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# The Future of Incidental Findings: Should They be Viewed as Benefits?

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The possibility of generating incidental findings — in both research and clinical contexts — has long been regarded as a risk of these enterprises. Should incidental findings (IFs) in research also be regarded as potential benefits? At first glance, it would seem they ought to be. After all, in particular circumstances or given a particular set of values, any piece of information can be beneficial. Therefore, it may seem incoherent or unduly paternalistic to regard IFs only as risks. Moreover, developments in science and technology increasingly transform what was once of uncertain meaning and dubious value into information that is likely to have clear meaning and potential personal value, if not obvious clinical utility. For these reasons, it would seem that in the future, IFs should be treated as potential benefits in the design and regulation of research.

This paper argues, however, that there exist sound reasons *not* to treat IFs as benefits in the research context. To make this case for the asymmetrical treatment of IFs — for their status as risks, but not as benefits — it is necessary to consider how both IFs and benefits are defined and how the norm-governed concept of “benefit” functions at different stages in research regulation and human subjects protection. The argument here proposes that three distinguishable types of research IFs exist and suggests that during the process of informed consent, these should be treated somewhat differently by research investigators, regulators, and participants. To begin, we turn to an examination of how IFs have been conceptualized and why they have historically been treated as risks of both research and clinical intervention.

## **Incidental Findings as Risks**

Traditionally, IFs in research have been defined in terms of their unexpected or unanticipated nature.<sup>1</sup> Similarly, in the clinical context, the unsought information that was generated in the course of seeking the information one desired was termed an “incidental finding.”<sup>2</sup> The empirical and conceptual shortcomings of such definitions have become evident. Some research and clinical activities are so prone to generating findings not intentionally sought that it is disingenuous to term them “unanticipated” even if their precise nature cannot be anticipated in advance. More-

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over, many specific IFs are common and recurrent. Discovery of misattributed parentage during clinical genetic testing, discovery by mass tandem spectrometry of abnormalities not on a state's approved newborn screening panel, and detection of possible lesions or foreign objects during imaging studies are examples of IFs frequently generated. Based on experience, ophthalmologists now recognize that occasional findings of risk for systemic disease should be anticipated as the result of routine clinical examinations, but their patients generally do not realize that visiting the eye doctor with symptoms of eye irritation could result in learning of their possible increased risk for neurofibromatosis-1 or ankylosing spondylitis. "Incidental" is not a term that people would typically use to describe learning of misattributed parentage, risk of systemic disease, or other life-changing information.

The issue is not merely terminological. Attempting to characterize or define incidental findings raises the question of whose perspective, expectations, and interests should dictate their definition and inform policies governing their management. From the perspective of investigators, the occurrence of IFs may be (indeed, should be) anticipated, but they are largely incidental or irrelevant to study aims. From the perspective of research subjects, the generation of an IF may be a startling occurrence that is far from an incidental or insignificant blip in their understanding of themselves and their health.

Professionals involved in clinical care and their patients typically differ in terms of their recognition of the possibility and implications of generating information not specifically sought at the outset of a clinical consultation or testing, but they share a set of interests that guide their interaction — namely, the patient's health-related well-being. In research, this interest in the patient's well-being is not the animating principle guiding all parties' decision making. While all investigators must safeguard participants' welfare by minimizing risks, and clinician-investigators may also have a therapeutic obligation to their subjects as patients,<sup>3</sup> the goal of research with human subjects is not the promotion of subjects' welfare, but the increase of knowledge and future social benefit.

In the clinical context, patient and clinician can negotiate regarding the generation and possible disclosure of IFs in light of the shared goal of advancing the patient's health-related welfare. In recent decades, understanding of this notion of welfare has expanded to recognize that even when direct health benefit (e.g., cure or palliation) cannot be provided, health-related information can permit the patient to pursue other important goals and values (e.g., reproductive or end-of-life planning). In clinical care, not only the shared

and primary goal of advancing the patient's welfare, but also the existence of a professional-patient relationship enables the management of clinical IFs in a way that is conducive to the individual patient's well-being.<sup>4</sup> In the research context, typically no such relationship exists. This fact — coupled with there being no necessary connection between research subjects' interests and both the primary goal of research and the specific aims of a study — makes it critical to determine whose perspective and interests should inform the definition of incidental findings and development of policies to manage them in research.

