The unintended implications of blurring the line between research and clinical care in a genomic age

While the development of next-generation sequencing technology has had a paradigm-changing impact on biomedical research, there is likely to be a gap between discovery of therapeutic benefits in research and actual adoption of the new technology into clinical practice. This gap can create pressure on the research enterprise to provide individualized care more typical of the clinic setting because it is uniquely accessible in research. This blurring of the line between research and clinical care is understandable, and perhaps even inevitable. But even if the gap is only transitory, such a blurring can have lasting implications, both by expanding obligations imposed on researchers, but also by challenging long-held ethical views. We explore this idea, focusing on how the dissolving distinction between research and clinical care has influenced the vigorous debate around how researchers should manage genetic findings (sometimes separated into primary and incidental or secondary findings) resulting from research.

Keywords: ancillary care • incidental findings • legal liability • research ethics • secondary findings • whole-genome sequencing

There has been significant advancement of genomic sequencing technology in the decade since the completion of the Human Genome Project [1]. As the capacity to carry out sequencing has become more efficient, the cost of processing sequencing reactions has decreased dramatically; there has been a nearly 100,000-fold decrease since the sequencing of the first human genome [2]. The ever-decreasing cost of so-called 'next-generation' sequencing has made the use of this technology accessible to individual laboratories [3], and its use in medical research has become ubiquitous. These technological developments have fed long-standing enthusiasm regarding the potential contributions of genomics to the understanding and improvement of human health [4], and there is significant, publicly funded investment in bringing about this outcome in the foreseeable future [1,5].

While the development of next-generation sequencing technology has had a paradigm-changing impact on biomedical research,

adoption in the clinical realm has been understandably slower. To be sure, there are already early hints of genomics being integrated into the clinical setting [5–7]. Genomic sequencing is being used as a tool to explore the genetic variation underlying a broad range of both rare disorders and complex genetic phenotypes, to assess a patient's pharmacogenomic profile, and to screen for disease risk [8–12]. But much more research will be required to realize the full potential of genomics in the medical realm. In a note of realistic optimism, some leaders in the field have articulated a decades-long vision for the progression of genomics science along a path from basic research to improving the effectiveness of healthcare delivery [1]. Some have even argued that claims about the utility of genomics in clinical care have heretofore been unrealistic [13].

Even in a rapidly evolving field like genomic medicine, delivering on the promise of cutting-edge science does not happen overnight. There is often going to be a gap

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between discovery of therapeutic benefits in research and actual adoption of the new technology into clinical practice [14]. As such, there will usually be a period during which the benefits afforded by the new technology are primarily available in the research setting [5]. This gap can create pressure on the research enterprise to provide individualized care more typical of the clinic setting because it is uniquely accessible in research.

This blurring of the line between research and clinical care is understandable, and perhaps even inevitable. But even if the gap is only transitory, such a blurring can have lasting implications, both by expanding obligations imposed on researchers, but also by challenging long-held ethical views. In this article, we explore this idea, focusing on how the dissolving distinction between research and clinical care has influenced the vigorous debate around how researchers should manage genetic findings (sometimes separated into primary and incidental or secondary findings) resulting from research. We begin by discussing the reasons for the increasingly blurry line between genomic research and clinical care and why that might generally be problematic. We then explore the genetic findings problem through the lens of specific issues, where the blurring line between research and clinical care has been of central concern:

- Our difficulty in defining the scope of an obligation to disclose genetic findings;
- Whether there is an ethically significant distinction between different kinds of genetic research findings;
- Whether researchers have an obligation to actively search for high value variants;
- The self-fulfilling nature of possible future legal liability.

The blurring distinction between genomic research & clinical care

While commentators have raised general questions about the collapsing space between research and clinical care [15–17], this phenomenon has been particularly acute in the field of genomics where our knowledge base and technological capabilities are evolving so rapidly. Take, for example, research on rare genetic disorders. When patients with difficult-to-diagnose conditions turn to genomic sequencing for answers, ascertaining when clinical care has morphed into research (or *vice versa*) can be quite difficult. Using genomic sequencing as a hypothesis-generating tool [18] is analogous to “an informed fishing trip” [19] that occupies the space between clearly indicated clinical actions and rigorous, systematic production of generalizable

knowledge. Existing in such liminal space can be disorienting; in one study of rare familial disorders, participants had trouble remembering that they had provided written consent to participate in a study, perhaps because they did not perceive a clear demarcation between clinical and research procedures [20].

A similar story can be told by the highly translational field of cancer genetics. Clinical genetic testing for cancer patients can often closely resemble genomic research undertaken to study a new set of mutations, particularly when that research produces genetic information that is clinically relevant to participants [21]. The relationship between research and clinical care in this field seems almost impossible to untangle. In one qualitative study of cancer genetics researchers, the data suggested that investigators view “the relationship between research and clinical care as flexible, permeable, and permanently shifting,” particularly because the evidence base in this field is still in an early stage of development [21]. Another qualitative study concluded that these views about the merging of research and clinical care are not just held by investigators; research participants were equally likely to understand that there is an overlapping relationship between the two realms [22].

Why do we care about the blurring line between research & clinical care?

