Biospecimens, Research Consent, and Distinguishing Cell Line Research

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Abstract

Newly revised regulations for human research affecting translational oncology will become effective in January 2019. A substantial component of the debate leading to this revision was how to regulate biospecimen research; specifically, whether all biospecimens should be considered inherently “identifiable,” thereby necessitating informed consent for use in research. The famous cases seminal to this discussion involve cancer cell lines, but the unique features of this kind of biospecimen research were largely missing from the regulatory deliberation. However, special aspects of cell line research—at the stages of procurement, generation, evolution, and sharing—alter how society should balance participant interests against the goals of research. Recommendations are offered to cancer researchers and policymakers going forward to enable ethically appropriate regulation of biospecimen research across its diverse spectrum.

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Introduction

During the past decade, the appropriate ethical and legal parameters of research using human biospecimens have been the subject of substantial debate and regulatory revision, culminating in revised regulations that became effective in January 2019.¹ The famous cases seminal to this ongoing discussion involved cancer cell lines specifically—although, ironically, the unique features of research involving this kind of biospecimen have been largely missing from the deliberation about the regulatory revision.² Cell lines are a population of potentially immortal cells typically harvested from a tumor that can continue to divide indefinitely, providing an invaluable resource for biomedical discovery. Particularly given the importance of the concept of “identifiability” in the regulations, cell lines are distinct from traditional fixed specimens in ways that might lead to unintended consequences for current science policy. Failure to give due attention to these differences in applicable regulatory approaches has the potential to profoundly disrupt critical areas of cancer research.

US Regulation of Human Biospecimen Research

Regulatory standards for federally funded research with biospecimens collected for another purpose (ie, secondary research) are determined by the identifiability of the specimen.² If the researcher can readily trace a biospecimen to the patient or participant (“contributor”) from whom it was derived, Common Rule regulations categorize the work as human research. These regulations, in turn, require either contributor consent for the research use or an Institutional Review Board waiver of consent, unless some exemption applies. In contrast, if the research specimens are not identifiable, the regulations do not apply.²

Since adoption of the Common Rule in the early 1990s, concerns for the property, privacy, and autonomy interests of biospecimen contributors (as well as their blood relatives) have evolved alongside more sophisticated research techniques. Proposed regulatory revisions challenged the model of treating identifiability as the deciding factor for determining whether consent is needed for secondary research using biospecimens.³ Regulators proposed that the rules apply to research with all human biospecimens, regardless of identifiability—a change that would have dramatically affected cancer research. These revisions were debated for nearly 6 years, from an advance notice of proposed rulemaking in 2011 to promulgation of a final rule in 2017, and received thousands of public comments.^{4,5}

The final revised rule abandoned the proposal to treat all human biospecimens as inherently identifiable (and therefore subject to regulation). Ultimately, as discussed below, regulators argued that concerns regarding contributor property, privacy, and autonomy interests (which had been advanced in favor of treating all specimens as identifiable) were outweighed by arguments regarding public beneficence and justice. Research and patient advocacy communities argued that requiring informed consent for secondary research with deidentified specimens would substantially hinder scientific advancement and thus diminish the public benefit of the work.⁶ Regulators agreed, but added additional protections for contributors, including a requirement for additional disclosures regarding how biospecimens

left over after primary research may be used in future studies, as well as a new option for “broad” consent to future research with identified biospecimens.² More important, however, the revised rule maintains the status quo that secondary research with biospecimens that are not readily identifiable remains outside the purview of the Common Rule.

Although the final rule retains identifiability as the threshold for invocation of regulatory protections, it does not permanently settle the question of identifiability. Going forward, the regulations also mandate that “appropriate experts (including experts in data matching and re-identification)”^{2(p7260)} reexamine the definition of identifiability, and may “alter the interpretation of these terms”^{2(p7260)} via guidance (a process less stringent than updating regulations and without the same required opportunity for public comment). Thus, a biospecimen that is presently deemed nonidentifiable could be recategorized as identifiable, and thus regulated, in the future.⁷ This continued uncertainty and any future shifts in interpretation will have important implications for biospecimen and cancer research.