Thus, in this symposium, Wolf et al. propose reconceptualizing research IFs as findings outside the study's aims. They define an IF as "a finding concerning an individual research participant that has potential health or reproductive significance and is discovered in the course of conducting research but is beyond the aims of the study."<sup>5</sup> Such a definition avoids the incoherence of defining IFs as unanticipated findings, and therefore allows one to urge investigators to develop plans to manage what is otherwise, by definition, unexpected and unanticipated. A preventive ethics approach advocates recognizing recurrent problems and taking steps to prevent their future occurrence or to limit their negative effects. In clinical care, for example, genetic counselors and clinics have established policies regarding the management of misattributed parentage and other IFs. Prior to testing, as part of the informed consent process, they typically disclose the possibility of discovering such an IF and state — or negotiate — whether and to whom such findings will be disclosed, as well as whether and where they will be recorded. Wolf et al. advocate a similar anticipatory approach to managing IFs in research.

For the purpose of determining how IFs should be treated in such preventive ethics plans, as well as for evaluating research protocols, it is instructive to consider why IFs have typically been treated as risks, with their potential to afford benefit seemingly ignored. In genetics, where much explicit attention has been paid to the anticipation and management of IFs, findings of misattributed parentage have a lot to do with casting IFs in a negative light.<sup>6</sup> The possibility of discovering misattributed parentage presented multiple concerns in early, prominent cases of genetic counseling and testing, including predictive testing for familial conditions such as Huntington disease and reproductive counseling about the risk of autosomal recessive conditions in subsequent pregnancies following the birth of an affected child. Disrupting individuals' self-understanding, as well as family dynamics and stability, risking domestic violence, and straining families already stressed by children with special needs or by

debilitating illness were considered negative sequelae of revealing misattributed parentage. The goal of much of the literature on this topic was to urge counselors and those developing policy for genetic testing not only to consider the implications of sought test results, but also to anticipate concomitant findings that might be of primarily social and psychological significance. One can hypothesize that, perhaps in light of the medical maxim to “first, do no harm,” emphasis was placed on maintaining the client’s social and psychological status quo, providing counseling when the results of testing were psychologically or socially disruptive, and warning about the potentially disruptive effect of unwanted information. It was — and still is — rare to consider discovery of misattributed parentage to be a potentially good thing. Ross is one of the few commentators to describe how learning of misattributed paternity can be beneficial and to argue that it is inappropriately paternalistic and contrary to genetic counseling’s nondirective ethos to refrain from disclosing such a finding to social, but nongenetic fathers.<sup>7</sup>

study aims,<sup>9</sup> the relatively low rate at which IFs have turned out to have clinical significance, coupled with the expense and anxiety of clinical testing to determine such significance, may similarly encourage a view of such findings as generally presenting greater risk than potential benefit.

Outside of professional and bioethical discourse, in everyday anecdotal experience, learning health-related information that one had not specifically sought is perhaps not as uniformly regarded as unwelcome. For example, a patient visits a doctor about lower back pain and is unexpectedly informed of a suspicious spot on his back, and is subsequently evaluated, diagnosed, and treated for early-stage melanoma. The patient might say, “The car that rear-ended me saved my life. My back hurt, I went to the doctor, and she saw this spot I had never noticed.” From the same initial facts, however, the story could end differently: “...she saw this spot I had never noticed, so I worried about it, finally took a day off work. The first clinic couldn’t do the biopsy so I had to take another day off work and go to a different clinic.... It turned out to be nothing.

**As counterintuitive as it may seem, from the fact that a study may benefit some participants, it does not follow that the study ought to be considered to afford potential benefits. While the nature, magnitude, and probability of benefit are relevant to determining whether a study should be regarded as affording potential benefit, these empirical factors alone do not warrant describing a study as (potentially) beneficial.**

In many discussions of IFs, misattributed parentage functions as the paradigmatic or “poster-child” case. Faced with such a finding, many people can imagine the pain of disrupted beliefs and relationships. Moreover, bioethical analyses since the inception of the Human Genome Project have stressed that people have not only a right to know, but also a *right not to know* information about themselves.<sup>8</sup> It is reasonable to hypothesize that this stance, coupled with the generally negative aura surrounding the “classic” IF of misattributed parentage, has fed the assumption that unexpected or unsought information should be treated as presumptively disruptive and undesired, and that the generation or acquisition of such information should be treated as a risk of clinical and research encounters.

In the neuroimaging literature, which is the second domain in which sustained attention has been paid to the management of suspicious findings not related to

Soon as he could, the boss fired me. I think it was because of my missed work.” Like the generation of any piece of information, in particular cases discovery of an IF can be a benefit or harm. The positive or negative outcome depends partly on one’s circumstances (e.g., whether one has insurance to cover follow-up evaluation or must shoulder crippling costs and even job loss, whether discovery of the IF saves one’s life or leads only to expensive and burdensome tests yielding no useful medical information) and one’s values (e.g., whether a diagnosis of untreatable cancer prompts a clarification of one’s priorities, provides the opportunity for salvific suffering, or lowers a black cloud of depression over one’s final months).<sup>10</sup>