The field of research ethics has long sought to draw a clear distinction between research and clinical care as a way to delineate which biomedical activities require additional oversight to protect human participants [23]. Concerns about drawing a stark boundary flow from the fact that there are important differences between research and clinical care, even though they often look quite alike [15]. First, the goals of the two activities are quite dissimilar. Clinical care has the purpose of providing a benefit to the patient being treated, while research is designed to produce generalizable knowledge that can benefit society. Individual research participants can often receive direct benefit from the research intervention, but the prospect of individual benefit is not required and should generally be secondary to societal benefit in evaluating the ethical appropriateness of the research. Second, researchers employ methodologies that do not have an analog in clinical care, such as randomization and placebo controls – or in the context of genomics, the use of not-yet-validated analytic tools. Third, the justifications for exposure to risk differ in important ways. In clinical care, any risks associated with treatments are justified by the possible clinical benefit to the patient. By contrast, research procedures present risks that are justified by the production of generalizable knowledge. Finally, physicians

have a fiduciary duty to act in the best interest of their patient, but researchers do not have the same obligation. While researchers must protect their participants from avoidable or unnecessary harm, they have duty towards their scientific pursuits, which can often come into conflict with what is in the best interest of a given individual participant [24].

Given the ethical tensions inherent in the distinctions between research and clinical care, clearly differentiating between the two whenever possible is useful. This allows for the appropriate regulatory oversight of research [25], for example, ensuring that there is an important research question, that the risk–benefit ratio is favorable, and that appropriate informed consent will be obtained [26]. It also enables investigators and clinicians to demarcate the extent of their responsibilities towards their participants/patients. Without clearly demarcating these two activities, problematic conflicts of interest can arise when an individual is occupying both clinician and investigator roles [27].

The problem of too much data: the controversy around how to manage genetic findings generated in research

The rapid advances in genomic sequencing technology and subsequent ubiquitous adoption into biomedical research have created the conditions for acute concerns about the dissolution of the distinction between research and clinical care. In particular, heated discussions have surrounded the question of what obligations attach to researchers who become aware of ‘incidental’ or ‘secondary’ genetic findings with potential value (clinical or otherwise) for a participant. A widely endorsed view that researchers have at least some obligation to disclose some genetic findings to some research participants has emerged in the literature. Any such view requires accepting to a certain degree that obligations traditionally circumscribed to the clinical sphere – here, an affirmative disclosure obligation – can stem from genetic research. Yet how far the line between research and clinical care can and should blur, and the underpinning ethical rationale(s), remains highly contentious. The result is a seemingly intractable variation in efforts to formulate frameworks for assessing obligations to disclose incidental or secondary genetic research findings.

Wolf *et al.* published what has become an influential framework supporting an ethical requirement to disclose incidental findings “of likely health or reproductive importance” in 2008 [28]. Adopting Richardson and Belsky’s ancillary care framework, they concluded that “when research unexpectedly yields information of likely importance to the participant’s health or reproductive decision-making, the researcher may

have an obligation or discretionary option to communicate that information depending on the seriousness of the finding” [28]. Two National Heart, Lung, and Blood Institute working groups have endorsed providing research participants with genetic information provided, among other criteria, it contains “important health implications” for the participant and preventive or therapeutic interventions are available (which some people refer to as ‘actionability’ of the information) [29,30]. Broadly, these frameworks hinge genetic researchers’ disclosure obligations on their privileged access to information with clinical value for research participants [31].

Some go even further, recommending that disclosure obligations should cover a more holistic spectrum of genetic research findings, for example, results that have personal (but not necessarily clinical) value for participants. The 2010 Canadian Tri-Council Policy Statement, for example, proclaims an obligation to return all “material incidental findings,” defined to include “findings that have been interpreted as having significant welfare implications for the participant, whether health-related, psychological or social” [32]. Others justify broad disclosure obligations through reciprocity, respect for participants, and the potential welfare interests of the research participant [33,34]. These more extensive obligations on researchers to act in participants’ best interests further extend the researchers’ relationship with participants to cover the kinds of fiduciary duties more commonly ascribed to clinicians.

Difficulty defining the scope of an obligation to return genetic research findings

Although no consensus exists in the literature, it does seem that there is an emerging majority view that investigators have at least a limited obligation to disclose something. The specific content of that disclosure remains disputed, leading to confused investigators and variable practice. For example, there is a lack of clarity about whether an obligation to disclose findings is universal, or whether it only applies to some studies and not others (e.g., secondary research involving deidentified samples obtained from biobanks) [35,36]. There are questions about the extent to which finite research resources should be allocated towards supporting the infrastructure necessary to properly return secondary findings [37].

The contours of investigators’ responsibilities towards these findings could be more easily defined if the ethical principle(s) on which they were based could be clearly articulated. If, for example, the obligation to disclose research findings flowed from the principle

of beneficence, then researchers might have a more expansive duty to disclose any findings that might be beneficial, in a broad sense of the term. By contrast, if the obligation flows from a duty to rescue, the responsibility would take a much narrower shape; researchers would only have to disclose very high value information (e.g., relating to immediate risk of significant morbidity or mortality) when it would not impose an undue burden on the research enterprise. In the end, however, while the literature is full of postulated principles (e.g., autonomy, beneficence, duty to rescue/warn, reciprocity, professional responsibility, public trust in research, right to know, institutional reputation, legal liability and the participant–investigator relationship), no one has been able to clearly articulate a case for any one principle taking primacy.

