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Do Researchers Have an Obligation to Actively Look for Genetic Incidental Findings?

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Abstract

The rapid growth of next-generation genetic sequencing has prompted debate about the responsibilities of researchers toward genetic incidental findings. Assuming there is a duty to disclose significant incidental findings, might there be an obligation for researchers to actively look for these findings? We present an ethical framework for analyzing whether there is a positive duty to look for genetic incidental findings. Using the ancillary care framework as a guide, we identify three main criteria that must be present to give rise to an obligation to look: high benefit to participants, lack of alternative access for participants, and reasonable burden on researchers. Our analysis indicates that there is no obligation to look for incidental findings today, but during the ongoing translation of genomic analysis from research to clinical care, this obligation may arise.

Keywords

genetics (clinical); genetic research; human subjects research; research ethics

Genomic science is in the midst of a revolution. For the past few decades, relatively inefficient and expensive genetic sequencing technologies have limited researchers to targeted genetic research, focused on only the most promising genes or genomic regions. Over the past few years, however, new next-generation sequencing techniques have broken through this data production bottleneck. With these technologies rapidly advancing, and a \$1,000 genome now imaginable, researchers have begun to enthusiastically sequence their participants' whole exomes and genomes (Green and Guyer 2011; Tabor et al. 2011). This shift to using whole-genome sequencing (WGS) in medical research, however, creates a new analytic bottleneck. WGS generates unprecedented amounts of raw genomic data, and with

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the entire genome in play, the research community has started to grapple with questions about how best to manage and interrogate this rich resource.¹ Central to the debate is an important question: What are researchers' ethical obligations vis-à-vis this vast amount of data?

Most notably, researchers, institutional review boards (IRBs), and ethicists have been engaged in an active debate about the issue of incidental (or secondary) findings. In the course of sequencing and analyzing a participant's genomic data to answer a specific set of scientific questions, researchers will likely come across individual genetic findings that are unrelated to the aims of their research but that have clinical, reproductive, or personal significance for their participants (Wolf et al. 2008). Recent debate about incidental findings has been largely concerned with whether or not researchers have an obligation to disclose these findings to participants, and if so, which kinds of findings (Berg et al. 2011; Bredenoord et al. 2011; Wolf et al. 2008). Some believe analytically valid, clinically significant, and actionable information ought to be offered to participants (Fabsitz et al. 2010; Ravitsky and Wilfond 2006; Wolf et al. 2008; Wolf et al. 2012). In contrast, others see an obligation to disclose incidental findings as inappropriately emphasizing benefit to individual participants over the production of generalizable knowledge, and worry about the risks associated with conflating research and clinical care, and about the potential misallocation of limited scientific resources (Clayton 2008; F. A. Miller et al. 2008).

There has been disagreement in the literature about the relative merits of these different positions, but with the development of guidance documents outlining criteria and procedures for disclosure, opinion seems to be moving toward the idea that there is some obligation to offer to disclose a limited set of findings, generally understood as findings that meet an exacting standard of validity, severity, and actionability (Bookman et al. 2006; Fabsitz et al. 2010; Wolf et al. 2008). Even among those who support the existence of an obligation to disclose, however, the contours of that obligation remain murky (Bredenoord et al. 2011). We recognize the nuance of this ongoing debate, but in this article we set this issue aside with the general assumption that there is an obligation to offer to disclose at least a limited set of incidental findings.²

We are instead interested in exploring what we believe is an even more challenging question: Assuming there is some obligation to *disclose* certain incidental findings that are inadvertently discovered in the course of research, is there ever a positive obligation to *search for* these findings? In other words, when researchers generate and interrogate sequence data, do they have any obligation to actively look within the data for potential variants associated with severe or life-threatening diseases? The standard view has been that "researchers generally have no obligation to act as clinicians and affirmatively search for IFs" (Wolf et al. 2008, 236), but this assumption seems to be relatively unexamined (Cho 2008; F. G. Miller et al. 2008; Van Ness 2008; Wolf et al. 2008). In this article, we aim to

¹For convenience we use "genome" and "genomic" throughout the article, although in many cases "exome" or "exomic" would also apply.

²There has also been considerable debate about the proper role of informed consent in the disclosure of genetic incidental findings. An obligation to look for and disclose incidental findings, as discussed here, rests on the assumption that participants have agreed to receive these findings.

provide a comprehensive analysis of whether there might ever be an obligation for researchers to look for genomic incidental findings. We begin by highlighting why this question is important to answer, move on to identifying the criteria that would be required for such an obligation to exist, and then assess the characteristics of both the current state of genomic research and its projected future to determine whether and when there may be an obligation to look.

