¹⁹⁴ and maintaining a reasonable relationship between risks and anticipated

benefits. As discussed above, the risks of IFs include psychological distress. This makes it important to confirm the analytic validity of the finding, and ensure that the finding really belongs to this research participant and was derived correctly. It also means making sure that the test result indeed indicates the clinical problem of concern. For genetic research, this is likely to mean confirmation of the finding in a laboratory approved under the Clinical Laboratory Improvement Amendments (CLIA).¹⁹⁵

Some would point to the likelihood of false-positives and any unnecessary anxiety they might cause as a reason to limit all disclosure of IFs. However, concerns over incorrect data or false-positives only point toward increased diligence in managing IFs, not to a blanket policy of nondisclosure of even the most important information. Also, while the problem of false-positives cannot be avoided in the biomedical enterprise, it should be mitigated. We agree with others in calling for more research on the rate of false-positives in identifying IFs,¹⁹⁶ but in the meantime, false-positives are another risk to be minimized in the evaluative process.

The legal support for the duty to address apparent IFs includes the duty to warn and the loss of a chance doctrine, as discussed above. The duty to warn is based here on the researcher's access to information of likely clinical significance for the research participant. According to the *Grimes* court, researchers are generally in a better position than research participants to "anticipate, discover, and understand the potential risks to the health" of those participants,¹⁹⁷ who are often "poorly placed to protect themselves from risk."¹⁹⁸ The *Blaz* court stated that "[a] duty to warn exists when there is 'unequal knowledge and the defendant possessed of such knowledge, knows or should know that harm might occur if no warning is given.'"¹⁹⁹ This lost opportunity to avert harm by failure to warn may be recognized through the loss of a chance doctrine.

The next two steps — a researcher's decision on whether to consult an expert and the researcher's (and consultant's) decision as to whether a finding should be offered to the research participant — allow researchers to distinguish those IFs that should be offered to participants, may be offered, and should not be offered.²⁰⁰ IFs that should be offered are generally findings with high likelihood of clinical or reproductive importance, for example, when the IF indicates a clinical condition that is likely to be life-threatening or a condition likely to be grave but that may be avoided or ameliorated, as with increased surveillance or clinical treatment.²⁰¹ We recognize that given the risks posed and the subjective preferences of individual participants, not all IFs should be disclosed. These two steps in evaluating findings therefore help ensure that the risks of IFs to be offered are reasonable in relation to the benefits.

Thus, an important first step is for the researcher to make an initial determination whether evaluating the IF requires clinical expertise beyond that of the research team. Verifying and evaluating an IF can be challenging and call for expertise beyond that of the researchers.²⁰² However, we are not urging that researchers with limited resources routinely have all research data and scans reviewed by a clinician. We are recommending that researchers obtain expert review of those suspected IFs whose verification and assessment requires clinical expertise beyond that of the team. It falls to the principal investigator as leader of the research team to determine when consultation is needed because assessing a suspected IF and determining whether an expert consult is needed may be challenging, particularly for researchers without medical training.²⁰³

There may be several objections raised to this step. Researchers may be concerned about the costs of consulting an expert. This burden may be lessened through assistance from the research institution or funding agencies. There may also be several liability concerns for the researchers regarding research participant privacy and confidentiality of participant information, as well

as liability concerns for any potential clinician experts regarding the quality of scans or data from which they must make a determination. We discuss these in turn.

As discussed above, IFs pose risks to the research participant. These risks include disclosure of the IF to third parties when the research participant has not consented to that. The federal regulations require such risks to be minimized by requiring that the researcher must provide, when appropriate, “adequate provisions [in the research plan] to protect the privacy of subjects and to maintain the confidentiality of data.”²⁰⁴ Researchers should have procedures in place for the protection of confidentiality and should disclose to research participants in the informed consent process when their IFs will be shared and under what circumstances, seeking consent to this plan.

Disclosure of an IF to a consultant thus raises privacy and confidentiality concerns. A related concern is that in contacting a consultant, the researcher will be violating privacy rules under HIPAA.²⁰⁵ HIPAA privacy rules apply to researchers who use and disclose “protected health information.”²⁰⁶ The determination of whether a particular researcher is subject to the Privacy Rule is beyond the scope of this paper. However, assuming that the researcher is covered and IFs constitute “protected health information,” there may be three permissible pathways for obtaining a consult on an IF. First, the researcher ideally will have planned for this possibility in the research protocol and thus had an opportunity to obtain prospectively the subject’s authorization for uses and disclosures not otherwise permitted by the HIPAA Privacy Rule, including consulting an expert on IFs.²⁰⁷ However, when prospective authorization has not been obtained, the researcher may still be able to consult an expert by de-identifying the IF according to HIPAA-defined standards.²⁰⁸ Alternatively, if the IF cannot be de-identified (or would not be diagnostically useful if it were), consultation with an expert to obtain a clinical evaluation of the IF may be permitted as “treatment,” that is, coordination or management of health care, including consultation.²⁰⁹ “Health care” under the HIPAA Privacy Rule includes, but is not limited to, “preventive [or] diagnostic...counseling, service, [or] assessment.”²¹⁰ Thus, although the best alternative is to obtain the subject’s authorization prospectively, the lack of authorization may not tie a researcher’s hands, should the researcher need to consult an expert.²¹¹