The probability and magnitude of an IF’s potential benefit also depends on factors associated with the finding itself. How good is the information? How reliable is it? Do we know enough to make sense of the finding, to understand what it means for the indi-

vidual? How can it be used either to prevent or mitigate harm, or to make one better off? Do we have other relevant information — for example, about the causal mechanisms of disease or about preventive or curative interventions — so that the finding has clinical utility? Or will the information be useful primarily for planning one's life in light of the discovered risks? Progress in understanding the genetic contribution to the manifestation of disease, for example, increases the likelihood that genetic IFs may afford a benefit. Yet the pace of progress toward clinical utility is usually gradual and irregular, and often slow. The promise of being able to replace so-called “bad” genes with “good” ones is still an unfulfilled promise of the rhetoric justifying the mapping and sequencing enterprise. In many cases, characterization of relevant mutations has not yet led to treatment, cure, or prevention.

Nevertheless, one must guard against assessing benefit solely in medical terms. Health risk information has enabled people to engage in reproductive and other life planning and has afforded many individuals psychological benefit, even when nothing could be done medically. This means, however, that some people will regard the generation of the health risk information to be a clear benefit, and some will not. If every health risk were associated with an accessible, effective, and not-too-burdensome preventive intervention, and every diagnosis had a reasonable chance of cure by accessible and not-too-onerous means, then discovery of deleterious health conditions and risks would be obvious goods, even if some individuals failed to regard them as such.<sup>11</sup> When we remain far from this ideal, reasonable people can disagree about whether the prospect of learning health-related information not specifically sought is a potential benefit or a risk.

The question then is how such IFs should be treated as a matter of policy, specifically in the research context in the absence of an individualized, clinical professional-patient relationship through which the patient's values and circumstance may become known. Although IFs have traditionally been regarded as a risk of research, should they also be considered as a potential benefit?

### The Concept of Benefit in Research

The Common Rule states that risks to subjects must be proportionate to “anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result,”<sup>12</sup> and that reasonably expectable benefits should be described as part of informed consent.<sup>13</sup> Although a great deal has been written about research risks, relatively little attention

has been paid to explicating the normative, nonempirical nature of the concept of benefit.<sup>14</sup>

To say that the concept of benefit plays a normative role and has a nonempirical component is to recognize that simply because someone may benefit from a study does not by itself mean that the study should be said to present potential benefits. As counterintuitive as it may seem, from the fact that a study may benefit some participants, it does not follow that the study ought to be considered to afford potential benefits. While the nature, magnitude, and probability of benefit are relevant to determining whether a study should be regarded as affording potential benefit, these empirical factors alone do not warrant describing a study as (potentially) beneficial. The statement that a study presents potential benefit is a claim about the kind of study it is, about the normative criteria that it meets.

In parallel fashion, to say that a favorable or welfare-enhancing outcome is a “benefit of research” is not merely to make an empirical claim about a person having been made better-off. Instead, to be a (potential) benefit of research, an outcome must not only stand in a particular causal relationship to the welfare of an individual (or group of individuals), but also stand in a particular norm-governed relationship to the aims of the study. Under the current ethical and regulatory framework, there are three points at which the concept of benefit plays a normative role in the regulation, design, and evaluation of research: (1) assessment of the social or scientific value of the research question; (2) assessment of the acceptability of the risk/benefit ratio presented by the research design; and (3) anticipation and disclosure during informed consent of the risks and potential benefits of the study. Therefore, to determine whether IFs should be considered as benefits of research, it is necessary to consider them in relation to each of these assessments.

### Do IFs Satisfy the Normative Criteria Defining Research Benefit?

#### *Stage One: Assessment of Social Value and Aspirational Benefit*

Evaluating the research question is the initial point at which the notion of benefit plays a normative role in the design and evaluation of research. Does the research seek to answer a socially valuable question? If successful, will the research provide a social benefit? If this potential practical benefit is not immediate, does the research instead seek important scientific understanding? The possibility of mere benefit — of some people being rendered better off in the future because of the study's findings — is necessary, but not sufficient for the study to be considered to offer the

prospect of benefit. Given not only the reality of limited resources to expend on research, but also the burdens and risks that research imposes on participants, in order to be considered to have social or scientific value, research must be potentially beneficial socially or scientifically.<sup>15</sup>

Evaluation of the social and scientific value of the research is closely followed by consideration of the scientific validity of the methods by which the research is pursued. Determining the importance of the research question and the validity of the proposed methods are two distinct points of evaluation that together assess whether a proposed project may afford “aspirational benefits,” benefits to society, or to people relevantly similar to those enrolled in the research (e.g., future patients). Because a trivial question could be pursued by rigorous methods, or an important question could be studied by either invalid methods or methods likely

had relatively less scientific merit and social value, but great potential to benefit participants, to “trump” another study that had the potential to substantially advance understanding of an important issue, but that held almost no prospect for benefiting individual participants (e.g., phase I clinical drug trials). As such, a study that was likely to afford some benefit to participants — including payment for their participation — could increase its “social value” simply by enrolling a larger number of subjects.