REEXAMINING THE “STUMBLE STRATEGY”

Thinking about whether researchers have an obligation to look for incidental findings is important for several reasons. First, even early genomic research has demonstrated that disclosing certain identified variants can be highly beneficial to individual patients, and the discovery of these kinds of variants will continue to accelerate. Yet despite the growing number of variants that can be linked to serious disease, genomic analysis has been slow to enter clinical medicine (Green and Guyer 2011). At least at present and likely in the near future, WGS and genomic analysis will be primarily available through research, giving researchers unique access to benefits that only they can provide to their participants. Second, most of the existing literature about genomic incidental findings assumes that incidental findings will be relatively uncommon and that they will be rarely “stumbled upon” during the course of research. This assumption, however, is at odds with the realities of genomic research: If one looks carefully enough, any individual genome is likely to reveal important medical information (Tabor et al. 2011). Our goal in this article is to challenge the notion that a “stumble strategy” is universally acceptable, arguing that researchers who generate and analyze genomic sequences could also generate certain positive obligations for themselves vis-à-vis the data. It is conceivable that in specific circumstances researchers might have an obligation to actively examine their data for clinically significant findings beyond those required for their research.

This is not merely an academic question. A number of groups have recently discussed the possibility of building standard lists of variants that could or should be disclosed as incidental findings (Green et al. 2012; National Human Genome Research Institute 2012). For example, the American College of Medical Genetics and Genomics has undertaken to create a list of specific genetic variants that should be reported to research participants (Hayden 2012). These kinds of lists would presumably include variants proven to dramatically increase the risk of certain diseases, where early detection can save lives. But while the existence of a list (or lists) of variants that should be disclosed will help researchers to determine whether or not they can disclose an identified variant, it does not address the more fundamental question of whether researchers should seek to identify such variants within genomic data.

To answer this question, we begin by exploring the ancillary care literature, which describes the circumstances under which investigators should provide care for research participants that is not independently required for safe, scientifically sound trials (Richardson and Belsky 2004). Our goal in this first section is to explain how the ancillary care framework—which is often used to convincingly support an obligation to *disclose* incidental findings—also suggests reasons why researchers might have a positive obligation to *look for* incidental

findings. As we subsequently argue, if one holds the view that researchers have an obligation to *disclose* certain incidental findings, then it is plausible to believe that, under certain circumstances, there could be some obligation to *look* for these variants as well.

Using the ancillary care framework as a guide, we identify three criteria of genomic studies that must be present together to give rise to an obligation to look for incidental findings. First, the act of looking must provide *benefit* to the research participants: The genetic information sought must be strongly associated with severe disease, and there must be a medical action that has been proven to reduce or eliminate the disease risk. Second, the investigators must provide *unique access* to WGS and genomic analysis for research participants: The participants must lack reliable, simple, or financially feasible alternative access to this information outside of research. Finally, looking must *not unduly burden* the researchers: Any potential benefit from looking for incidental findings must be weighed against the time, effort, and resources such a task requires. Although any one of these characteristics may be present independently in genomic research, only when they all are concurrently satisfied might there be an obligation to look for incidental findings in the participants' genomes.³

The subsequent section of the article considers these three criteria—benefit, uniqueness of access, and reasonableness of burden—in the context of genomic research *today*, carefully reviewing the value of the information that can be learned, participants' access to genomic analysis via clinical care, and the difficulty of the analysis given existing technology. We then conclude by looking forward to the *projected course* of WGS in research and genomic medicine, and revisit these three criteria at select points in the future. Our analysis indicates that today there is generally no obligation to actively look for incidental findings. Similarly, in the far future, with genomic medicine well incorporated into clinical practice, there will also be no obligation to look. Between these two periods, however, it is possible—but not certain—that an obligation may arise.

CAN THE ANCILLARY CARE FRAMEWORK BE EXPANDED TO ENCOMPASS AN OBLIGATION TO LOOK?

As use of WGS expands, researchers will have access to a large amount of information that is potentially highly significant for their study participants. What is the extent of researchers' responsibilities with regard to interrogating (i.e., actively analyzing) these genomic data? In order to define the bounds of these obligations, it is helpful to start by looking at the ethical justifications that have been proposed to support the notion that researchers have any sort of obligation with respect to incidental findings (namely, the obligation to disclose certain findings). Many supporting principles have been suggested, from respect for persons to beneficence to reciprocity, but there has been no overwhelming

³If one accepts our argument that an obligation to look could exist, it remains open whether investigators could, through robust and transparent informed consent, waive such an obligation. While reasonable minds could disagree, we do not believe that simply informing subjects of an intention not to look is sufficient to defeat an investigator's *prima facie* obligation to look. As our analysis will make clear, however, we believe a determination that an obligation to look exists may be modulated by special characteristics of an individual study. For example, if researchers can convincingly make a case that this obligation would pose an undue burden on their specific research, then our analytic framework would suggest that it is inappropriate to impose an obligation to look in that case.

agreement on a single ethical underpinning that supports the obligation to disclose. Instead, most theories rely on a collage of principles and considerations (Bredenoord et al. 2011).