We believe that one of the reasons this uncertainty has been so hard to resolve flows directly from the collapsing distinction between genomic research and clinical care. While genomic sequencing is slowly becoming available clinically, it is still largely being performed in the research setting. This creates a gap that puts pressure on the research enterprise to take on responsibilities usually associated with the clinical realm. Specifically, through the act of sequencing their genomic data, researchers are learning potentially important genetic information about their participants that might not be uncovered in the course of normal clinical care. Perhaps unsurprisingly therefore, arguments in favor of an obligation to disclose often appeal to principles more closely associated with clinicians, such as beneficence ('if we know something that can help a research participant, we should tell them'), investigator–participant relationship ('I have a responsibility to help my research participants if I can') and professional responsibility ('I couldn't sleep at night if I did tell my research participant about an important finding'). This conflation of research and clinical care has created significant tension; some researchers feel that they are being unfairly asked to act like clinicians to the detriment of their research, while others feel like they are appropriately helping their research participants and do not understand why some of their colleagues disagree.

This tension seems to be coming to a head following the publication of the American College of Medical Genetics and Genomics (ACMG) recommendations. To date, the various frameworks for assessing the obligations to disclose secondary findings have generally shared a baseline belief that disclosure obligations are limited to findings that researchers stumble across in the course of their research. In other words, researchers are not under an obligation to search for genetic information beyond the scope of their research. However,

recent recommendations from the ACMG are challenging this assumption. Specifically, the ACMG recommends that laboratories performing clinical sequencing actively seek and report a list of 56 specific 'incidental' genetic mutations [6]. The recommendations have been subject to considerable controversy [38,39] and, at least for now, apply only in the clinical context. Yet the very availability of a list of variants for which disclosure is recommended may prompt a 'bleeding over' into the research domain, further diluting the clinical/research divide. As discussed below, the ACMG recommendations also stretch the very notion of 'incidental' or 'secondary' findings, raising important terminological questions. The next two sections address this pair of issues.

Terminological confusion: what is the ethical significance of the distinction between different kinds of genetic research findings?

Accepting that genetic researchers have at least some clinical care obligations has inherent ethical and practical tensions. Most importantly, how can we balance researchers' dual obligations to promote the clinical interests of research participants and maximize the production of socially beneficial generalizable knowledge? As one means of delineating the clinical obligations to which researchers are subject, scholars have sought to develop new terminology. Unfortunately, because of their goal-oriented origins – namely, drawing a pragmatic line around the findings subject to onerous disclosure obligations – resulting terminological distinctions can lack clear ethical significance. Distinguishing 'primary' from 'incidental' genetic research findings is a prime example of this phenomenon.

The foundational 'incidental findings' definition applies to "a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study. This means that IFs may be on variables not directly under study and may not be anticipated in the research protocol" [28]. Despite the definition's widespread uptake [40–42], many are now questioning its applicability to modern genomic research practices [43–45]. In particular, scholars note that many 'next-generation' sequencing studies have very open-ended research questions, making it very difficult to determine what findings, if any, are outside the aims of the study [43,44,46]. The traditional 'unforeseeability' element of incidental findings is also challenged by techniques such as whole-genome sequencing (WGS), which, by its very nature, generates findings that researchers have not intentionally sought out [44,47,48]. The recent ACMG recommendations stretch 'incidental findings' terminology

further by extending the term to apply to variants for which laboratories have deliberately searched [6]. As other scholars have noted, it is hard to see how these results can be classified as ‘incidental’, rather than positive findings from new recommendations for mandatory testing [38,45,49].

One response has been searching for new, and potentially less terminologically fraught, ways of distinguishing disclosure obligations based on whether the findings were within or outside the aims of research. For example, some scholars advocate ‘secondary variants’ as a means of separating ‘primary variants’ – the aim of the particular genetic test – from the kind of information for which provision “is a bonus that should not be counted upon” [50,51]. Similar reasoning may have motivated the inclusion in the ACMG recommendations of ‘incidental (or secondary)’ findings [6]. Because the nature of genome-wide arrays and WGS techniques “is such that, in principle, data will be generated that are not related to the initial diagnostic question”, the European Society of Human Genetics adopts the term “unsolicited findings” [52]. No doubt some terms fit better with modern genetic research practices than others. Yet, in our view, the issue at the heart of these terminological tweaks is the ongoing relevance of incidental findings (and variants thereof) in determining ethical obligations to disclose information.