The pathway for handling IFs, including expert consultation when needed, should be explained in the informed consent process. Researchers should clarify for participants the level of review that IFs will receive, so that participants do not mistakenly rely on the belief that more work-up will be provided than the research protocol actually calls for. Kulynych has suggested that such reliance may lead to researcher liability.²¹² She states that “[r]esearchers should also be aware that they may incur liability for negligence if the subject reasonably believes that a medical professional will review neuroimages obtained in the study and the subject is not informed promptly of foreseeable harms (*e.g.*, diagnostically useful indications of risk or abnormality).”²¹³

E. Duty to Offer to Disclose Incidental Findings of Likely Clinical or Reproductive Significance

The researcher’s duty to handle IFs culminates in a duty to offer to disclose based on ethical and legal considerations including the duty to warn and the loss of a chance doctrine. While the federal regulations do not explicitly refer to IFs, as discussed above, general considerations of research ethics — respect for persons, minimizing risks, and providing a reasonable relationship between risks and anticipated benefits — help determine the standard for the duty to disclose IFs.

Only a subset of IFs need be offered to research participants. The consensus paper in this symposium suggests three levels of IFs and the corresponding disclosure responsibilities.²¹⁴

The paper specifies those IFs that should be offered, those that may be offered, and those that should not be provided. That schema is informed by the human subjects regulations and ethical consideration, as that paper explains.

If the research participant does not decline the IF information, thereby asserting a right not to know (discussed above), then disclosure of the IF should be conducted so as to communicate effectively and offer appropriate support and referral to clinicians for further clinical work-up and care. This kind of communication aims to minimize the risks to research participants of receiving this information while maximizing anticipated benefits. Addressing IFs in genetic research, the OHRP *IRB Guidebook* states that “[a]ppropriate counseling should be provided to educate subjects about the meaning of the genetic information they have received, and to assist them in coping with any psychosocial effects of participation.”²¹⁵ This is consistent with minimizing risks to research participants. As noted above, respecting a participant’s right *not* to know is a part of respecting the participant’s autonomy; this right is well established in genetics.

Once the researcher has communicated the IF to the research participant, it reasonably falls to the participant to pursue clinical work-up and care. The underlying clinical problem revealed by the IF was not caused by the research; the researchers came upon the IF in the course of meeting research aims. Thus, we see no basis for placing on researchers the duty to provide and fund the clinical work-up and care.²¹⁶ That said, researchers should stand ready to communicate with the participant’s physicians, if the participant authorizes this. Certainly, research participants who lack health insurance or otherwise face obstacles to securing clinical care will raise special concerns. Researchers should anticipate this problem and may prudently identify in advance referral options that would effectively assist a research participant confronting these problems.

IV. Conclusion

This article explores the ethical and legal theories that ground researchers’ duties to manage IFs in human subjects research. Based on those theories, we suggest that researchers indeed shoulder duties to research participants. In making this argument, we challenge the traditional line drawn between robust physician duties of care toward patients and minimal researcher duties of care toward research participants. We advocate an intermediate researcher duty of care, supported both by provisions of the federal human subjects regulations and recent case law. We argue that this researcher duty of care applies to incidental findings discovered during the course of research and requires that the researchers plan for IFs in the protocol development, discuss the possibility of IFs with research participants during the informed consent process, responsibly address IFs that arise, evaluate IFs (with a consultant if needed), and in some cases offer to disclose IFs directly to research participants. As research technologies become more powerful, their potential to generate incidental findings will only increase. It is crucial to clarify the responsibilities that researchers bear to handle IFs responsibly.

