Policy Uncertainty, Sequencing, and Cell Lines

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The circumstances surrounding the creation of the HeLa cell line are now well known. The best-selling book by Rebecca Skloot, *The Immortal Life of Henrietta Lacks* (Skloot 2010), detailed both the creation of the cell line and the associated ethical and social controversies. The Skloot book received a great deal of praise and media attention–which often used the book to surface a range of ethical issues associated with biomedical research (Nisbet and Fahy 2013). The recent sequencing and publication of the genome of one HeLA cell line (Landry *et al.*, 2013) has further intensified public attention on the circumstances surrounding the Lacks case and the associated ethical challenges, particularly in relation to ownership and control of samples and data (Skloot 2013).

While we should not over-interpret the story of the HeLa cell line as being emblematic of how research involving human tissue is conducted, it provides an opportunity to reflect on the profound and enduring lack of clarity that surrounds many relevant legal and ethical concepts (Callaway 2013). Given the advances in sequencing technology, the growing significance and investment in biobanking, and the push for open access to the results of scientific inquiry, it is essential that current policy uncertainties be acknowledged and addressed. Otherwise, we risk creating misconceptions, undermining public trust, and unwittingly derailing advances in the field.

This article seeks to highlight two important issues in need of immediate policy attention, as underscored by the public response to the HeLa story: ownership and control of biological specimens, and obligations to third party relatives in genomic research.

LEGAL AND POLICY UNCERTAINTY

Much of the relevant media coverage associated with the Skloot book touched on specific issues of consent and ownership, as noted by Nisbet and Fahy in their interesting analysis of the significant popular culture response (Nisbet and Fahy 2013). The implied message seemed to be, rightly or not, that individuals should retain some degree of control over biological specimens that are removed from their bodies. The reaction to the 2013 publication of the genome sequence of a HeLa cell line and its data likewise implied a baseline expectation regarding the procurement of consent from biological relatives prior to releasing genome sequence data. (See box.) But are there clear existing legal and ethical norms that can be used to direct us on these key issues?

In fact, despite decades of research involving human tissue and billions of dollars of investment, the law surrounding the ownership and control of human biological material remains remarkably uncertain (Charo 2006; Feldman 2011). There have been several highly relevant cases in the U.S.–such as the well-known cases of *Moore v Regents of the University of California* (1990), *Greenberg v Miami Children's Hospital Research Institute* (2003), and *Washington University v Catalona* (2007) – but a definitive picture of who has a right to control samples remains elusive. While the law seems to reject the idea that individuals who contribute samples to research have a definitive property right to their contributed material, case law also affirms the idea that those individuals retain a degree of control, primarily in the form of the right to withdraw or to request destruction of the sample (*Washington University v Catalona* 2007). And, as highlighted by cases from other jurisdictions, such as the UK decision of *Yearworth v. North Bristol NHS Trust* (2009), courts seem willing to accept and rely on notions of property if, from the perspective of the court, the policy goals justify the approach. (*Yearworth* dealt with interest in reproductive material.)

In Canada, there is case law, including jurisprudence from the Supreme Court of Canada, that suggests that individuals maintain a continuing interest in health information. In the case of *McInerney v McDonald*, for example, the court concluded that health information "is information that goes to the personal integrity and autonomy of the patient … [and] remains in a fundamental sense one's own" (*McInerney v McDonald* 1992). With the availability of increasingly low-cost DNA sequencing technology, such as that used to sequence the genome of the HeLa cell line, this kind of jurisprudence increasingly seems pertinent to human cell research. Will human cells be viewed through the lens of the law as nothing more than receptacles of sensitive personal health information and thus subject to all the same rigorous consent and privacy norms (Burningham 2013)?

And what, if any, interest do biological relatives have in the use of samples and publication of genetic data? Since genomic information is

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uniquely identifying and familial by nature, publication of an individual's sequence has implications for that person's biological relatives (Gymrek *et al.* 2013). It therefore seems like good policy to engage biological family members before making genome sequence data public–particularly in the case of the HeLa lines where the family is well-known and has already expressed concern–and there is emerging consensus among ethicists that suggests that should be done whenever possible. For example, Canada's national research ethics guidelines, The Tri-Council Statement, point out that genetic data "may reveal information about biological relatives and others with whom the individual shares genetic ancestry", thus triggering the need for extra caution in the ethics review and consent process (Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada 2010). Some genome sequencing projects have consent forms that explicitly note the importance of engagement with family members. The consent form for the Personal Genome Project, for example, states that "You are strongly encouraged to discuss your wishes with your family" (Personal Genome Project 2012).

Nevertheless, the law and policy on this point is, once again, far from authoritative. There is no existing law that compels a researcher, at least in North America, to obtain formal consent from a biological relative prior to the publication of genome sequence data of a cell line, a reality that was rarely noted in the public response to the HeLa story. In the United States, research regulations and publication policies largely ignore third parties, even when they are indirectly impacted by the research (Botkin 2001). In the context of genetics, a major challenge lies in identifying who the relevant biological relatives are. How far up the family tree must one climb? And at what point should an individual's autonomy rights be outweighed by the rights and interests of that person's family? These questions highlight the degree to which the controversy over the publication of the HeLa sequence, and subsequent response and temporary withdrawal of online access to the data by researchers (Oransky 2013), sit at the center of a very uncertain state of affairs.