One frequently cited framework that we find particularly persuasive, however, is the ancillary care model, which has been proposed to justify an obligation to disclose. Ancillary care is defined by Richardson and Belsky as “care [for research participants] not required by sound science, safe trial conduct, morally optional promises, or redressing subject injury” (Richardson and Belsky 2004, 26). The framework, initially intended to describe researchers’ obligations in developing countries, has been recently used to more generally consider when researchers should provide medical treatment or information to their participants, even if these interventions are supplemental to the research (Belsky and Richardson 2004). If we believe, as many suggest, that the disclosure of stumbled-upon incidental findings can be characterized as a kind of ancillary care (Richardson 2008), it seems reasonable that this framework can possibly be extended to similarly support an obligation to seek out incidental findings that are unnecessary to answer the study’s specific questions yet likely to provide significant, beneficial information for study participants.

The fundamental conflict surrounding ancillary care in medical research is the balance between using limited resources for the advancement of science versus for the care of participants. The purpose of research is to create generalizable knowledge; therefore, researchers should try to maximize the societal benefit of their work. With limited resources, this often means prioritizing the research agenda over supplemental individualized care (while still taking fundamental precautions to protect participants and minimize harms). Yet medical researchers are often in a unique position to help their participants through application of an experimental therapy or simply the knowledge, abilities, and resources they hold as scientists and/or physicians (Richardson and Belsky 2004).⁴ In genomic research, looking for (and disclosing) significant incidental findings may reduce morbidity or mortality for individual participants, but the time and energy needed to do so could detract from the primary research effort. When researchers have the ability to help but are working with limited resources, what do they owe participants?

One extreme position on ancillary care obligations views medical researchers as pure scientists, devoted solely to research and without any duty to provide extraneous care. The opposite side views medical researchers as doctors first, devoted to the health of their patients above all else. Most, however, agree that neither of these positions is ethically tenable, and that medical researchers must strike a balance between their obligations to medicine and those to research (Richardson and Belsky 2004). International guidance on the subject is vague. Some documents prioritize the role of researcher as physician (World Medical Association 2008), but many critics agree this charge is unrealistically expansive (Participants in 2006 Georgetown University Workshop 2008). Other guidance documents do not include any provisions for ancillary care, or are vague in their recommendations. For example, the Council for International Organizations of Medical Sciences calls ancillary

⁴This tension is apparent in one of Richardson and Belsky’s examples, in which providing participants in a malaria study with treatment for schistosomiasis would enhance the health of the participants, but the resources required might mean the malaria study itself is impeded or delayed (Richardson and Belsky 2004).

care “morally praiseworthy” but does not recognize it as a general obligation of researchers (CIOMS and WHO 2002, commentary on Guideline 21). There is an identified need for clearer advice and regulation on this issue (Participants in 2006 Georgetown University Workshop 2008).

Several bioethicists have outlined intermediate positions that offer justification and direction for providing ancillary care while maintaining sound research ethics. Richardson and Belsky, in their foundational paper on the topic, set forth a “partial entrustment model” of the researcher-participant relationship (Richardson and Belsky 2004). Their view holds that research participants entrust certain discrete aspects of their health to researchers, who consequently have an obligation to respond to the participants’ needs in these areas. The scope of researchers’ obligations to their participants is derived from their special access to health-related information and ability to diagnose and/or treat certain conditions. Once a condition is determined to be within the scope of entrustment, the strength of the obligation to provide care is determined by a number of factors, including the relationship between researcher and participant and the vulnerability of the participants. Richardson and Belsky’s analysis identifies a unique professional role of someone doing medical research, one that is separate from that of a strict bench scientist or a primary-care physician but that incorporates aspects of both (Belsky and Richardson 2004; Richardson and Belsky 2004).⁵

In general, there is an emerging sense that there exists some obligation to provide ancillary care, although the type and amount of care and the strength of the obligation will necessarily depend on the nature and design of the research and the population being studied. Although many of these factors will vary widely from study to study, even within a specific field, it is clear that the literature recognizes strong justification for ancillary care obligations in the special knowledge and expertise of the medical researcher (Joffe and Miller 2008; Resnik 2009; Richardson and Belsky 2004). This includes the professional responsibilities of clinicians and scientists, whose access to information and “competence to interpret” it can create a moral responsibility to provide ancillary care (F. G. Miller et al. 2008, 277).⁶ Dickert and colleagues (2007) similarly hold that the scope of ancillary care obligations is influenced by the researchers’ ability to help.

In the genomic context, while it seems less controversial to say that there is an ancillary care obligation to disclose incidental findings that are stumbled upon, we argue further that there is at least a *prima facie* claim that ancillary care obligations could require researchers to actively seek out incidental findings. A genomic researcher has access to such unique resources as the participants’ DNA, sequencing technologies and the resulting data, advanced computer software and high-powered databases, knowledge of variants and pathologies, expertise to interpret genome sequences, and trained genetic counselors. This

⁵Other bioethicists have largely accepted Richardson and Belsky’s views, with a few minor adjustments. Joffe and Miller argue that the responsibilities of researchers flow only from the ethical obligations of science and research, not those of primary care (Joffe and Miller 2008; see also Litton and Miller 2005). Still, the practical implications of their arguments are aligned. Resnik (2009) holds that ancillary care obligations are variable depending on the context of the study, but in certain cases can be quite broad. Dickert and colleagues (2007) seek to expand even further the obligation to provide ancillary care, suggesting that when the researcher has the ability to help, when the participant is especially vulnerable, and/or when there is a strong level of engagement between the researcher and participant, this obligation may be strengthened.