Cell Lines That Started the Controversy: Lacks and Moore

This national debate about research with human biospecimens was inspired by several cases, but 2 of the most important involve cancer cell lines. Rebecca Skloot’s bestselling book, *The Immortal Life of Henrietta Lacks*,⁸ tells the story of Henrietta Lacks, a young African American woman who received treatment at Johns Hopkins Medical Center in the 1950s for cervical cancer. Cells collected from a biopsy of her tumor were cultured without her knowledge or permission, in the hopes of generating a self-perpetuating cell line that would live ex vivo. Lacks’s experience was typical at the time, but her cells were not: they generated the most valuable cell line in history (known as “HeLa”) and were the foundation of major breakthroughs in cancer research and therapy.

Forty years after Lacks, John Moore presented with hairy-cell leukemia to the University of California, Los Angeles. After Moore underwent successful treatment, his physician continued to ask him to provide additional specimens.⁹ Moore believed that these follow-up collections were clinically indicated, but the physicians were actually collecting his specimens to develop a financially and biomedically valuable cell line.⁹ The Supreme Court of California, when reviewing Moore’s resulting lawsuit, argued that recognizing a property interest for Moore in his specimens “threaten[ed] to destroy the economic incentive to conduct important medical research.”^{10(pincite 146)} The court argued that a physician’s duty of informed consent was enough to protect patients from having their tissue unwittingly harvested for research (although it acknowledged that, for Moore, this standard had not been met).

Public response to the debate over biospecimen research has been varied. From an ethics perspective, some argue that research use of even deidentified specimens without consent unacceptably constrains contributors’ autonomy interests.^{11,12} Others maintain that it is unnecessary to give contributors control over their biospecimens, given the lack of individual risk and substantial public beneficence and justice interests in research.² Although stripping identifying information from biospecimens for secondary research avoids regulatory hurdles under the current system, several problems remain. First, because many

patients believe that they should control the use of all materials derived from their bodies, proceeding with research using deidentified biospecimens without consent might lead to distrust in the research enterprise. Second, research with identified specimens has scientific advantages, including enabling the collection and use of clinical correlates after the time of procurement, rendering deidentification an inferior approach. Last, as regulators reconsider the meaning of identifiability, it is possible that many, if not all, biospecimens will eventually be considered identifiable.

These problems apply to all biospecimen research, but different types of specimens invoke unique ethical, practical, and regulatory nuances. Other renewable patient-derived research methods (eg, organoid models, tissue microarrays, and tumor-derived xenografts) have related issues.¹³ This commentary will focus on cell lines as an example of this inherently diverse area of work and the complexity of science policy and regulation across such a spectrum.

Why Cell Lines Are Different

Cell line research is unique in many ways across different stages of research, including procurement of the biological material, generation of the cell line, evolution of the cell line, and sharing the material with other researchers. We highlight the most important of these differences across the cell line life cycle.

For research involving fixed or frozen tissue collected in the clinic, a patient can potentially be approached at a later time to seek consent for use of the tissue in research. Creating a cell line, by contrast, requires transformation of the specimen typically while it is still fresh, generally within hours of procurement. Cell line generation is research in and of itself (ie, not for clinical purposes). If researchers are to practically obtain consent, it must happen before the patient undergoes surgery to allow for immediate harvesting. Therefore, informed consent procedures for clinical and cell line research are often performed in tandem. However, at the bedside, patients are likely to be distracted by more immediate and physical risks of the (likely invasive) procedure they are about to undergo, resulting in a potential deemphasis of questions and concerns regarding the research.¹⁴

After procurement of the specimen, the generation of a cell line is an expensive and time-consuming process. Researchers must create their own scientific medium and not all attempts are successful.^{15,16} Although many disease-related cell lines have now been developed, there is also a need to continually generate new models that are responsive to changes in cancer epidemiology and demographics. In addition, researchers might face challenges gathering enough specimens related to a rare disease or a genetic subset of a common disease to enable their work. Thus, compared with other types of biospecimens used for research, the creation and characterization of cell lines requires a greater commitment of time, money, and expertise. As the court argued in *Moore v Regents*, this commitment makes clarity of property interests particularly important, as “companies are unlikely to invest heavily in developing, manufacturing, or marketing a product when uncertainty about clear title exists.”¹⁰(pincite 143)

Once derived, cell lines are dynamic and evolve uniquely from the original biospecimen. Many are grown without supporting cells from the tumor microenvironment. These cells remain mitotically active and “alive,” distinct from fixed or frozen “dead” tissue. Intentional genetic manipulation of the cell line is common, as is phenotypic drift and inadvertent contamination¹⁶ (the HeLa cell line has been especially implicated in the contamination of other cultures⁹). Genetic alterations in cancer cell lines can also include those that would otherwise monitor and repair DNA damage, increasing the risk of unintentional mutation. However, how this genetic drift affects the identifiability of research cell lines remains a matter of debate as the science evolves.¹⁵