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References

1. The Common Rule governs research on human beings funded by the federal government or conducted by institutions providing the federal government with an assurance that all research conducted there will follow the federal rules. See 45 C.F.R. § 46.101 (2007). Sixteen federal agencies subscribe to that rule. See Office for Human Research Protections (OHRP) *Common Rule Agencies/Departments*, available at <<http://www.hhs.gov/ohrp/related.html#com>> (last visited January 14, 2008). The Food and Drug Administration (FDA) follows a variant. See 21 C.F.R. Parts 50, 56 (2007).
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6. See Vernooij MW, et al. Incidental Findings on Brain MRI in the General Population. *N. Engl. J. Med* 2007;357(18):1821–1828. [PubMed: 17978290] Kumra S, et al. Ethical and Practical Considerations in the Management of Incidental Findings in Pediatric MRI Studies. *Journal of the American Academy of Child and Adolescent Psychiatry* 2006;45(8):1000–1006. [PubMed: 16865043] at 1002 Alphas HH, et al. Findings on Brain MRI from Research Studies of Occupational Exposure to Known Neurotoxicants. *American Journal of Roentgenology* 2006;187(4):1043–1047. [PubMed: 16985155] at 1044 see also Katzman GL, Dagher AP, Patronas NJ. Incidental Findings on Brain Magnetic Resonance Imaging from 1000 Asymptomatic Volunteers. *JAMA* 1999;282(1):36–39. [PubMed: 10404909] Kim BS, et al. Incidental Findings on Pediatric MR Images of the Brain. *American Journal of Neuroradiology* 2002;23(10):1674–1677. [PubMed: 12427622]
7. See Gluecker TM, et al. Extracolonic Findings at CT Colonography: Evaluation of Prevalence and Cost in a Screening Population. *Gastroenterology* 2003;124(4):911–916. [PubMed: 12671887] Hara AK, et al. Incidental Extracolonic Findings at CT Colonography. *Radiology* 2000;215(2):353–357. [PubMed: 10796907] Yee J, et al. Extracolonic Abnormalities Discovered Incidentally at CT Colonography in a Male Population. *Radiology* 2005;236(2):519–526. [PubMed: 16040909]
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9. See Lawrenz Sobotka, *supra* note 4.
10. See Wolf, *supra* note 2.
11. We urge that principal investigator bears the ultimate responsibility for IFs. Other players in the research enterprise also shoulder obligations to plan for and manage IFs. For example, IRBs should review the informed consent plan and forms and the research protocol to ensure that proper processes are in place to deal with IFs. Funding agencies should help fund the costs of managing IFs appropriately in research.
12. See Wilfond BS, Carpenter KJ. Incidental Findings in Pediatric Research. *Journal of Law, Medicine & Ethics* 2008;36(2):332–340.
13. See Additional Protections for Children Involved as Subjects in Research, 45 C.F.R. subpart D, §§ 46.401 et seq. (2007). Additional Safeguards for Children in Clinical Investigations, 21 C.F.R. subpart D, §§ 50.50 et seq. (2007).
14. While there are currently no specific federal regulations regarding the protection of subjects with diminished capacity, several governmental policy bodies have addressed the issue. See National Bioethics Advisory Commission (NBAC) *Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity* 1998 December Rockville, MD National Human Research Protections Advisory Committee (NHRPAC) Workgroup on Decisional Incapacity, available at <[Final Report on Informed Consent and the Decisionally Impaired](http://www.hhs.gov/ohrp/nhrpac/documents/nhrpac10.pdf) <http://www.hhs.gov/ohrp/nhrpac/documents/nhrpac10.pdf>> (last visited April 7, 2008) Office for Human Research Protections

- (OHRP)Secretary's Advisory Committee on Human Research Protections (SACHRP), Subcommittee on Inclusion of Individuals with Impaired Decision-Making in Research (SIIDR), available at <<http://www.hhs.gov/ohrp/sachrp/subcommittees.html>> (last visited April 7, 2008).
15. See, e.g., Morreim EH. Litigation in Clinical Research: Malpractice Doctrine Versus Research Realities. *Journal of Law, Medicine & Ethics* 2004;32(3):474–484.
 16. For commentary on researchers' traditionally limited duties of care, see, e.g., Richardson HS, Belsky L. The Ancillary-Care Responsibilities of Medical Researchers: An Ethical Framework for Thinking about the Clinical Care that Researchers Owe Their Subjects. *Hastings Center Report* 2004;34(1): 25–33. [PubMed: 15098404]We discuss in text cases such as *Grimes* that are among the very few cases finding a researcher duty of care owed directly to the research participant.
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 18. See Richardson Belsky, *supra* note 16.
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 22. See Shalowitz Miller, *supra* note 20, at 738 (describing existing policies that would limit disclosure of individual results).
 23. See, e.g., Clayton EW, Ross LF, Letter. Implications of Disclosing Individual Results of Clinical Research. *JAMA* 2006;295(6):37. [PubMed: 16391213] Dressler LG, Juengst ET. Thresholds and Boundaries in the Disclosure of Individual Genetic Research Results. *American Journal of Bioethics* 2006;6(6):18–20. [PubMed: 17085396]
 24. See Clayton Ross, *supra* note 23.
 25. *Id*; Parker, *supra* note 20, at 7
 26. See Lawrenz Sobotka, *supra* note 4.
 27. See Ossorio PN Letting the Gene Out of the Bottle: A Comment on Returning Individual Research Results to Participants. *American Journal of Bioethics* 2006;6(6):2425, at 25. [PubMed: 17085399]
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 29. See Cho MK. Understanding Incidental Findings in the Context of Genetics & Genomics. *Journal of Law, Medicine & Ethics* 2008;36(2):280–285.
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 31. See Wolf, *supra* note 2, at Table III.
 32. See Clayton EW. Incidental Findings in Genetics Research Using Archived DNA. *Journal of Law, Medicine & Ethics* 2008;36(2):286–291.
 33. See The Database on Genotype and Phenotype (dbGaP), available at <<http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap>> (last visited April 7, 2008) see also National Institutes of Health Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies (GWAS), *Federal Register* 72, no. 166 (2007)4929097, available at <<http://edocket.access.gpo.gov/2007/pdf/E7-17030.pdf>> (last visited April 7, 2008).
 34. The fMRI Data Center asks submitting authors to submit the following data: (1) raw, reconstructed image volumes from the scanner; (2) pre-processed images used for statistical analyses and detailed descriptions of the image processing steps that were applied; (3) high-resolution anatomical images