For example, two of the authors of this paper (B Berkman and L Eckstein) have argued that ‘incidental findings’, as a concept grounded in a finding’s nexus with research aims and objectives, lacks the ethical significance necessary to ground distinctions in researchers’ disclosure obligations [53]. By way of justification, consider two hypotheticals involving findings outside the scope of research aims and objectives, but leading to quite different intuitions about the relevant disclosure obligations. First, a researcher who wants to sequence the BRCA regions in a population of minority women with newly diagnosed breast cancer. By constructing the aim of the study as the identification of novel mutations in this population, the researcher could claim that any positive findings in already characterized BRCA variants are ‘incidental’ to the research aims. Yet a decision not to look out for and return these results appears deeply disturbing because the researcher appears to be intentionally avoiding a clear opportunity to profoundly help sick patients at little cost to himself. Compare this with a researcher whose scientific goals require analysis of five genetic regions. Since it is cheaper than sequencing these genetic regions separately, the researcher obtains WGS for participants, but discards all but the five regions of interest. This appears far less problematic than the previous example. Since a researcher is free

to just sequence the specific genetic regions of interest, her selection of WGS should not necessitate additional and onerous analyses.

Our differing intuitive judgments about these hypotheticals suggest that whether findings are within the aims or objectives of a research project has limited importance in determining disclosure obligations. The more pertinent question appears to be the respective costs and benefits of finding the relevant information. If the information has clear clinical value to an individual, the context under which the information was discovered should not matter. Once the information is at hand, disclosure decisions depend on the nature of the information (its analytic and clinical validity, potential value for the participant, and whether the participant has expressed a preference to receive these kinds of findings). This approach moves beyond the field’s outdated terminological placeholders to more nuanced ethical analyses based on findings’ informational properties. Note, however, that such a move could have an interesting unintended effect: removing the terminological distinction between different kinds of findings might lead to a further muddying of the line between research and clinical care by removing an artificial construct that did little ethical work, but that provided some insulation for researchers who wanted to narrowly define their clinical obligations to participants.

Over the past decade, much thought has been given to questions about how to deal with the massive amounts of data that will be generated by genomic sequencing technologies. Consensus has been elusive, in large part because of the terminological confusion discussed above. Our hope is that by taking a step back to robustly define the core concepts that have broad support, we can build a conceptual apparatus that will help us to identify the areas where substantive disagreement actually exists.

The ‘stumble strategy’ versus the duty to look: should researchers have an obligation to actively search for high value variants?

As discussed above, the debate about genetic research findings has focused on questions of whether there is a duty to disclose findings that researchers happen to uncover in the course of their research. But the conflation of research and clinical care is forcing researchers to ask an even more fundamental question: assuming that researchers have an obligation to disclose certain findings that are stumbled upon in the course of research, is it plausible that researchers could also have to proactively seek these findings in every genome they sequence? [54]. The standard view has been that there is no obligation for researchers to take on the

more proactive role of clinicians [55]. Accordingly, to the extent that an obligation to disclose incidental findings exists, it only extends to those variants that the investigator happens to discover.

But at least on the surface, it seems that it would not be an insurmountable leap from a ‘duty to disclose’ to a ‘duty to look’. The ACMG recommendations draw just such a conclusion in the clinical context [6]. But in order to ascertain whether such a duty does in fact exist in the research world, it is important to elucidate the characteristics that would be necessary in order to create a ‘duty to look’ for a broad range of genetic research findings. As one of the authors has argued elsewhere, there are three features that would need to exist simultaneously in order for such a duty to arise (satisfying Richardson and Belsky’s ancillary care framework): high benefit, strong need and low burden [54].

First, the benefit of requiring researchers to look for clinically beneficial genetic information arguably should be quite high. If we are going to require researchers to act like clinicians, actively seeking out findings beyond the scope of their research for the clinical benefit of participants, then we should be sure that the information they would be seeking will actually be beneficial. This means that the variants that must be sought should be associated with serious conditions for which there is a preventative or clinical intervention available that could change the course of the disease. High benefit also requires that the evidence base establishing the relationship between a given genotype and phenotype must be particularly strong. The second relevant factor is need. Imposition of a duty to look should be dependent on researchers having unique access to genomic information. If participants could have access to the same genetic analysis through their standard medical care or direct-to-consumer services, it seems unnecessary to impose a duty to look on researchers. Finally, the third factor is burden: the act of looking must not be unduly burdensome to researchers (e.g., financial costs, time spent, administrative burden, and so on) such that it significantly impairs their ability to conduct research.

Taking these three factors into account, Gliwa *et al.* assess whether researchers are presently under a duty to look [54]. They conclude that researchers do not currently have a broad duty to look. While patients do not necessarily have access to the (somewhat beneficial) genomic information presently available elsewhere, the burden on researchers seems unreasonable. In the distant future, a duty to look probably will be obviated for different reasons. Burden will have decreased and benefit will have increased, but need will have dissipated since patients will have access to

genomic analyses through the regular medical system. Yet there is one scenario where a possible duty to look might emerge. As our genomic knowledge base grows and improved analytic tools make looking easier, an intermediate point may eventuate where burden is very low and benefit is very high. If need still exists because of a lag between research discoveries and clinical adoption, one could make the case that researchers have a broad obligation to look for findings during that delay.

Highly validated lists of clinically significant variants, such as the one produced by ACMG, further increase the likelihood that researchers will be considered to have a duty to disclose at least some genomic research findings now or in the near future. These lists make the process of looking for variants much easier, and thus significantly reduce the burden on investigators. It is certainly plausible to argue that there is currently an obligation to search for variants on such a list.