⁶F. G. Miller and colleagues (2008), however, do not believe the ethical obligations of the investigator–subject relationship include any affirmative duty to seek out incidental findings.

unique ability to provide access to genetic information, however, is a necessary but not sufficient condition. Broadly speaking, there are three chief concerns when considering whether there is an obligation to provide any ancillary care in genomics research: first, whether the provided service or care will be useful (is it beneficial?); second, whether participants lack access to the service outside of research (is it uniquely available within the context of research?); and third, whether the service may be reasonably provided (will it cause no undue burden on the research team?). When the service, information, or care is beneficial, when it is uniquely available from the research team, and when it does not require too much of the research team, it should be provided. The rest of this section lays out a framework for considering when there is an obligation to look for genetic incidental findings by exploring these three factors.

First, the information sought by looking must be beneficial to individual participants: It must be of high quality (analytically and clinically valid) and must represent a high probability of benefit to participants. In other words, the kind of information that would be sought and provided must be clearly intended as “care” and not simply “information,” and finding and disclosing this information will serve some beneficial medical purpose beyond simply increasing knowledge or awareness about oneself. The level of medical benefit necessary to justify looking must be carefully bounded; in order to justify taking resources away from research to look for incidental findings, any sought-after finding must clear an extraordinarily high bar of usefulness, beyond that required in clinical practice or even in disclosing a stumbled-upon finding. There must be the best available scientific evidence that the genetic variant is linked to a severe disease, and there must be a specific medical action that can be taken that is demonstrated to be clinically effective at mitigating risk.

Second, the researchers must be in a unique position to assess the utility of this genetic information and provide it to their participants. For studies done in developed countries, it seems unnecessary for a researcher to provide ancillary over-the-counter drugs or access to basic medical tests because most participants can easily and inexpensively access these outside of research. Similarly, if quality genomic sequencing and analysis is part of routine medical care, or if it could be reliably and inexpensively obtained via a direct-to-consumer service, researchers would not have a particularly unique claim on the ability to do this sequencing and analysis, and therefore would not have a responsibility to provide it as ancillary care. In general, the highly specialized knowledge and resources held by the research team can drive or enhance an obligation to provide ancillary care to participants; obligations to provide this care are further strengthened when it is unlikely that this care can be accessed elsewhere.

Third, the act of analyzing the genome to look for incidental findings must not be unreasonably difficult. Any obligation to provide compassionate medical care must be balanced against the responsibilities and constraints inherent in the conduct of research to produce generalizable knowledge. This criterion is perhaps the most significant, and in most practical situations, this debate will hinge on the question of reasonableness—that is, whether the benefit provided to participants will outweigh the costs to researchers, and whether the effort to provide care will not unduly hamper the research effort.

We now analyze these three considerations—benefit, uniqueness of access, and burden—in the context of the current state of genomics research, to determine whether there is a current obligation to look. Then, acknowledging the rapidly moving growth in next-generation sequencing and genomic analysis, we consider the anticipated future of genomic research to explore whether there might be a future obligation to look. It is important to be clear that the constant changes and advancements in this area make pinpointing characteristics of specific future time periods quite difficult. Our analysis of these future eras is rough-grained, then, and focuses on identifying situations in which these characteristics could arise, rather than attempting to predict the future precisely.

Is There an Obligation to Look for Genomic Incidental Findings Today?

Benefit

We start by looking at the state of genomic research today, first considering the question of benefit: How useful is it to look proactively for incidental findings in genomic data, given current technology and knowledge? Genomic science is still in its infancy, and the amount we know about the relationship between genomic data and human disease is dwarfed by the amount we do not yet know. Currently, much of the broad genomic analysis being performed in research is done to find the cause of specific phenotypic traits, such as rare, highly penetrant conditions. As such, there is not yet rigorous empirical evidence quantifying the chances of finding serious genetic variants in a representative sample of research participants, healthy or with unrelated conditions.

Attempts to clarify these chances are promising, but early. A study by Cassa and colleagues (2012) pulled a representative sample of genomic variants catalogued in various databases and classified them according to standards set forth in the NHLBI 2010 working group recommendations for returnable individual genetic findings: namely, analytic validity and association with significant health implications that can be treated or prevented. The results of their sample indicated that under a conservative interpretation of what constitutes severe disease, 6.9% of reviewed variants met criteria for disclosure; extrapolated to a genomic scale, with perfect knowledge of the genome about 7171 variants might qualify. The authors further analyzed 36 whole-genome sequences from asymptomatic individuals and found that each carried about 2000 of the most serious category of variants included in their knowledge base (Cassa et al. 2012).