from all subjects; and (4) image volumes of final statistical results for each subject as well as statistical group maps. See fMRIDC Data Center, “Frequently Asked Questions .,” *available at* 2008 (last visited March 28, 2008). <<http://www.fmridc.org/fmridc/help/faq.html>>

35. See 45 C.F.R. § 46.101 (b) (4) (2007) (exempting research in which the only involvement of “human subjects” is “the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens...if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects”); OHRP, *supra* note 30.
36. See, e.g., *Grimes v. Kennedy Krieger Inst.*, 782 A.2d 807 (Md. 2001).
37. See Section IIB, *infra*.
38. McGuire AL, Caulfield T, Cho MK. Research Ethics and the Challenge of Whole-Genome Sequencing. *Nature Genetics* 2008;9(2):152–156., at 152.
39. 45 C.F.R. § 164.524 (2007) National Institutes of Health (NIH) Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule, Access to Protected Health Information, *available at* <http://privacyruleandresearch.nih.gov/pr_08.asp#8j> (last visited April 7, 2008). See also Section IIID below.
40. See NIH, *supra* note 39 National Human Genome Research Institute (NHGRI) Federal Policy Recommendations Including HIPAA, *available at* <<http://www.genome.gov/11510216>> (last visited April 7, 2008).
41. 45 C.F.R. § 160.102 (2007) (defining a covered entity as a health plan, health care clearinghouse, or health care provider that transmits any health information electronically in connection with a covered transaction).
42. 45 C.F.R. § 164.524 (a) (iii) (2007) (exempting PHI maintained by a covered entity subject to CLIA when access is prohibited by law (§ 164.524 (a) (iii) (A)) or when a covered entity is exempt from CLIA under 42 C.F.R. § 493.3 (b) (2)).
43. See *Grimes*, 782 A.2d 807. The litigation was followed by a larger discussion of the research that was at the center of litigation. See, e.g., National Research Council and Institute of Medicine Ethical Considerations for Research on Housing-Related Hazards Involving Children 2005 National Academies Press Washington, D.C.
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46. See Grossman Bernat, *supra* note 44, at 849
47. See Illes, “Ethical and Practical Considerations in Managing Incidental Findings in Functional Magnetic Resonance Imaging,” *supra* note 44, at 359
48. Beauchamp, TL.; Childress, JF. *Principles of Biomedical Ethics*. 5th. Oxford University Press; New York: 2001. p. 174
49. *Id.*