PUBLIC PERCEPTIONS AND PUBLIC TRUST

The practical implications of the legal uncertainty and public sensitivity to these issues is reflected in the response of the public and media to the Lacks case, and to other recent tissue research controversies (Harmon 2010), such as the Texas lawsuit that resulted in the destruction of over five million newborn blood samples that were legally collected and used for research without parental consent (Doerr 2010).

This kind of reaction is hardly surprising and, in fact, seems likely to occur more frequently. As thoughtfully noted by Hank Greely, "As more and more people find out what can be done—or is being done—with their health information, their family histories, and their DNA, the pressure for change should grow" (Greely 2010).

Public perception research tells us there is very little consensus among the general public on key issues related to genetic and tissue banking research (Rachul *et al.*2012; Master *et al.* 2012). The public is very supportive of biomedical research, and survey data and experience tells us that the majority is willing to participate in a wide range of research activities, including the donation of tissue samples. But outside of a few areas (such as the desire to have researchers return results and incidental findings (Rachul *et al.* 2012)), there is virtually no public agreement on many of the core issues touched on in the Lacks case, from the type of consent required to who owns tissue samples. A recent survey of over one thousand Albertans, for example, found that 44.3% thought the research institutions owned the sample, 25.7% thought the donor owned the sample and 23.1% thought the samples belonged to the researchers (Caulfield *et al.* 2012). Fifty three percent thought they had a continuing right to decide what was done with a sample.

CONCLUSION

This lack of clarity on fundamental legal and ethical issues – including who controls donated samples, the nature of the consent process, and the rights of biological relatives – creates challenges for both the research community, as exemplified by the controversy surrounding the sequencing of the genome of HeLa cells, and for those who contribute biological specimens to research. Over the past few years a handful of highly publicized controversies have shed new light on the policy uncertainties surrounding these important issues. A coordinated and definitive policy that considers the perspectives and interests of all stakeholders will help create a degree of certainty for researchers and enumerate participants' rights and interests. And, if the policy-making process is done in a transparent and fair manner, it should also help to maintain public trust, which is essential to biomedical research (Critchley *et al.* 2012).

Several scientific and social trends highlight the urgency for clear guidance but, at the same time, make policy development even more challenging. For example, there is increasing pressure to commercialize the products of biomedical research (Caulfield 2012). This incentivizes investment in research and facilitates translation, but it has been shown in many studies to decrease public trust (Critchley 2008; Caulfield *et al.* 2012). In fact, much of the public reaction to the Skloot book related to a sense of outrage over the extensive commercialization of Lacks' cells, without any financial benefit flowing to her family.

There is also tension between the desire to make research data broadly available and maximize its utility by linking multiple data elements, and the need to protect the privacy of individuals who contribute samples and data to research. Recently, an alliance of more than 70 organizations in 41 countries agreed to create an organized way to openly share research data, with participant consent (Broad Institute 2013). The hope is that this will help standardize the data and make them more widely available (Kolata 2013), which is consistent with what most research subjects want (McGuire *et al.* 2011). At the same time, however, we are quickly realizing how vulnerable genomic information is: it is possible to identify individuals based on their genomic data by matching publicly available de-identified Y-chromosome data to genetic geneology databases, linking surnames between individuals and any distant relative on their paternal side (Gymrek *et al.* 2013). Indeed, it has been noted that a major privacy breach involving genomic data are probably inevitable. "[T]he question is not how to prevent a leak but how to mitigate the fall-out."(Brenner 2013). This reality has led many groups to point out the need for clarity and to call for policy change (Presidential Commission For The Study Of Bioethical Issues 2012; Rodriguez *et al.* 2013).

This will not be easy to accomplish. In some jurisdictions definitive action might require new legislation that codifies the relevant rights, interests, and obligations. More fundamentally, it is not always clear what the correct policy response should be. There is, in fact, little consensus in the academic community on many of the issues raised in the Lacks case (Master *et al.* 2012). These are complex legal and ethical matters, management of which will require consideration of multiple perspectives and balancing of divergent interests, including public rights and the desire for scientific progress. However, as the HeLa case highlights well, the current policy uncertainty serves only to create confusion and undermine public trust. A patchwork approach will do little to resolve the issue.

EXAMPLE RESPONSES IN POPULAR PRESS TO SEQUENCING OF HELA LINE

"One of the oddest things about this event was why it didn't occur to either scientists or reporters to consider whether some sort of permission was required to publish the HeLa genome" (**Powledge 2013**).

"Much controversy and debate was provoked last week after it emerged that the genome of the HeLa cancer cell line had been sequenced and published online by researchers without having obtained consent to do so" (**Leese 2013**).

"The publication of the HeLa genome without consent isn't an example of a few researchers making a mistake. The whole system allowed it" (**Skloot 2013**).

"The Lacks family was in fact outraged. 'That is private family information,' said Jeri Lacks-Whye, Henrietta's granddaughter. 'It shouldn't have been published without our consent'" (**Entine 2013**).

"The cells have been genetically sequenced once again without consent" (**Npr 2013**).

"A widespread outcry arose, demanding more respect for the human subjects from whom cell lines are derived" (**Ball 2013**).

"This new chapter of the story is more troublesome to many than was the book, it seems, presumably because it's much less ambiguous. Everyone now seems to agree that this personal genetic information, that the family hadn't even asked to know themselves, shouldn't have been made public without their consent " (**Buchanan 2013**).

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