But the existence of an obligation to look for at least some genomic research findings could have profound implications on the already blurry line between research and clinical care. First, it might lessen the differences between the goals of the endeavors by making at least one distinct objective of genomic research a hunt for clinically beneficial findings. Second, it could put pressure on nonclinician researchers to take on something that begins to look like a clinical responsibility towards their subjects and might require the creation of new infrastructure (e.g., genetic counselors) that might divert resources away from production of generalizable knowledge. Finally, creating a duty to look may result in changing the assumptions or motivations of participants – they might begin viewing genomic research as an opportunity to receive genomic screening rather than an opportunity to play an altruistic role in producing generalizable knowledge for society’s benefit.

Legal liability for failure to disclose genetic research findings: a self-fulfilling prophecy?

Traditionally, researchers have not been held to the same standard as clinicians for purposes of determining legal liability. There is very little case law about the obligations of researchers to provide clinical care to participants, and there is some recognition that researchers cannot have a clinician-level fiduciary responsibility to provide care that is in the best interest of the research participant, providing some protection in the case of suit by a research participant [56]. Nevertheless, there is a real possibility that in blurring the line between research and clinical care, this protection might begin to dissipate.

As discussed above, there has been no agreement about a universal approach to disclosing genetic research findings. A number of commentators have attempted to build frameworks, but in the absence of definitive guidance, it is unsurprising that the research world has responded to this problem in a variety of ways. Some investigators have chosen to build robust and expansive return of results systems, with sophisticated rules for determining whether or not a given finding should be disclosed. Others have taken a more minimalist approach, leaving an option to exercise their clinical judgment about whether or not a given finding is clinically significant enough to warrant disclosure. Still others have decided not to disclose any findings, making this policy clear in the consent form. Finally, there is some set of researchers who have not explicitly addressed the problem in their protocol or consent form [57].

If one juxtaposes these variable policies with the emerging idea that there is some ethical obligation to disclose genetic research findings, significant concerns about the risk of legal liability for researchers conducting genomic research immediately become clear. A paradigmatic case might look something like this: a researcher studying a specific infectious disease is using genomic sequencing of affected participants in order to learn more about genetic susceptibility to the disease. One of these participants later contracts hereditary nonpolyposis colorectal cancer, an aggressive kind of cancer that is not normally caught with standard colonoscopies. The research participant brings suit, arguing that had she known about her genetic risk for this cancer, she could have sought targeted screening that would have caught her cancer earlier, and could have led to a better prognosis. Her suit alleges that the researcher had access to her entire genome, and should have known that she possessed the relevant genetic variant. Her lawyer presents testimony from similarly situated researchers that had contemporaneous policies in place that would have resulted in discovery and disclosure of the genetic variant, arguing that the researcher violated the prevailing standard of care.

Whether someone is liable under tort law is really a question about defining the prevailing standard of care. If the actor complied with the given standard of care, they are generally safe. But failing to provide the standard of care can (subject to a number of other factors) open the actor up to a possible judgment that they have been negligent and are thus liable for damages. The key issue in this kind of case would be to define what standard of care a genomic researcher owes to his or her research participants. As the bioethics literature coalesces around the notion that there is an obligation

for researchers to disclose genetic findings, particular researchers and research institutions will increasingly begin to act on that obligation. This will likely cause the legal standard of care to start shifting toward a requirement of disclosure, where failure to disclose incidental findings will possibly open researchers up to increased liability. Such a story represents something of a self-fulfilling prophecy. The call by ethicists, researchers and others to blur the line between research and clinical care in the context of incidental or secondary genomic research findings could have the net result of creating a legal standard where the law actually begins to treat researchers much more like clinicians.

Conclusion & future perspective

The distinction between research and clinical care has never been absolute. Some overlap is inevitable and should perhaps even be encouraged. The research environment does need to acknowledge the ultimate goal of translating genomics into clinical care; maximizing the utility of genomics in the clinical arena calls for a research agenda in which the bench sciences collaborate with the communication, social and behavioral sciences [58]. Such research (e.g., studying the best way to clearly and effectively return results, or how to best solicit participant preferences) can help both anticipate and resolve ethical tensions in genomics, including the challenges surrounding the management and disclosure of various types of genomic information.

Unfortunately, the current debates surrounding genomic incidental findings have emerged, at least in part, from a muddying of the line between research and clinical care rather than a deliberate multidisciplinary translational research agenda. This effectively has led to the early adoption of a new clinical technology in the research setting before sufficient translational research was completed, creating a set of 'clinical-esque' obligations for genomic researchers that has been accompanied by much confusion about the scope of researchers' obligations to participants in genomic research, as well as the ethical principles underlying these obligations. This is problematic not only because it has led to inconsistencies in practice across different research settings, but because it has the potential to threaten the efficient conduct of genomic research. If this continues over the next decade, there is a real possibility that researchers could be held liable for failure to disclose genetic findings, which could cause researchers to act defensively, spending significant time and resources to return findings in order to avoid being sued. This could be detrimental to socially beneficial research, diverting