50. See National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, Federal Register 44 (1979)2319297 [hereinafter *Belmont Report*].
51. National Bioethics Advisory Commission (NBAC) Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries 2001: at 59. Rockville, MD The discussion of reciprocity centers on the provision of post-trial medical interventions to individuals participating in clinical trials in developing countries. *Id*
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58. See Illes Incidental Findings in Brain Imaging Research. *supra* note 44, at 783
59. See Belmont Report, *supra* note 50.
60. See Shalowitz Miller, *supra* note 20, at 738
61. *Id*.
62. See *supra*, note 1.
63. See Mello MM. The Rise of Litigation in Human Subjects Research. *Annals of Internal Medicine* 2003;139(1):40–45. [PubMed: 12834317] Hoffman SBerg JW The Suitability of IRB Liability. *University of Pittsburgh Law Review* 2005;67:2365–427, at 367.
64. For criteria for IRB approval (including risk minimization and risk-benefit assessment), see 45 C.F.R. § 46.111 (2007) 21 C.F.R. § 56.111 (2007) For elements of informed consent, see 45 C.F.R. § 46.116 (2007) 21 C.F.R. § 50.25 (2007) Note that federal rules on “adverse events” do not appear to address IFs, as the condition revealed by an IF is not caused by the research. See generally Office for Human Research Protections (OHRP) Department of Health and Human Services. Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events 2007 January 15, at 8, available at <<http://www.hhs.gov/ohrp/policy/AdvEvtGuid.pdf>> (last visited April 7, 2008).
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66. See Office for Human Research Protections (OHRP): at ch. 5, Biomedical and Behavioral Research: An Overview. Institutional Review Board Guidebook (1993) section H. (“Human Genetic Research”), available at <http://www.hhs.gov/ohrp/irb/irb_chapter5ii.htm#h12> (last visited April 7, 2008).
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68. 45 C.F.R. § 46.116 (a) (2007) see also 21 C.F.R. § 50.25 (a) (2007)
69. 45 C.F.R. § 46.116 (b) (2007) see also 21 C.F.R. § 50.25 (b) (2007)
70. 45 C.F.R. § 46.109 (b) (2007) 21 C.F.R. § 56.109 (b) (2007).
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74. *Id.*, at 5–7 see also 21 C.F.R. Part 56 Subpart E (2007), “Administrative Actions for Noncompliance.”
75. See, e.g., Wright v. Fred Hutchinson Cancer Research Center, 269 F. Supp. 2d 1286 (W.D. Wa. 2002) *Abdullahi v. Pfizer*, No. 01 Civ. 8118 (WHP), 2005 WL 1870811, at *11 n.4 (S.D.N.Y.) (“[T]he FDA regulations do not provide any private right of action.”) (citing *Summit Tech. v. High-Line Med. Instruments Co*, 933 F. Supp. 918, 932–33 (C.D. Cal. 1996) *PDK Lab. v. Friedlander*, 103 F. 3d 1105, 1113 (2d. Cir. 1997)).
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77. See *Robertson v. McGee*, No. 01CV60, 2002 WL 535045, at *3 (N.D. Okla. 2002) (citing *Robinett v. U.S.*, 62 F.3d 1433, at *1 (Fed. Cir. 1995) (unpublished); *Washington v. Catalona*, 437 F. Supp. 2d 985, 1000 (E.D. M.O. 2006)).
78. See *Merrell Dow Pharmaceuticals v. Thompson*, 478 U.S. 804, 810 (1986).
79. See, e.g., *Wright*, 269 F. Supp. 2d 1286; *Robertson*, 2002 WL 535045.
80. See 42 U.S.C. § 1983 (2007).
81. 269 F. Supp. 2d at 1289
82. *Robertson*, 2002 WL 535045, at *3 (citing *Chapman v. Houston Welfare Rights Org.*, 441 U.S. 600, 617 (1978)).
83. *Id.*; *Wright*, 269 F. Supp. 2d 1286, at 1290
84. *Wright*, 269 F. Supp. 2d 1286, at 1290 n.1 (citing S. Rep. No. 93-381, at 197390
85. *Id.*, at 1290
86. 437 F. Supp. 2d 985, 1000 (E.D. Mo. 2006).
87. *Id.*
88. *Washington v. Catalona*, 490 F.3d 667, 677 (8th Cir. 2007), *cert. denied*, 2008 U.S. LEXIS 1203 (U.S. 2008).
89. For a comprehensive discussion of common law doctrines used in medical research litigation, see Morreim EH. Medical Research Litigation and Malpractice Tort Doctrine: Courts on a Learning Curve. *Houston Journal of Health Law and Policy* 2003;4(1):1–86. For a discussion of claims brought by research subjects, see Mello, *supra* note 63.
90. Furrow BR2000260(hornbook).
91. See *Restatement of the Law, Second, Torts* (St. Paul, MN: American Law Institute Publishers, 1965) 116 (§ 314: Duty to Act for the Protection of Others), 118 (§ 314A: Special Relations Giving Rise to Duty to Aid or Protect).
92. The court stated that as a matter of state law, a duty of informed consent created by federal regulation translates into a duty of care arising out of the unique relationship that is researcher-subject, as opposed to doctor-patient. *Grimes* 782 A.2d 807, at 849.
93. *Id.*, at 858
94. *Id.*
95. See Morreim, *supra* note 89, at 192. Morreim criticizes one famous case, *Moore v. Regents of the Univ. of Cal.*, which was limited to recognizing a breach of the fiduciary duty. *Id.*, at (citing *Moore v. Regents of the Univ. of Cal.*, 793 P.2d 479 (Cal. 1990)). 2324
96. *Id.*, at (citing *Moore v. Regents of the Univ. of Cal.*, 793 P.2d 479 (Cal. 1990)). 2324
97. *Id.*, at 2829
98. *Id.*, at 29
99. 637 F. Supp. 1463, 1467 (M.D.N.C. 1986).
100. *Id.*, at 147071
101. *Id.*, at 146466
102. *Id.*, at (citing 45 C.F.R. § 46.116 (a) (2) (1985)). 1471
103. *Id.*, at 1472
104. *Whitlock v. Duke University*, 829 F.2d 1340 (4th Cir. 1987).
105. See *Blaz v. Michael Reese Hosp. Found.*, 74 F. Supp. 2d 803 (N.D. Ill. 1999). *Grimes*, 782 A.2d 807, at 846. The *Grimes* court stated, “[W]e know of no law, nor have we been directed to any applicable in Maryland courts, that provides that the parties to a scientific study, because it is a scientific, health-related study, cannot be held to have entered into special relationships with the subjects of the study that can create duties, including duties, the breach of which may give rise to negligence claims.” 782 A.2d 807, at 835
106. See *Grimes*, 782 A.2d 807, at 812
107. *Id.*, at 82526, 828-29.
108. *Id.*, at 83435. The Maryland Court of Appeals found that the lower courts were incorrect to rule that “as a matter of law a research entity conducting an ongoing non-therapeutic scientific study does