At best, these data suggest that even genomes of asymptomatic individuals would likely contain a number of known variants; however, it still does not allow us to accurately estimate how many of these variants in each individual genome would meet the disclosure criteria. Based on recent surveys, experts can agree on only a handful of variants that should be routinely disclosed. One study found that 100% of genetic specialists were in agreement in favor of disclosing to adults 21 conditions or genes classified as “known pathogenic mutations” (more than 80% agreed on 64 conditions or genes; Green et al. 2012).

From any individual’s perspective, the chance of finding a result that meets our threshold is low, but such a result could be profoundly important.⁷ The challenge, however, is that when making far-reaching recommendations about an obligation to look for incidental findings,

we must consider not the individual but the population-wide public health implications. Because our body of knowledge is still relatively shallow, we cannot conclusively say that looking for incidental findings today will benefit participants enrolled in genomic research studies as a group.

Uniqueness of Access

Next, we consider the question of uniqueness of access: Do researchers have a special claim on the provision of genomic sequencing and analysis? Today, they do: Careful genomic sequencing and analysis is rarely available outside of research. When genetic testing is done in clinical practice, it is ordinarily targeted and aimed at confirming a diagnosis or informing the therapeutic approach; there is very little role for WGS or analysis in general clinical medicine (Biesecker 2012; Burke et al. 2011; Institute of Medicine 2012). This means that most people today will not have their whole genomes interrogated for potentially beneficial information unless they are involved in research. There are a number of direct-to-consumer companies that offer genetic sequencing and analysis to anyone willing to pay a significant fee, but they clarify in their terms that these tests are not intended to be used for clinical decision making (Brunham and Hayden 2012; see also, e.g., 23andMe 2012a).⁸

Additionally, inadequate patient education and a lack of professional oversight can potentially cause harm to individuals who do not fully understand the meaning of these tests (American College of Medical Genetics Board of Directors 2004; Brunham and Hayden 2012). Ultimately, since researchers do have a unique ability to provide to participants the information gained from high-quality genomic sequencing and analysis today, this criterion weighs in favor of an obligation to look.

Burden

With uncertain benefit, but unique access, the question of whether looking should be obligatory today depends greatly on its burden: how difficult and resource-consuming genomic analysis actually is, given current technology. By carefully examining the processes required now, we demonstrate that genomic analysis is currently quite difficult. The amount of time, effort, and resources necessary to disclose even a single secondary finding means that proposing an obligation to look for these findings has very real implications for the progress of research.

Currently, the process of investigating a genomic sequence to identify serious pathogenic variants requires considerable time, effort, and resources. In order to look for an incidental finding, a researcher must manipulate, filter, and interrogate a massive amount of raw sequence data. This involves: (1) confirming the quality of the genomic data; (2) confirming the analytic validity of the variant to make sure that the expected change is actually present; (3) comparing the participant's data to reference samples to identify unexpected variants; (4)

⁷It is worth noting that some commentators have argued that disclosing incidental findings could plausibly be construed as a risk or harm to participants, rather than a benefit (see, e.g., Parker 2008). For example, disclosing incidental findings could cause anxiety or depression, require the participant to have expensive and invasive follow-up tests, and/or lead the participant to take prophylactic steps such as mastectomy that are both painful and costly. These potential risks are well worth considering, but within the scope of this article we focus on the benefits possible from seeking and disclosing incidental findings.

⁸23andMe, one of the leading direct-to-consumer genetic sequencing firms, is currently piloting a whole-exome sequencing service. See 23andMe (2012b).

analyzing the variants to determine which are most likely to be disease-causing; and (5) verifying the scientific validity of each variant's association with human disease by digesting the existing published literature (Biesecker 2012; Stitzel et al. 2011). Additionally, physical constraints and costs of data storage, processing, and transfer create further burdens on the resources available (Pollack 2011).

Once the exome or genome is sequenced, the number of genetic variants can be determined by comparison to a database of reference sequences. These variants will include both the variant(s) of interest (mutations that cause the disease that is being studied), if applicable, and an enormous number of secondary variants, or incidental findings. Before any filtering, each exome typically has around 80,000 variants; each genome, 3 to 4 million (Biesecker 2012; Stitzel et al. 2011). This raw number of variants is enormous, especially in a study with multiple participants, and would be overwhelming to analyze. Thus, the first step in identifying *significant* mutations is filtering the results to leave only those variants most likely to cause disease: mutations that fundamentally change or delete amino acids and protein structure.⁹ This reduces the number of relevant exome variants to around 10,000–15,000 (Stitzel et al. 2011). The computer can then quickly perform a number of other filtering steps by considering the quality of the sequencing, the chance that the variant is disease-causing based on its prevalence in the overall population (minor allele frequency), and how likely any particular variant is to be seriously problematic in terms of anticipated changes to protein structure (Biesecker 2012; Stitzel et al. 2011).