A last area of difference is how cell lines are shared with other researchers. The examples of Moore and Lacks focused on property interests and considerations of justice as they related to another person benefiting from a contributor’s specimen. In these cases, researchers did in fact benefit, either directly or indirectly, from work on the cell line. However, modern cell lines are often provided liberally to other researchers. Cell lines are complicated to generate and expensive to characterize, but, once created, they become a renewable resource (unlike other types of biospecimens that have a set and limited use). The cost, both financial and in terms of effort, of growing a new batch of cells to share from a cell line is minimal in relation to the value that might come from additional research. Likewise, it is important to maintain rigor in the scientific community by replicating and advancing work from multiple independent laboratories using the same models. As a result, cell lines with a more robust record of experimentation are even more important to the field than are cell lines that are newly generated. Thus, distributions of cell lines are typically reimbursed at a nominal monetary cost, rather than for significant profit.^{10,17} Although this sharing is sometimes with private industry, a public model is typical of the field. These unique properties of cell line research—the procurement, generation, evolution, and sharing of cell lines—have implications for evaluating contributors’ interest in their biospecimens from both ethical and legal perspectives (Table 1).

Contributor Interests in Cell Line Research

Cases such as those of Moore and Lacks have raised the question of whether contributors should have property interests in their specimens as a function of those specimens being procured from their bodies. As Skloot notes: “someone is taking part of you. And people often have a strong sense of ownership when it comes to their bodies. Even tiny scraps of it. Especially when they hear that someone else might be making money....”¹⁸

Courts and federal regulators have thus far rejected recognizing a contributor property interest in the case of “abandoned” and deidentified specimens, as described in the case of Moore, but cell lines raise distinct challenges that underscore the importance of clarity. Under a labor theory of property, if a person takes something from its natural state and improves on it by mixing it with labor, “it hath...something annexed to it, that excludes the common right” of others.¹⁹ In other words, when something is rendered more valuable by the addition of someone’s effort, that person has a reasonable claim to increased rights in the thing. Cell lines have more value for research because of the intensive labor and improvement added to develop the lines to the point at which they will reliably reproduce

indefinitely. This scenario is different from that of traditional biospecimens in their unrefined state, which require little effort on the part of researchers to procure and maintain. This difference is important because, even if contributors can be viewed as having some property interest in their biospecimen, when researcher labor is added to develop a cell line, the contributor's interest becomes at least shared with the interest held by researchers. In fact, the researchers may even have a superior interest based on their labor (an argument also recognized in patent law¹⁰).

Consider 2 examples: Neighbor A places a slab of marble in the trash on the sidewalk in front of his house. Neighbor B picks it up and uses it to cover an unsightly patch in her garden. Neighbor A later changes his mind and asks that the marble be returned. If Neighbor B returns the marble, she will lose the item and be no worse off than she was before (although she does not necessarily have any obligation to return the marble, if it had truly been discarded by Neighbor A). In a second case, Neighbor C retrieves the marble from the sidewalk and sculpts a figure to be placed in a museum for the enjoyment of the community. If Neighbor C is asked to return the marble, she and the community would both be worse off, as she would lose the value of her labor and the augmented value of the marble as it now exists in sculptural form, and the community would lose the enjoyment of the art.

Now, imagine that biospecimens left over after other clinical or research uses are the marble in the above example. Traditional specimens are like the marble placed in the garden, but cell lines are the marble sculpture: their value is owing to the intensive improvement added by others, including the researchers who originally generated the cell line as well as those who continue to define additional characteristics of the model (eg, genetic status or response to specific therapy) and validate its use. Therefore, even if contributors had a compelling interest in the biospecimen at the start, researchers have a mixed-labor justice argument to defend an overriding interest in the derived cell line.