not have a duty to warn...when the researcher has knowledge of the potential for harm to the subject and the subject is unaware of the danger.” *Id.*, at 81819

109. See *Grimes*, 782 A.2d 807, at 851
110. *Id.*, at 846
111. *Id.* at 849, 858.
112. *Id.* at 849
113. *Id.* at 858
114. See *Blaz*, 74 F. Supp. 2d 803.
115. *Id.*, at 804
116. *Id.*
117. *Id.*
118. *Id.*
119. *Id.*
120. *Id.* In 1979 Dr. Schneider and the Hospital had submitted a research proposal to NIH stating that a study based on the program had showed “strong evidence” of a connection between x-ray treatments such as those received by Blaz and various sorts of tumors. *Id.*
121. *Id.*
122. *Id.*
123. *Id.* (quoting *Kokoyachuk v. Aeroquip Corp.*, 526 N.E.2d 607, 610 (Ill. App. Ct. 1988)).
124. *Id.*, at 80607
125. *Id.*, at 805 The Maryland court in *Grimes* presented factors to consider when determining negligence: “(1) that the defendant was under a duty to protect the plaintiff from injury, (2) that the defendant breached that duty, (3) that the plaintiff suffered actual injury or loss; and (4) that the loss or injury proximately resulted from the defendant’s breach of the duty.” *Grimes*, 782 A.2d 807, at 84142
126. *Id.* (citing *Kirk v. Michael Reese Hosp.*, 513 N.E.2d 387, 396 (Ill. 1987)).
127. *Id.* (citing *U.S. v. Carroll Towing Co.*, 159 F.2d 169, 173 (2d Cir. 1947)).
128. See *Grimes*, 782 A.2d 807, at 814 On the scope of the duties recognized in *Grimes*, see, e.g., Hoffman DE, Rothenberg KH. Whose Duty Is It Anyway? The Kennedy Krieger Opinion and Its Implications for Public Health Research. *Journal of Health Care Law and Policy* 2002;6(1):109–147. [PubMed: 15017954]
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130. See, e.g., *Grimes*, 782 A.2d 807, at 849
131. *Id.*, at 84950
132. *Vodopest v. McGregor*, 913 P.2d 779, 861 (Wash. 1996).
133. Mastroianni A. Liability, Regulation and Policy in Surgical Innovation: The Cutting Edge of Research and Therapy. *Health Matrix* 2006;16:235–242, at 413 [PubMed: 16948248] (citing Jansson RL. Researcher Liability for Negligence in Human Subjects Research: Informed Consent and Researcher Malpractice Actions. *Washington Law Review* 2003;78(1):229–263. [PubMed: 15732212])
134. See, e.g., *Whitlock*, 829 F.2d 1340, at 1475 *Grimes*, 782 A.2d 807, at 851
135. *Pate v. Threlkel*, 661 So. 2d 278, 279 (Fla. 1995).
136. *Id.*
137. *Id.*, at 282
138. *Id.*
139. *Schroeder v. Perkel*, 432 A.2d 834, 839 (N.J. 1981)
140. *Tarasoff v. Regents of the Univ. of Cal.*, 551 P.2d 334 (Cal. 1976).
141. 551 P.2d 334, 342 (Cal. 1976).
142. See Restatement, Third, of Torts, Liability for physical harm § 26 (2005). The classic article on loss of a chance is King JH. Causation, Valuation, and Chance in Personal Injury Torts Involving

Preexisting Conditions and Future Consequences. *Yale Law Journal* 1981;90(6):1353–1397. See also Fischer DA. Tort Recovery for Loss of a Chance. *Wake Forest Law Review* 2001;36(3):605–655. Bruer RS. Loss of a Chance as a Cause of Action in Medical Malpractice. *Missouri Law Review* 1994;59(4):969–996.