The third reason, which grounds the other two, is that in order to consider the discovery of IFs an aspirational benefit of research, we would have to substantially alter our understanding of research’s social function. We would have to embrace the idea that the social value of research resides not only in its creation of knowledge that can then be employed in the future to benefit individuals and populations,

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to yield ungeneralizable results, in order to be considered reasonably likely to yield benefits to society, a study must attempt to answer a valuable question by valid methods. Here a final normative judgment enters the assessment of aspirational benefit. The prospect of benefit must be reasonable; mere theoretical possibility of benefit is not sufficient. Thus, research whose results cannot be practically implemented lacks social value.

IFs cannot be considered aspirational benefits of research for three reasons. First, they are not consequences — harm or benefit — that accrue to society or future patients as a result of the research. An IF is a finding about an individual participant, which may or may not be of benefit to her; it is not a generalizable finding. Second, an IF is a finding “beyond the aims of the study,” while social value and aspirational benefit are to be assessed solely in terms of the study aims. Because one of the reasons to evaluate these aspects of a proposed study is to enable a comparison of its value to that of other possible studies, it is important not to consider the benefits that might accrue to the participants when assessing social value and aspirational benefit. Doing so would allow a study that

but also, like health care, in the provision of benefit to individuals who enroll in research.<sup>16</sup> While it is true that some people enroll in research to obtain health care because they lack either health insurance or adequate resources, this is a situation to be regretted and redressed, not a condition to be accepted and regularized by allowing the goal of clinical care to co-opt the research enterprise. Instead, under the current conception of research, the participation of individual human subjects is and should be a means of achieving a research goal.<sup>17</sup> Individual subjects are not thereby treated *solely* as means to social ends, in violation of the Kantian injunction, but neither is their benefit an end or goal of research *qua* research. Requirements of both informed consent and the respectful and ethical conduct of investigators reflect the fact that subjects have not merely instrumental value, but intrinsic worth as persons. In this regard, research resembles other contexts in which people voluntarily engage in activities whose primary benefit accrues to others (e.g., donating goods, services, or body parts, or teaching students). Constraints on such activities, as well as compensatory factors (including feelings of satisfac-

faction and altruism), prevent participants from being treated solely as means to others' ends.

*Stage Two: Assessment of the Risk/Benefit Ratio*

Concern for the welfare of participants (rather than the integrity of research) is the primary reason to avoid considering IFs as potential benefits at the second stage of assessing benefit. Here, those designing or evaluating a study must establish that it presents an acceptable risk/benefit ratio. The design must minimize risks to subjects and enhance potential benefits to them so that "the benefits to individual subjects and society are proportionate to or outweigh the risks."<sup>18</sup> Why should the prospect of generating IFs that may benefit individual subjects not be considered in this assessment? Emanuel et al. argue:

The specification and enhancement of potential benefits to individual subjects should consider only health-related potential benefits derived from the research.... [C]onsistent with the scientific objectives, tests and interventions should be arranged to increase benefit to subjects. However, extraneous benefits, such as payment, or adjunctive medical services, such as the possibility of receiving a hepatitis vaccine not related to the research, cannot be considered in delineating the benefits compared with the risks, otherwise simply increasing payment or adding more unrelated services could make the benefits outweigh even the riskiest research.<sup>19</sup>

Emanuel et al. employ the distinction between direct and indirect benefit, a distinction traditionally drawn in clinical research in terms of the benefit's relationship to the investigational intervention.<sup>20</sup> Direct benefits to the subject are those "arising from receiving the intervention being studied," while an indirect, collateral, or extraneous benefit is "benefit arising from being a subject, even if one does not receive the experimental intervention."<sup>21</sup> Examples include not only personal satisfaction derived from altruism, but also the medical testing and care that may be part of the research protocol. For regulatory purposes, financial payment to subjects, "though technically a collateral benefit," is treated separately under the regulations.<sup>22</sup>

Given this conceptualization of the direct/indirect distinction, two questions follow: why can only *direct* benefits be weighed in balancing risks and potential benefits, and why can IFs be only *indirect* benefits? It might seem that at least some IFs are candidates for being direct benefits because they arise from receiving

the study intervention. Consider, for example, a genetic study of aortic aneurysm that involves drawing blood. Because of pleiotropy, it may be impossible to study genetic risk for aortic aneurysm without generating risk information related to Alzheimer disease (AD).