The next step for determining precisely whether a specific variant is likely to cause disease (pathogenicity), however, must be done manually, and requires considerable time and diligence. There are several databases that catalogue literature documenting disease-causing mutations, such as the Human Gene Mutation Database (HGMD) or locus-specific databases (LSDB), which can be used to match existing primary research with identified variants. Although the curators of some databases may make a recommendation as to whether there is sufficient published evidence to suggest that the variant has been proven pathogenic or not, the irregular quality of these data means that currently, for every variant examined, a researcher still has to read all of the primary literature and assess for her- or himself the chances that the variant has a significant chance of causing disease in that individual. Is the scientific evidence compelling? Is the variant fully penetrant (i.e., does it cause disease in every person in whom it appears), or does it exist in healthy controls as well? If the variant shows carrier status of a recessive disease, how common is the variant? (Biesecker 2012) Finally, the researcher must consider the implications of disclosing each result. What are the dangers of not disclosing? Of disclosing a false positive (Kohane et al. 2012)?

This analysis requires meticulous review of all published literature, careful consideration of its value, and sound professional interpretation of the evidence. For a study with many participants, even a relatively robust filtering program may yield dozens of variants that need to be thoroughly scrutinized (Biesecker 2012; Stitzel et al. 2011). To confidently identify variants that have clinical significance, and avoid returning false positives that may be harmful, this analysis must be taken seriously and done carefully—which takes

⁹Specifically, nonsynonymous, stop, frameshift, and splice mutations.

significant time and dedication (Stitzel et al. 2011).¹⁰ In almost any scenario, the burden described here would likely be unsustainable. Given that the benefit at this time is uncertain—and thus not high enough to justify such a large amount of time, effort, and resources—the burden does not seem reasonable.

No Obligation to Look Given the Current Genomic Landscape?

Bringing these three categories together, we can determine whether there is any obligation to look at the current time (see Table 1). First, considering benefit: The results of genomic analysis are of largely uneven significance. Many identified variants will fail the thresholds we set, yet a small number may surpass them, with the capability of providing highly clinically significant information to individuals. On the other hand, participants' uniqueness of access to genomic analysis through research is uniformly strong, as genomic analysis is currently largely limited to medical research (and a few direct-to-consumer testing agencies whose price and variable quality make them impractical for most of the general public). The analysis, however, still requires significant time, effort, and resources, meaning the burden is also unreasonably high. Therefore, although researchers at this time do have special access to genetic data and are in the best position to interpret it, the interpretation is neither efficient nor consistently beneficial so as to justify an expansive obligation to look for genomic incidental findings.

One important note: Some researchers have proposed ways to lessen the burden of genomic analysis—and to increase the prospect of benefit—by prospectively deciding or defining which results are significant enough to disclose. For example, Berg and colleagues (2011) have suggested a system of “binning,” or sorting variants into different categories based on clinical validity, clinical utility, deleteriousness, and the associated risks, to help coordinate which variants could be disclosed in a clinical context. While this kind of approach is intriguing, specificity and consensus building will be required. There is little standardization within and between institutions and there are no current nationwide standards (Bredenoord et al. 2011; Green et al. 2012; Knoppers et al. 2006). Most laboratories performing WGS have created proprietary algorithms to ease the process of determining the significance of certain variants, but these tools are variable and idiosyncratic (see, e.g., Ashley et al. 2010).

To remedy this problem, some experts have recently been discussing the possibility of creating an authoritative list of variants that should be disclosed. There are active processes moving toward this goal, including conferences and surveys of experts seeking agreement (Green et al. 2012). The hope would be to build a process where a panel of genome experts together enumerates the variants that are known to be disease-causing and that could benefit from a prompt medical intervention, after a careful analysis of the literature. Researchers using WGS would then be encouraged or required to disclose these variants to their participants. With a highly validated list, it seems possible that looking for the variants on the list *could* be as easy as “pushing a button” to activate a standardized analytic tool. In this

¹⁰Right now, many scientific researchers may lack expertise and thus find it difficult to adequately analyze genomic sequence data and identify incidental findings with clinical significance. This will likely change, however, as genomic sequencing technologies and analytic tools continue to improve. In the mean time, the extra effort required of nonexperts can be considered as part of the burden of analysis.

case, the burden of looking would be significantly reduced, and the benefit clearly proven; as long as genomic analysis is still largely unavailable in clinical care, the existence of a list could yield an obligation to look for incidental findings.

It is unclear, however, whether such a list can ever be created, and if so, whether it can be a viable long-term solution. Recent discussions and attempts at consensus have thus far resulted in only vague recommendations, although efforts are underway to produce more definitive statements (see, e.g., American College of Medical Genetics and Genomics 2012). Even if a list were created, there is no guarantee that its recommendations would be followed; individual researchers and institutions often prefer to use their own judgment and adapt any advice to their own needs. For example, when the eMERGE consortium created a guide to disclosing the results of genome-wide association studies (GWAS), their suggested procedures were not uniformly adopted (McGuire et al. 2011). A list, also, would not obviate the need to exert any effort in genomic analysis: Genomic research is constantly evolving and changing, with new information often contradicting or amending old knowledge. Additionally, changes in the clinical understanding and management of certain diseases may affect whether variants are deemed severe or actionable. All of these advances would have to be carefully considered on a regular basis, and it seems unlikely that a simple list could be sufficiently nuanced and adaptable. Ultimately, it is not clear that creating a list would permanently establish an obligation to look for incidental findings. Although in an ideal world the list could solve two of our essential criteria for an obligation to look (it would reduce the magnitude of burden and increase the certainty of benefit), we have shown that this it is unlikely to be that simple. In any situation, the question of whether or not investigators can provide special access to WGS and analysis will exist independently of the list, and thus will require its own independent analysis. Overall, we see more potential value in expanding the power of databases and computer software to reduce the burden of analysis for researchers while allowing flexibility, judgment, and continuity to inform their decisions.