143. See, e.g., Fischersupra note 142.
144. *Id.*, at 610
145. See Furrow, supra note 90, at 304
146. See Evans BJ. What Will It Take to Reap the Clinical Benefits of Pharmacogenetics? *Food & Drug Law Journal* 2006;61(4):753–794. [PubMed: 17180771]; see HoffmanBerg, supra note 63, at 390 (discussing loss of a chance when an IRB improperly approves research in which a subject takes part); SaverRSMedical Research and Intangible Harm. *University of Cincinnati Law Review* 2006;74(3):1012, at 980 (calling these claims “speculative”).
147. HoffmanBergsupra note 63, at 390
148. JohnstonCKayeJDoes the UK Biobank Have a Legal Obligation to Feedback Individual Findings to Participants? *Medical Law Review* 2004;12(3):267, at 258. “If there is a breach of this duty and the harm eventuates, that is the participant develops symptoms of the genetic disease, or dies prematurely, then the issue is whether the breach of duty (failure to warn), has caused the harm.” *Id.*
149. *Id.*, at 258
150. *Id.*
151. See Morreim, supra note 89, at 3537
152. 264 F. Supp. 2d 1064, 1075 (S.D. Fla. 2003) (citing Fla. Stat. § 760.40 (2002)).
153. *Id.*
154. 647 N.W.2d 265, 270 (Wis. App. 2002).
155. *Id.*
156. *RockAnde v.*, 647 N.W.2d 265, 265 (Wis. App. 2002).
157. See Morreim, supra note 89, at 37
158. See Saver, supra note 146. But see *Grimes*, 782 A.2d 807, at 843 (applying a contract analysis to informed consent forms).
159. See, e.g., *Grimes*, 782 A.2d 807, at 843
160. See, e.g., *Vodopest*, 913 P.2d 779, at 781
161. See *Grimes*, 782 A.2d 807, at 843
162. *Id.*, at 843
163. *Id.*, at 844
164. 913 P.2d 779, 781 (Wash. 1996). Additionally, the defendant did not inform the plaintiff that the form had been rejected by the IRB. *Id.*, at 782
165. See *Vodopest*, 913 P.2d 779, at 785
166. *Id.*, at 785
167. *Id.*
168. *Id.*
169. *Id.*, at 789
170. 45 C.F.R. § 46.116 (2007) 21 C.F.R. § 50.20 (2007).
171. See 45 C.F.R. § 46.116 (2007) 21 C.F.R. § 50.25 (2007).
172. 45 C.F.R. § 46.116 (2007) (general requirements for informed consent) see also 21 C.F.R. § 5.25 (2007).
173. Parker LS. The Future of Incidental Findings: Should They Be Viewed as Benefits? *Journal of Law, Medicine & Ethics* 2008;36(2):341–351.
174. See Belmont Report, supra note 50.
175. See OHRP, supra note 66.
176. Cf. *id.* Psychological harms may also be due to the uncertain nature of genetic information, which is usually expressed in probabilities.