Risk information for AD arises from the blood draw intervention, but is no more a benefit derived in the relevant sense from receiving the research intervention than if such testing could only be done in an air conditioned environment and research participation thus helped participants avoid heat stroke on hot days. Neither preventing heat stroke nor providing information about Alzheimer disease risk is encompassed by the study's aims, although both are presumptive benefits within the causal pathway flowing from the study intervention. The distinction between direct and indirect benefit has normative force rather than merely descriptive content. In order to identify the direct benefits of research, it is necessary to examine not only causal relations, but also the intent or aim of the study.

The normative goal of assessing the risk/benefit ratio — to protect the welfare of subjects — demands that potential benefits not be multiplied and then taken into account to determine the balance of risk and potential benefit that a study presents. Therefore, as Emanuel et al. state, only benefits derived from the research may be weighed; otherwise, collateral benefits (including financial compensation and health-related perks of participation) could be "piled on" to counterbalance increasing levels of risk.

Generation of an IF — e.g., the AD genetic risk information — may flow *causally* from the research intervention or interaction with subjects, but it is by definition extraneous to the study's aims and overall goal, just like the receipt of the hepatitis vaccine that Emanuel et al. mention. Indeed, IFs are as likely to be generated for subjects serving as "normal controls" as for those who have the condition under study or who are receiving a research intervention. Even if they are generated as a direct causal result of the research intervention (e.g., the neuroimaging or microarray analysis), if they are properly considered benefits at all, IFs must be indirect benefits. It would undermine the protective function of the assessment of a study's risk/benefit ratio if the prospect of indirect benefit were permitted to counterbalance study risks.

Thus, there is an appropriate asymmetry in current regulatory practice: the possibility of generating IFs may be considered as a risk of research, but may not be counted as a potential counterbalancing benefit. Initially this asymmetry may seem puzzling, given

that reasonable people may differ on whether receiving particular health or reproductive risk information presents a harm or a benefit to them. However, the asymmetry is warranted by the protective stance of research regulations that requires taking into account the probability and magnitude of all reasonably foreseeable risks as well as by the social role and norms of research that make IFs unfit to be considered as potential counterbalancing benefits.

### *Stage Three: Informed Consent and IFs*

Informed consent — the third point at which the notion of benefit plays a prominent role in human subjects protections — is the stage at which both the possibility of IFs and the frequently subjective nature

enumerated during informed consent, is that prospective research subjects may fill the vacuum with imagined benefits fueled by personal hopes or by a general attitude that considers research to be “cutting-edge,” innovative, and “likely the best.”<sup>23</sup> This risk of feeding both the therapeutic misconception and overly optimistic views of research is a problem with consent forms and conversations that fail either to be explicit about anticipated benefits, if indeed there are any, or to stress the lack of such anticipated benefits.<sup>24</sup>

Whether being more explicit about the potential benefits of identifying IFs would fuel or dispel the therapeutic misconception is an empirical question. Where it is difficult to specify their precise nature or probability, it seems that prospective subjects would

be ill-advised to participate in a study with the expectation that useful information, beyond the aims of the study, will be generated about them. In such cases, care should be taken during informed consent not to raise expectations or oversell the possibility that incidental information may be generated that will benefit participants personally. In contrast, some IFs may be readily characterized, with their likelihood fairly predictable based on past experience. In this case, subjects might reasonably view the possibility of such IFs being discovered and disclosed to them to be an indirect benefit of participation. They might

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of their value to participants should be taken into account. Even those findings with clinical utility may be viewed as welcome or unwelcome, depending on the participant’s circumstances and values and on the specific nature of the IF. The possibility that IFs will be generated should be considered by investigators, and their probability of occurrence and general nature described to prospective participants, along with plans for recording and disclosing (or not disclosing) specific IFs to individual participants. Whether IFs should be characterized as risks or potential benefits during informed consent conversations and on consent forms is debatable; instead, it may be advisable to avoid labeling them as either.

Despite the Common Rule’s demand that reasonably expectable benefits should be disclosed, the informed consent process, like the regulations and commentaries about it, focuses more on risks than on potential benefits. A downside of this comparative lack of attention to benefits, especially when risks are exactly

also quite reasonably view discovering such information to be undesirable and thus either a risk of participation, or a reason to refuse to enroll. In the context of informed consent, therefore, it may be best to disclose the possibility (or fact) that such IFs will be generated, and characterize them as accurately as possible, without labeling them as either risks or potential benefits of research.

Two additional points merit elaboration. First, plans to offer to disclose specific IFs partly determine whether their discovery actually harms or benefits participants.<sup>25</sup> If a specific IF is not revealed to anyone — neither to the participant, nor to any third party — then its discovery presents little risk.<sup>26</sup> An IF cannot benefit the participant if it is not disclosed.