Will There Be an Obligation to Look for Genomic Incidental Findings in the Future?

Currently, we believe there is no obligation to look for genetic incidental findings. The progress of genomic science has been rapid, however, and we believe that it is valuable to look ahead and anticipate how this obligation may change over time. In the coming years, as the cost of sequencing drops and genomic research progresses, additional knowledge and technical developments will likely both increase the accuracy and benefit of genomic analysis and decrease the effort required to perform it. As the field of personal genomics becomes more efficient and useful, it will become better incorporated into standard clinical care. During the next few decades, as these transformations play out at different paces, we can imagine how each of our critical criteria—high benefit, high uniqueness of access, and low burden—may evolve, theoretically giving rise to an obligation to look for genetic incidental findings in genomic research. To paint a picture of these potentialities and their effect on this obligation, we next walk through the expected future of genomic research and translation, and consider how changes and advances in research and clinical care will affect each criterion (see Figure 1 and Table 1).

Figure 1 is a conceptual gradient timeline, showing the general expected shifts in each of our three criteria over time. The gradient shift demonstrates change, with a darker hue where the criterion is stronger. For example, the right end of the “benefit” bar is darker than the left, indicating higher benefit to participants at this later time. It is important to note that this timeline is rough and meant solely as a conceptual visualization; it has no strict underlying chronology. Although we may suggest a general range of time for each period, the characteristics are crucial, rather than the specific number of years that have passed.

Future Benefit

As demonstrated earlier, the current benefit to participants of genomic analysis is largely uncertain. The research, however, is greatly promising: Researchers are regularly discovering new variants—one estimate puts the number of total known variants growing from around 120,000 in 2012 to 150,000 in 2015—and it is likely that a significant portion of these will meet a threshold for disclosure (Cassa et al. 2012). Although this demonstrates the large-scale potential of genomic research, the transition between discovering a variant and fully understanding its clinical significance takes time. Although this kind of research may be slow at first, we anticipate that it will escalate to the point where the body of genetic knowledge includes a considerable number of known genetic variants that meet our high disclosure threshold. Figure 1 accordingly shows the benefit to participants as low now (at point A), but growing stronger (through point B) to become quite high (point C).

Future Burden

At the same time, we anticipate that various research and technological advances will continue to significantly reduce the current burden of genomic analysis. If sequencing technologies follow their current trends, the speed and accuracy of these techniques will improve greatly in the next several years, and there are already calls for more advanced and centralized databases that will compile information on meaningful variants (Institute of Medicine 2012). High-powered software and well-maintained databases—or even a well-maintained list of variants that should be disclosed—have the potential to lessen the burden of identifying which variants meet our high threshold. Overall, technological advances and the mobilization of an accumulation of evidence promise to reduce greatly both the time and effort required to examine whole-genome or whole-exome sequence for variants that should be disclosed. In Figure 1, we can therefore see that the burden at point A (now) is high, but it lessens quickly to become quite low at points B and C.

Future Uniqueness of Access

The advances necessary to properly utilize genomic analysis in medicine and reduce the uniqueness of access criterion, however, will likely be slower to develop. There are many elements that must be implemented into standard clinical practice, from training clinicians and counselors to manage genetic information and genetic risk to maintaining electronic records of genomes and identified variants, and the bureaucratic inertia that must be overcome to initiate even small changes is likely to be significant. This may cause the gap between established genomic tests and clinical implementation, for a certain period, to be quite broad. Until genomic analysis becomes the standard of care, people will continue to

have access to it primarily by participating in a research study or potentially by paying out-of-pocket to a commercial company.

During this period, then, researchers will still have a relatively unique ability to analyze a genome and provide beneficial information about a participant's health. Figure 1 shows the uniqueness of access for genomic analysis shifting slowly from point A; since this change is so gradual, at point B the uniqueness is still quite high (dark). Once these barriers are overcome, however, geneticists promise an era of "personalized medicine," when it will be common for an individual's primary care doctor to order whole-genome sequencing and analysis. At this time, the individual's genome could be used to determine disease risk factors, choose the best drug treatments, inform reproductive decision making, and prescribe diet or lifestyle changes (Green and Guyer 2011). Any physician—researcher or primary care—will be able to order and interpret genomic analysis, and therefore researchers will clearly no longer be uniquely able to offer genomic sequencing and analysis. Thus at point C, Figure 1 shows the uniqueness of access to be lower (lighter).