177. See Kulynych, *supra* note 129, at 349; see also Burke W, et al. Categorizing Genetics Tests to Identify their Ethical, Legal, and Social Implications. *American Journal of Medical Genetics* 2001;106(3): 233–240. [PubMed: 11778984]
178. See, e.g., Anderlik MA, Rothstein MA. Privacy and Confidentiality of Genetic Information: What Rules for the New Science? *Annual Review of Genomic and Human Genetics* 2001;2(1):401–433. Godard B, et al. Genetic Information and Testing in Insurance and Employment: Technical, Social and Ethical Issues. *European Journal of Human Genetics* 2003;11(Supplement 2):S123–S142. [PubMed: 14718940]
179. See Kulynych, *supra* note 129, at 352
180. See Office for Human Research Protections (OHRP), at ch. 3 (“Basic IRB Review. Institutional Review Board Guidebook”), available at <http://www.hhs.gov/ohrp/irb/irb_chapter3.htm> (last visited April 7, 2008).
181. See Office for Protection from Research Risks (OPRR) National Institutes of Health, Department of Health and Human Services. Protection of Human Subjects: Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure, Federal Register 63 (November 9, 1998):6036467, at 60,366, available at <<http://www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm>> (last visited April 7, 2008).
182. 45 C.F.R. § 46.109 (b) (2007) 21 C.F.R. § 56.109 (c) (2007).
183. On this right not to know, see, e.g., National Human Research Protections Advisory Committee Working Group on Genetics IRB Guidebook Chapter on Human Genetics Research, Draft 2, June 27200212, available at <<http://www.hhs.gov/ohrp/nhrpac/documents/nhrpac13.pdf>> (last visited April 7, 2008).
184. 45 C.F.R. § 46.116 (2007) 21 C.F.R. § 50.20 (2007).
185. See, e.g., Illes Ethical and Practical Considerations in Managing Incidental Findings in Functional Magnetic Resonance Imaging. *supra* note 44, at 362
186. As discussed above, courts may decide that the research participant had a right to this information. The human subjects regulations preserve any legal right that courts choose to recognize. See 45 C.F.R. § 46.116 (2007) 21 C.F.R. § 50.20 (2007). At least one state court has held that, insofar as a researcher attempts to obtain from the research participant a release from responsibility for negligent acts performed in the medical research, enforcing the agreement would violate public policy. See *Vodopost*, 913 P.2d 779, at 785
187. 45 C.F.R. § 46.116 (b) (3) (2007) 21 C.F.R. § 50.25 (b) (5) (2007).
188. 45 C.F.R. § 46.116 (b) (5) (2007) 21 C.F.R. § 50.25 (b) (5) (2007).
189. *Whitlock v. Duke University*, 637 F. Supp. 1463, 1472 (M.D.N.C. 1986).
190. See Illes Incidental Findings in Brain Imaging Research. *supra* note 44.
191. See Katz, *supra* note 17, at 121; Illes Incidental Findings in Brain Imaging Research. *supra* note 44; Richardson-Belsky *supra* note 16.
192. See Shalowitz-Miller 738, *supra* note 20, at
193. See, e.g., Illes, *supra* note 5; see also Wolf, *supra* note 2.
194. See 45 C.F.R. § 46.116 (b) (5) (2007) 21 C.F.R. § 50.25 (b) (5) (2007); risks should be reduced to those necessary to achieve the research objective. Belmont Report, *supra* note 50
195. See Wolf, *supra* note 2.
196. See Kulynych, *supra* note 129, at 349
197. See Grimes, 782 A.2d, at 851
198. *Id.*, at 846
199. See *Blaz*, 74 F. Supp. at 805 (quoting *Kokoyachuck v. Aeroquip Corp.*, 536 N.E.2d 607, 610 (Ill. App. Ct. 1988)).
200. See Wolf, *supra* note 2, at section III E.
201. *Id.*
202. *Id.*
203. See, e.g., Mamourian, *supra* note 44, at 521 (arguing that separating out the significant from the non-significant is very difficult even for imagers).

204. 45 C.F.R. § 46.111 (a) (7) (2007)21 C.F.R. § 56.111 (a) (7) (2007).
205. See 45 C.F.R. §§ 160 et seq. (2007)IllesIncidental Findings in Brain Imaging Research. *supra* note 44, at 784
206. The HIPAA Privacy Rule applies to covered entities and “protected health information.” as defined in 45 C.F.R. §§ 160.102-.103 (2007).
207. See National Institutes of Health (NIH), Department of Health and Human ServicesProtecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule2003, *available at* <http://privacyruleandresearch.nih.gov/pdf/HIPAA_Booklet_4-14-2003.pdf> (last visited April 7, 2008)IllesIncidental Findings in Brain Imaging Research. , *supra* note 44, at 784
208. See 45 C.F.R. §§ 164.502 (d), 164.514 (a)-(c) (2007)see IllesIncidental Findings in Brain Imaging Research. , *supra* note 44, at 784
209. 45 C.F.R. § 164.501 (2007)see also IllesIncidental Findings in Brain Imaging Research. , *supra* note 44, at 784 (“[C]ommunication even with identifiers may well be allowed under state and federal privacy law because it is for the purpose of potential treatment.”)
210. 45 C.F.R. § 160.103 (2007).
211. Note that another potential liability concern is that of the consultant, who may be reluctant to evaluate the IF based on research scans or data, which may not be of clinical grade or optimized for clinical diagnosis. See, e.g., KulynychJJThe Regulation of MR Neuroimaging Research: Disentangling the Gordian Knot. *American Journal of Law & Medicine*20073323295317, at 314-315. [PubMed: 17910161] While we do not undertake to analyze this concern here, it is important to recognize that the consultant is not being asked for a clinical diagnosis; the consultant is merely being asked to say whether he or she also sees an IF and whether it appears to have potential clinical or reproductive significance.
212. See Kulynych, *supra* note 129, at 348349
213. *Id.*, at 348
214. See Wolf, *supra* note 2.
215. See OHRP, *supra* note 66.
216. For a different view, see RichardsonBelsky, *supra* note 16.