Second, incidental findings, like research findings, are not homogeneous. They vary across myriad dimensions including their reliability, clinical utility, and degree of health impact or degree of importance for personal or reproductive planning. IFs differ in

their frequency and studies differ in their likelihood of generating IFs. Yet, the requirements of informed consent demand that investigators be able to characterize IFs in general terms at the outset of a study, prior to generating any specific IF at all. To facilitate this description of IFs, it may be useful to distinguish three types of incidental findings. The next section describes these types of IFs and argues that it is appropriate to treat each type somewhat differently with regard to disclosure.

### Three Types of IFs: Implications for Informed Consent and Disclosure Planning

Given the definition of an IF as “a finding concerning an individual research participant that has potential health or reproductive significance and is discovered in the course of conducting research but is beyond the aims of the study,” it is possible to distinguish three types of IFs.<sup>27</sup>

First, there are findings that will be routinely generated during the conduct of the study but that are not findings responsive to the study aims. Examples include findings related to the study’s inclusion or exclusion criteria. These constitute IFs because, although they are discovered in the course of the study, such information is not responsive to the study’s aims; the discovery of this information is not an aim of the study, but a collateral event. The possibility of these types of IFs should be disclosed to prospective participants. Whether the protocol should include plans to disclose (or offer to disclose) such an IF, however, depends on a variety of factors, including the nature of the IFs themselves. Although the details will affect these disclosure plans, it is possible to sketch a spectrum of IFs and their disclosure implications.

At one end might be a finding of an infection or high blood pressure that postpones an experimental surgical intervention, or results of a pregnancy test conducted to determine study eligibility. A protocol might reasonably include a plan to disclose such findings. These findings have clinical utility and, moreover, are generated by standard clinical tests. During informed consent, prospective subjects would need to consent to the possibility of learning such information.

At the other end of the spectrum might be discovery of symptoms of mild cognitive impairment (MCI), used as an exclusion criterion for a late-life mood disorder study. Evaluation and a finding of impairment that warrants study exclusion may not be equivalent to a clinical diagnosis of MCI. Moreover, the clinical utility of a MCI diagnosis has not been established. Indeed, its diagnostic criteria are not consistently utilized, and relevant clinical communities cannot agree on the meaningfulness of a finding of MCI.<sup>28</sup> Some

people would be very disturbed to learn that they have cognitive deficits, however mild or early. In addition, learning such information could impair their ability to purchase long-term care insurance or health insurance. Even if some prospective subjects would welcome learning of their quasi-diagnosis of MCI for use in personal planning, it may be reasonable for a research protocol to plan *not* to inform subjects of a specific finding of MCI, but instead to simply advise such subjects that they are not eligible for the study.

Although plans to disclose this class of IFs may differ by protocol, the fact that such findings will be routinely generated (e.g., pregnant/not-pregnant, blood pressure normal or not) should be disclosed during informed consent. Moreover, although regulations guiding informed consent and consent forms tend to divide possible outcomes and findings into either risks or potential benefits of participation, it would seem preferable to present the prospect of such findings being generated in a more neutral way. For example, a prospective subject can decide, in light of her circumstances and values, whether the prospect of learning she is pregnant or has high blood pressure constitutes a potential benefit, a risk, or a reason to refuse to enroll.

A second class of IFs is comprised of those that can reasonably be expected to arise because of the nature of the research being pursued, although unlike findings generated as part of the eligibility evaluation or adjunctive medical care, their generation is not an explicit part of the research protocol. Instead, they may be findings that frequently — or, as it may turn out, even necessarily — accompany the specifically sought research findings. This may be because the research modality frequently generates them (e.g., suspicious findings in neuroimaging or CT colonography studies outside the study’s aims, or misattributed parentage in genetic studies) because of pleiotropy (as with Alzheimer disease risk and cardiovascular risk), or because a particular research finding is associated with a health condition not under study (e.g., when a finding of male infertility suggests previously undiagnosed cystic fibrosis). Although such findings will not be generated in the case of each participating subject, their nature can be characterized and their frequency estimated. The nature and probability of generating these types of findings should be disclosed to prospective subjects during informed consent, along with plans for their management, including plans for disclosure or nondisclosure, recording, and privacy protection. When reasonable people can be said to disagree about whether learning such information would constitute a benefit or a harm, it would be preferable not to describe the possible generation (and disclosure) of

such IFs as either risks or potential benefits of participation. Instead, describing them more neutrally, as *possible consequences* of participation, would be more accurate. When the precise nature of the possible finding can be characterized and plans are made to offer to disclose it, for example misattributed parentage or an established instance of pleiotropy, it may be advisable to use language such as the following: “Many people find learning of [the IF] disruptive or disturbing, but others find it useful to know. You should think about what learning such information would mean to you, and also remember there is a [characterize the likelihood] chance of learning such information.”