Executive summary

Background

- There is likely to be a gap between discovery of therapeutic benefits in research and actual adoption of the new technology into clinical practice. As such, there will usually be a period during which the benefits afforded by the new technology are primarily available in the research setting. This gap can create pressure on the research enterprise to provide individualized care more typical of the clinic setting because it is uniquely accessible in research.
- Such a blurring can have lasting implications, both by expanding obligations imposed on researchers, but also by challenging long-held ethical views.
- While commentators have raised general questions about the collapsing space between research and clinical care, this phenomenon has been particularly acute in the field of genomics where our knowledge base and technological capabilities are evolving so rapidly.
- The rapid advances in genomic sequencing technology and subsequent ubiquitous adoption into biomedical research have created the conditions for acute concerns about the dissolution of the distinction between research and clinical care. In particular, heated discussions have surrounded the question of what obligations attach to researchers who become aware of 'incidental' or 'secondary' genetic findings with potential value for a participant.

Difficulty defining the scope of an obligation to return genetic research findings

- The contours of investigators' responsibilities towards these findings could be more easily defined if the ethical principle(s) on which they were based could be clearly articulated.
- One of the reasons this uncertainty has been so hard to resolve flows directly from the collapsing distinction between genomic research and clinical care.
- This conflation of research and clinical care has created significant tension; some researchers feel that they are being unfairly asked to act like clinicians to the detriment of their research, while others feel like they are appropriately helping their research participants and do not understand why some of their colleagues disagree.

Terminological confusion: what is the ethical significance of the distinction between different kinds of genetic research findings?

- As one means of delineating the clinical obligations to which researchers are subject, scholars have sought to develop new terminology. Unfortunately, because of their goal-oriented origins – namely, drawing a pragmatic line around the findings subject to onerous disclosure obligations – resulting terminological distinctions can lack clear ethical significance. Distinguishing 'primary' from 'incidental' genetic research findings is a prime example of this phenomenon.

The 'stumble strategy' versus the duty to look: should researchers have an obligation to actively search for high value variants?

- Assuming that researchers have an obligation to disclose certain findings that are stumbled upon in the course of research, is it plausible that researchers could also have to proactively seek these findings in every genome they sequence?
- The standard view has been that there is no obligation for researchers to take on the more proactive role of clinicians, and that to the extent that an obligation to disclose incidental findings exists, it only extends to those variants that the investigator happens to discover.
- But at least on the surface, it seems that it would not be an insurmountable leap from a 'duty to disclose' to a 'duty to look'.

Legal liability for failure to disclose genetic research findings: a self-fulfilling prophecy?

- There is very little case law about the obligations of researchers to provide clinical care to participants, and there is some recognition that researchers cannot have a clinician-level fiduciary responsibility to provide care that is in the best interest of the research participant, providing some protection in the case of suit by a research participant.
- Nevertheless, there is a real possibility that in blurring the line between research and clinical care, this protection might begin to dissipate. As the bioethics literature coalesces around the notion that there is an obligation for researchers to disclose genetic findings, particular researchers and research institutions will increasingly begin to act on that obligation. This will likely cause the legal standard of care to start shifting toward a requirement of disclosure, where failure to disclose incidental findings will possibly open researchers up to increased liability.

Future perspective

- The distinction between research and clinical care has never been absolute. Some overlap is inevitable and should perhaps even be encouraged.
- Unfortunately, the current debates surrounding genomic incidental findings have emerged, at least in part, from a muddying of the line between research and clinical care rather than a deliberate multidisciplinary translational research agenda.

resources away from producing important generalizable knowledge towards the provision of targeted genetic services for individual research participants. Ultimately, this could undermine the goal of efficient translation of genomic discovery into the clinical realm, which of course is not a desirable outcome. The goals of improving health through genomics will be better served by maintaining a clearer delineation between the research and clinical phases of the trajectory towards genomic medicine.

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References

Papers of special note have been highlighted as:

• of interest; •• of considerable interest

- Green ED, Guyer MS, National Human Genome Research Institute. Charting a course for genomic medicine from base pairs to bedside. *Nature* 470(7333), 204–213 (2011).
- Collins FS, Hamburg MA. First FDA authorization for next-generation sequencer. *N. Engl. J. Med.* 369(25), 2369–2371 (2013).
- Teer JK, Mullikin JC. Exome sequencing: the sweet spot before whole genomes. *Hum. Mol. Genet.* 19(R2), R145–R151 (2010).
- Collins FS. Medical and societal consequences of the human genome project. *N. Engl. J. Med.* 341(1), 28–37 (1999).
- Manolio TA, Chisholm RL, Ozenberger B *et al.* Implementing genomic medicine in the clinic: the future is here. *Genet. Med.* 15(4), 258–267 (2013).
- Green RC, Berg JS, Grody WW *et al.* ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet. Med.* 15(7), 565–574 (2013).
- These recommendations call for laboratories performing clinical sequencing to actively seek and report a list of 56 specific ‘incidental’ genetic mutations. The recommendations have prompted considerable controversy, particularly because they challenge the so-called ‘right not to know’ and traditional limits on pediatric genetic testing.**
- Johansen Taber KA, Dickinson BD, Wilson M. The promise and challenges of next-generation genome sequencing for clinical care. *JAMA Intern. Med.* 174(2), 275–280 (2013).
- Dixon-Salazar TJ, Silhavy JL, Udupa N *et al.* Exome sequencing can improve diagnosis and alter patient management. *Sci. Transl. Med.* 4(138), 138ra78 (2012).
- Bainbridge MN, Wisniewski W, Murdock DR *et al.* Whole-genome sequencing for optimized patient management. *Sci. Transl. Med.* 3(87), 87re3 (2011).
- Ng SB, Buckingham KJ, Lee C *et al.* Exome sequencing identifies the cause of a Mendelian disorder. *Nat. Genet.* 42(1), 30–35 (2010).
- Hull SC, Berkman BE. Grappling with genomic incidental findings in the clinical realm. *Chest* 145(2), 226–230 (2014).
- Biesecker LG. Opportunities and challenges for the integration of massively parallel genomic sequencing into clinical practice: lessons from the ClinSeq project. *Genet. Med.* 14(4), 393–398 (2012).
- Evans JP, Meslin EM, Marteau TM, Caulfield T. Deflating the genomic bubble. *Science* 331(6019), 861–862 (2011).
- Varmus H. Ten years on – the human genome and medicine. *N. Engl. J. Med.* 362(21), 2028–2029 (2010).
- Brody H, Miller FG. The clinician–investigator: unavoidable but manageable tension. *Kennedy Inst. Ethics J.* 13(4), 329–346 (2003).
- Brody H, Miller FG. The research–clinical practice distinction, learning health systems, and relationships. *Hastings Cent. Rep.* 43(5), 41–47 (2013).
- Kass NE, Faden RR, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. The research–treatment distinction: a problematic approach for determining which activities should have ethical oversight. *Hastings Cent. Rep.* 43(1), S4–S15 (2013).
- Biesecker LG. Hypothesis-generating research and predictive medicine. *Genome Res.* 23(7), 1051–1053 (2013).
- Parker M, Ashcroft R, Wilkie AOM, Kent A. Ethical review of research into rare genetic disorders. *BMJ* 329(7460), 288–289 (2004).
- Ponder M, Statham H, Hallowell N, Moon JA, Richards M, Raymond FL. Genetic research on rare familial disorders: consent and the blurred boundaries between clinical service and research. *J. Med. Ethics* 34(9), 690–694 (2008).
- Hallowell N, Cooke S, Crawford G, Parker M, Lucassen A. Healthcare professionals’ and researchers’ understanding of cancer genetics activities: a qualitative interview study. *J. Med. Ethics* 35(2), 113–119 (2009).
- Hallowell N, Parry S, Cooke S, Crawford G, Lucassen A, Parker M. Lay and professional understandings of research and clinical activities in cancer genetics and their implications for informed consent. *AJOB Prim. Res.* 1(2), 25–34 (2010).