A Potential Obligation to Look in the Future?

In the full-fledged future of genomic medicine (at point C), there will be little obligation to look for genomic incidental findings. Although benefit is high and the burden low, the uniqueness of access is low as well (see Table 1). Before we reach this state, however, might there be a time during which there is an obligation to look? In order to prepare for this transitional period, it is important to imagine the conditions that would have to exist in order for an obligation to look to emerge.

It is conceivable that we will experience an intermediate period during which genomic science will be more advanced and precise, but the logistics of incorporating it into clinical practice will not yet have been fine-tuned. In fact, this is likely to occur if the process of sequencing and analysis improves significantly through research and enterprise before the clinical realm has time to catch up. A lack of trained clinicians and the general obstacle of the health care and health insurance infrastructure could cause a significant delay in translation. Recall that an obligation to look for incidental findings would only exist when our three criteria are simultaneously fulfilled: high benefit, low burden, and high uniqueness of access. This idealized period is represented in Figure 1 as the point marked with an asterisk. As Figure 1 shows, the period that comes closest to reaching this level is the intermediate point B, where we can see that the benefit and uniqueness of access are relatively high (dark) and the burden is low (light). At this point, an obligation to look for genomic incidental findings would be quite strong.

It is, however, impossible to predict whether this scenario will ever become fully realized. The constantly evolving landscape of genomic research and clinical care makes identifying a specific time point like trying to hit a moving target. Figure 1 is only speculative, and it is possible if not likely that the changes—represented by the gradient's color shifts—in each criterion will take place at a significantly different pace, throwing off the overall balance. The potential ethical obligation to look for incidental findings is tied to this precise equilibrium of uniqueness of access, benefit, and burden, and implementing it in the wrong

situation can have harmful—and expensive—impacts on both research and the health of the research participant population.

Other, more subtle, factors may also modulate the clinical and research terrain. For example, a lack of education or expertise for researchers and clinicians may lead them to underestimate the possible negative consequences of divulging a false positive result. The significant physical requirements of data storage and transfer must also be considered as a potential burden (Pollack 2011). Finally, vulnerable populations—people with limited or no access to basic health care services—will also lack access to genomic analysis, even if it is typically available to the general population. Even at point C, when WGS and analysis are an established part of clinical care and there is generally no obligation to look, researchers should consider whether specific characteristics of their study or their population of participants might change the contours of their landscape and thus affect their obligations.

CONCLUSION

The growth of next-generation sequencing is defining a new era in genetic research, leaving researchers with both a large amount of data and an unclear ethical responsibility toward this data. So far, most attention has been paid to the question of whether researchers have an obligation to disclose certain findings that are stumbled upon in the course of research. If this obligation exists, however, is it plausible that researchers should simply proactively look for these findings in every genome? Most commentators so far state that there is no obligation to look—but it is not clear why. In this article, we have tried to provide a framework for thinking analytically about this question, laying out three criteria of genomic analysis that should be considered: benefit to participants, uniqueness of access for participants, and burden on researchers.

Given the current state of genomic research, we believe there is no obligation to look for incidental findings today—although a definitive list of “disclosable” variants could shift the balance and create an obligation to look, at least for the variants on the list. In the far future, when genomic medicine has achieved its full clinical promise, there will likely also be no obligation to look. It is possible, however, that the translation of genomic analysis from research to clinical care may be slow enough that at some point the analysis itself will be quite valuable and efficient, yet only available through research. At this point, researchers performing WGS would have an obligation to look for incidental findings.

It is clear that whole-genome sequencing will play a fundamental part in the future of both medicine and research. Ultimately, this timeline and analysis is not meant to be either definitive or prescriptive, but to help prepare researchers, institutions, and policymakers to fully consider the ethical obligations that come along with this growth of genomic sequencing.

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Figure 1. Conceptual gradient timeline of the three critical criteria. The expected shifts of our three criteria over time are conceptually illustrated here. The gradient shift demonstrates change, with a darker hue where the criterion is stronger.

Table 1

Projected Timeline of the Three Critical Criteria

	Now	Future	
		Intermediate	Far
Benefit	Low: Our body of knowledge about genetic risk and disease variants is still relatively shallow. We do not have enough data to estimate the probability of clinical benefit for any individual.	High: A large body of knowledge about the disease risk from specific variants has accumulated. Genomic analysis is likely to yield clinically beneficial information for any individual.	High: A large body of knowledge about the disease risk from specific variants has accumulated. Genomic analysis is likely to yield clinically beneficial information for any individual.
Uniqueness of access	High: Access to genomic sequencing and analysis is available almost exclusively through research.	High: Access to genomic sequencing and analysis is available almost exclusively through research.	Low: Genomic sequencing and analysis is widely available through standard clinical care.
Burden	High: Considerable time, effort and resources are needed to manually evaluate a large number of potentially significant variants.	Low: Technological advances make identifying significant variants in a genome simple and efficient.	Low: Technological advances make identifying significant variants in a genome simple and efficient.