Of course, even when information will not be disclosed to subjects, its management is still material to them. This is true in part because of the risk that third parties will learn the information. Moreover, even if the discovery of IFs presents little risk — for example, because they will be recorded anonymously — subjects still have interests regarding the management of such information. They might, for example, object to the collection of this information, and thus might choose not to participate in the study. Personal risk is not the only reason to refuse study participation. Just as people may refuse to participate because they do not endorse a study’s aims — in effect, they do not wish to contribute to the discovery of particular sorts of information — the same concern might apply to information beyond the study’s aims whose discovery is nevertheless anticipated in the course of the study (e.g., because of pleiotropy). For these reasons, whether information about IFs will be collected, and whether and how it will be recorded (e.g., with or without identifiers), is relevant. These plans should be delineated during informed consent.

Finally, a study may generate IFs of an as yet unpredictable nature and frequency that can be characterized only in general terms as part of the informed consent disclosure. This third class of IFs will be the most difficult to explain during informed consent and may be impossible for subjects to evaluate as likely to either harm or benefit them. An example would be possible, but as yet uncharacterized pleiotropy: without specific details about what condition will be revealed, individuals would be unable to evaluate the personal relevance of such a finding. Nevertheless, the possibility of generating such IFs should be disclosed, along with

a statement of the circumstances, if any, under which such findings would be offered to participants.

Elaboration of the criteria that should guide such offers of disclosure is beyond the scope of this discussion; however, a conservative approach seems warranted. The likelihood of any particular participant benefiting from the generation of an IF whose nature and probability cannot be characterized at the outset is quite remote, especially if criteria for disclosing IFs are stringent (i.e., at minimum requiring that the finding have clinical utility, and perhaps requiring that learning the information through study participation be the only reasonable path to its acquisition). Thus, especially for this type of IF, the possibility of their

**When reasonable people can be said to disagree about whether learning such information would constitute a benefit or a harm, it would be preferable not to describe the possible generation (and disclosure) of such IFs as either risks or potential benefits of participation. Instead, describing them more neutrally, as *possible consequences* of participation, would be more accurate.**

generation and disclosure should not be characterized as a potential benefit of participation. If there is the possibility that such findings would be disclosed to participants, however, then that should be stated as a possible consequence and perhaps even characterized as a risk of participation. The role of informed consent in the protection of human subjects — i.e., to afford subjects the information necessary to avoid risk of harm — justifies this asymmetrical treatment of these IFs as risks, but not as potential benefits of research.

### Conclusion

This paper has argued that there are good reasons to adopt a definition of incidental findings that focuses on the aims of the study. IFs should not be considered potential benefits of research when assessing the social or scientific value and scientific validity of proposed research, or determining the appropriateness of the risk/benefit ratio presented by a research study design. IFs do not meet the normative criteria defining either aspirational or direct benefit. With

regard to informed consent, the third stage at which questions of benefit arise in the design and regulation of research, IFs should at most be considered *indirect* potential benefits. Care must be taken in the informed consent process to avoid overselling the potential for any given participant to benefit from the discovery of information beyond the aims of the study.

During informed consent discussions (and in consent forms), prospective participants should be informed of the possibility that IFs will be generated and insofar as possible, their probability and nature should be described. Thus, investigators may find it helpful to distinguish among three different types of IFs, namely: (1) those that will be routinely generated during the conduct of the study but that are not findings responsive to the aims of the study (e.g., results of testing to determine eligibility to enroll); (2) those that can reasonably be expected to arise and that can be characterized in terms of their nature and frequency of generation (e.g., findings of misattributed parentage in genetic studies); and (3) those of an as yet unpredictable nature and frequency that can be characterized only in general terms. Prospective participants should also be informed of plans to manage IFs actually generated during the study, including whether and how IFs will be recorded, measures to prevent breach of participant confidentiality, and to whom and according to what criteria IFs will be disclosed or offered.

Whether IFs should be disclosed to research participants when they are generated is an issue not fully addressed in this paper, but one that is material to the question of whether IFs are a risk or potential indirect benefit of research participation. IFs that are not disclosed to the participant, and that are safeguarded from third parties, present little risk of making a subject worse-off, but also cannot afford individual benefit. It is likely that each of the three classes of IFs might be treated differently with regard to disclosure, although two IFs of the same type might also be treated differently based upon each finding's clinical utility. Moreover, because reasonable people can differ regarding whether learning of a particular IF would be a harm or a benefit, it may be preferable to describe most IFs more neutrally, as a possible consequence of participation whose functional status as a risk or benefit must be determined by each individual participant. Thus, even in the context of informed consent, incidental findings should not be regarded categorically as potential benefits of research participation.