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- 23 The Belmont Report.
www.hhs.gov/ohrp/humansubjects/guidance/belmont.html
- 24 Danis M. *Research Ethics Consultation: A Casebook*. Oxford University Press, Oxford, UK (2012).
- 25 Miller FG, Rosenstein DL, DeRenzo EG. Professional integrity in clinical research. *JAMA* 280(16), 1449–1454 (1998).
- 26 Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA* 283(20), 2701–2711 (2000).
- **A foundational article that describes a framework for assessing whether a given research protocol is ethically acceptable.**
- 27 King NMP, Churchill LR. Clinical research and the physician-patient relationship: the dual roles of physician and researcher. In: *The Cambridge Textbook of Bioethics*. (2008).
http://dx.doi.org/10.1017/CBO9780511545566.034
- 28 Wolf SM, Lawrenz FP, Nelson CA *et al.* Managing incidental findings in human subjects research: analysis and recommendations. *J. Law Med. Ethics* 36(2), 219–248 (2008).
- **This has been a very influential article in the incidental findings literature, as it was among the first to clearly articulate that researchers have an obligation to disclose incidental findings.**
- 29 Bookman EB, Langehorne AA, Eckfeldt JH *et al.* Reporting genetic results in research studies: summary and recommendations of an NHLBI working group. *Am. J. Med. Genet. A*. 140A(10), 1033–1040 (2006).
- 30 Fabsitz RR, McGuire A, Sharp RR *et al.* Ethical and practical guidelines for reporting genetic research results to study participants updated guidelines from a National Heart, Lung, and Blood Institute working group. *Circ. Cardiovasc. Genet.* 3(6), 574–580 (2010).
- **Represents one of the more comprehensive attempts to provide clear guidance about the genetic information that should or should not be returned as an incidental findings.**
- 31 Bredenoord AL, Kroes HY, Cuppen E, Parker M, van Delden JJM. Disclosure of individual genetic data to research participants: the debate reconsidered. *Trends Genet.* 27(2), 41–47 (2011).
- 32 Canadian Institutes of Health Research. Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada. *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*. Public Works and Government Services, Ottawa, Canada (2005).
- 33 Ormond KE. Disclosing genetic research results: examples from practice. *Am. J. Bioeth.* 6(6), 30–32 (2006).
- 34 Dressler LG, Smolek S, Ponsaran R *et al.* IRB perspectives on the return of individual results from genomic research. *Genet. Med.* 14(2), 215–222 (2012).
- 35 Beskow LM, Burke W. Offering individual genetic research results: context matters. *Sci. Transl. Med.* 2(38), 38cm20 (2010).
- 36 McGuire AL, Robinson JO, Ramoni RB, Morley DS, Joffe S, Plon SE. Returning genetic research results: study type matters. *Pers. Med.* 10(1), 27–34 (2013).
- 37 Bledsoe MJ, Clayton EW, McGuire AL, Grizzle WE, O'Rourke PP, Zeps N. Return of research results from genomic biobanks: cost matters. *Genet. Med. Off. J. Am. Coll. Med. Genet.* 15(2), 103–105 (2013).
- 38 Burke W, Matheny Antommara AH, Bennett R *et al.* Recommendations for returning genomic incidental findings? We need to talk! *Genet. Med.* 15, 854–859 (2013).
- 39 Allyse M, Michie M. Not-so-incidental findings: the ACMG recommendations on the reporting of incidental findings in clinical whole genome and whole exome sequencing. *Trends Biotechnol.* 31(8), 439–441 (2013).
- 40 Richardson HS. Incidental findings and ancillary-care obligations. *J. Law Med. Ethics* 36(2), 256–270 (2008).
- 41 Simon CM, Williams JK, Shinkunas L, Brandt D, Daack-Hirsch S, Driessnack M. Informed consent and genomic incidental findings: IRB chair perspectives. *J. Empir. Res. Hum. Res. Ethics Int. J.* 6(4), 53–67 (2011).
- 42 Van Ness B. Genomic research and incidental findings. *J. Law Med. Ethics* 36(2), 292–297 (2008).
- 43 Cho MK. Understanding incidental findings in the context of genetics and genomics. *J. Law Med. Ethics* 36(2), 280–285 (2008).
- 44 Kohane IS, Taylor PL. Multidimensional results reporting to participants in genomic studies: getting it right. *Sci. Transl. Med.* 2(37), 37cm19 (2010).
- 45 Parens E, Appelbaum P, Chung W. Incidental findings in the era of whole genome sequencing? *Hastings Cent. Rep.* 43(4), 16–19 (2013).
- 46 Wolf SM, Crock BN, Ness BV *et al.* Managing incidental findings and research results in genomic research involving biobanks and archived data sets. *Genet. Med.* 14(4), 361–384 (2012).
- 47 Parker LS. The future of incidental findings: should they be viewed as benefits? *J. Law. Med. Ethics* 36(2), 341–351 (2008).
- 48 Knoppers BM, Dam A. Return of results: towards a lexicon? *J. Law Med. Ethics* 39(4), 577–582 (2011).
- 49 Ross L, Rothstein MA, Clayton E. Mandatory extended searches in all genome sequencing: 'incidental findings', patient autonomy, and shared decision making. *JAMA* 310(4), 367–368 (2013).
- 50 Christenhusz GM, Devriendt K, Dierickx K. Secondary variants – in defense of a more fitting term in the incidental findings debate. *Eur. J. Hum. Genet.* 21, 1331–1334 (2013).
- 51 Johnston JJ, Rubinstein WS, Facio FM *et al.* Secondary variants in individuals undergoing exome sequencing: screening of 572 individuals identifies high-penetrance mutations in cancer-susceptibility genes. *Am. J. Hum. Genet.* 91(1), 97–108 (2012).
- 52 Van El CG, Cornel MC, Borry P *et al.* Whole-genome sequencing in health care. *Eur. J. Hum. Genet.* 21(6), S1–S5 (2013).
- 53 Eckstein L, Garrett JR, Berkman BE. A framework for analyzing the ethics of disclosing genetic research findings. *J. Law Med. Ethics* (2014) (In Press).
- 54 Gliwa C, Berkman BE. Do researchers have an obligation to actively look for genetic incidental findings? *Am. J. Bioeth.* 13(2), 32–42 (2013).

- Provides a more sustained exploration of questions (raised above) about whether or not researchers should have a duty to actively look for incidental findings.
- 55 Wolf SM, Lawrenz FP, Nelson CA *et al.* Managing incidental findings in human subjects research: analysis and recommendations. *J. Law Med. Ethics* 36(2), 219–248 (2008).
- 56 Pike ER. Recovering from research: a no-fault proposal to compensate injured research participants. *Am. J. Law Med.* 38(1), 7–62 (2012).
- 57 Pike ER, Rothenberg KH, Berkman BE. Finding fault? Exploring legal duties to return incidental findings in genomic research. *Georgetown Law J.* 102, 795–843 (2014).
- Engages in a detailed analysis of questions (raised above) about whether researchers could be held liable for failure to disclose genetic information generated in the course of next-generation sequencing.
- 58 McBride CM, Bowen D, Brody LC *et al.* Future health applications of genomics: priorities for communication, behavioral, and social sciences research. *Am. J. Prev. Med.* 38(5), 556–565 (2010).