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4. Of course, sometimes IFs are managed according to a one-size-must-suit-all policy established at the institutional or clinic level. Nevertheless, such policies — like all clinical practice guidelines — should be developed with the welfare of the typical patient or majority of patients in mind.
5. S. M. Wolf et al., "Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations," *Journal of Law, Medicine & Ethics* 36, no. 2 (2008): 219-248. In 1993, the Office of Protection from Research Risks (OPRR) came close to this definition in its *IRB Guidebook* section on human genetic research, which described IFs as "genetic information that is learned during the course of the study that does not directly relate to the research." U.S. Department of Health and Human Services, Office of Protection from Research Risks, *Protecting Human Research Subjects: IRB Guidebook* (Washington, D.C.: U.S. Government Printing Office, 1993): at 5-54.
6. A. L. Lucassen and M. Parker, "Revealing False Paternity: Some Ethical Considerations," *The Lancet* 357, no. 9261 (2001): 1033-1035; see Davis, *supra* note 2.
7. L. F. Ross, "Disclosing Misattributed Paternity," *Bioethics* 10, no. 2 (1996): 114-130. Ross's argument would apply equally well to any finding of misattributed parentage or ancestry, although she focuses her argument on the most commonly discussed finding of paternity. Davis describes the range of harms and benefits associated with learning one's ancestry is different from what one had previously believed. See Davis, *supra* note 2. Note that Ross makes her argument in support of disclosing misattributed paternity with regard to the context of clinical care, not research, where she generally finds a higher degree of paternalism appropriate. See Ross, *supra*. Although there are points of similarity between them, clinical care and research contexts are importantly different. See, for example, S. M. Wolf et al., "The Incidentalome," *JAMA* 296, no. 23 (2006): 2800-2801.
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10. Indeed, it is because of the personal nature of the value of information, its subjective value, that Ross argues it is epistemically incoherent and inappropriately paternalistic not to disclose a finding like misattributed paternity in the *clinical* context.
11. In most cases, interventions that preserve or restore health are objectively ascribable goods because they are good for an individual no matter what her particular conception of the

- good is. On the other hand, when such interventions involve costs and thus trade-offs with other goods, it is reasonable for individuals to reject such interventions in favor of goods they value more.
12. 45 C.F.R. § 46.111(a) (2) (2007).
  13. 45 C.F.R. § 46.116(a) (3) (2007).
  14. An exception is N. M. P. King, "Defining and Describing Benefit Appropriately in Clinical Trials," *Journal of Law, Medicine & Ethics* 28, no. 4 (2000): 332-343.
  15. E. J. Emanuel et al., "What Makes Clinical Research Ethical?" *JAMA* 283, no. 20 (2000): 2701-2710.
  16. Public health interventions are obviously an exception to this individual focus of health care. Nevertheless, the contrast between research and (public) health care stands. The difference between public health research and public health practice is more obviously temporal: current populations are the subject of research so that future populations may benefit.
  17. See Emanuel et al., *supra* note 15.
  18. *Id.*, at 2705.
  19. *Id.*
  20. Distinguishing between direct and indirect benefit in terms of its causal relationship to the research intervention — whether it "arises from" or "is derived from" the intervention — may suit research in which an intervention's efficacy is being tested. However, identifying the relevant causal relation (between research intervention and positive effect) or distinguishing causation from mere association is challenging and perhaps impossible for many studies, especially those whose goal is to characterize a condition, track physiological changes, or examine quality of care or adequacy of health services. Even in clinical research it would be preferable to focus on the study aims, not solely on causal pathways, in determining whether a study presents a reasonable prospect of (direct) benefit.
  21. See King, *supra* note 14, at 333.
  22. *Id.*
  23. J. Durant et al., "Public Understanding of the New Genetics," in T. Marteau and M. Richards, eds., *The Troubled Helix: Social and Psychological Implications of the New Human Genetics* (Cambridge, U.K.: Cambridge University Press, 1996): at 235-248.
  24. See King, *supra* note 14; P. S. Appelbaum et al., "False Hopes and Best Data: Consent to Research and the Therapeutic Misconception," *Hastings Center Report* 17, no. 2 (1987): 20-24.
  25. The definition of harm utilized here is one of being made worse off; the failure to afford a benefit — that is, failure to take an opportunity to make someone better off — is not a harm in this view.
  26. The risk would be that of (1) the confidentiality of the recorded IF being breached; (2) the information being identifiable as pertaining to a particular subject; and (3) it being used to that person's detriment.
  27. See Wolf et al., *supra* note 5.
  28. S. Gauthier and J. Touchon, "Mild Cognitive Impairment Is Not a Clinical Entity and Should Not Be Treated," *Archives of Neurology* 62, no. 7 (2005): 1164-1166; S. Gauthier et al., "Mild Cognitive Impairment," *The Lancet* 367, no. 9518 (2006): 1262-1270; P. Whitehouse and H. Brodaty, "Mild Cognitive Impairment," *The Lancet* 367, no. 9527 (2006): 1979.