This distinction is critical from a legal standpoint because, generally, identified participants in research who provide consent have the right to withdraw from that research. The US Food and Drug Administration released guidance in 2008 stating that this right does not extend to identified data—participants may discontinue participation in further generation of data, but they cannot withdraw data that have already been collected.²⁰ The guidance does not expressly extend that limitation on the right to withdraw to biospecimens; however, similar reasoning ought to apply. Therefore, whether participants have a right to withdraw their identified biospecimens from research remains an open legal question. This question can currently be avoided for research with deidentified biospecimens,²¹ but if all biospecimen research were to be deemed identifiable—as it may still be—whether the right to withdraw applies to biospecimens will become critical for regulators to resolve. Given the absence of an explicit exclusion of identifiable biospecimens from the right to withdraw, it appears that participants at present may retain that right (ie, to “take back their marble”), with potentially serious implications for research.¹³ Regulators should recognize the labor that has been mixed with specimens to create cell lines and preclude withdrawal in these cases, as they have for data.

There are also other ways in which the interests of contributor autonomy may be distinct for cell line research. As Skloot¹⁸ points out, and has been empirically validated, some contributors are particularly concerned about the commercialization of their specimens.^{22,23} However, given the magnanimous culture among researchers of sharing cell lines, exchange for profit is not common in cell line research. Contributors may also wish to preclude use of their biospecimens in research they disagree with on “moral, religious, or cultural grounds” (ie, “nonwelfare” interests).^{11(p1)} But, again, the level of dynamism and manipulation of cell lines is unmatched by more traditional biospecimen research, moving the research model even further from the specimen contributor and diminishing claims based on autonomy.

A third type of contributor concern comes from the privacy implications of research with biospecimens, even those that are considered deidentified.²³ Because cell lines will always harbor DNA linked to the parent tumor, there will always be a risk of misuse and reidentification. However, as described above, because of phenotypic drift, as well as intentional or accidental contamination, this risk is less likely for work with cell lines. Thus, privacy-based arguments for contributor control of biospecimens in the context of cell line research are less compelling.

In summary, contributor property, autonomy, and privacy interests are each weaker in the context of cell line research than in other types of biospecimen work based on the way in which cell lines are generated, evolve, and are shared (Table 2). In addition, to the extent that these interests exist for cell line research, typical mitigating approaches, such as disclosing relevant information during the process of procuring informed consent, are likely to be less useful given the existing challenges of achieving concurrent research and clinical consent. Therefore, when balancing contributors’ interests against the goals of research in this space, we should acknowledge that both the property and privacy interests of contributors are less compelling, and the public beneficence and justice interests of future patients and researchers are likewise heightened.

The Future of Biospecimen Regulation

In 2017, regulators ultimately concluded that requiring informed consent for secondary research with deidentified biospecimens would unacceptably “allow autonomy to trump beneficence and justice.”^{2(p7165)} Nonetheless, the mandated future expert panel reexamination of the concept of identifiability, and its effect on the scope of the regulations regarding human research, may fundamentally undermine the present compromise.⁷ Owing to critical differences in the way we procure, generate, evolve, and share cell lines (and the unique implications those differences have on contributor interests), redefining identifiability to include all biospecimen research is likely to have more serious public beneficence and justice implications for cell lines (and other types of nontraditional specimens) than other types of biospecimens. Thus, the lack of nuance in defining regulations related to specific classes of biospecimens may unintentionally impede the rate of research progress and drive up costs associated with specific biospecimens, such as cell lines, requiring continual generation and characterization of models.

In addition, while the recent regulatory debate focused in large part on contributor autonomy and other interests balanced against public beneficence and justice, the future expert panel assessment of identifiability appears to focus exclusively on the technological capacity for identification. Given technological indeterminacy and individual contributor preference, however, identifiability should not be considered a binary concept. Guidance regarding deidentification under the Privacy Rule of the Health Insurance Portability and Accountability Act acknowledges that, even for technically deidentified data, some risk of reidentification will always remain.²⁴ How much risk is acceptable is ultimately a policy question that requires ethical analysis. The future advisory committee should therefore not allow the technical aspects of the concept of identifiability to eclipse policy considerations, as the term itself requires a balancing of both. Given the policy-oriented nature of the decision, a notice-and-comment process open to the public—rather than the proposed expert guidance approach—is all the more important.

With these distinctions in mind, we argue that as regulators take on their charge to reassess the concept of identifiability, they also ensure that:

1. Expertise in ethics and health policy is represented on future panels reconsidering the concept of identifiability to advise on the critical balance between autonomy, public beneficence, and justice inherent to the definition of the concept;
2. Future expert panels approach the definition of identifiability with the understanding that the creation and use of biospecimens in research is not methodologically homogenous, as the potential for identifiability and its implications vary along with different types of specimens and require nuance; and
3. If, in the future, such an expert committee labels all biospecimens as inherently identifiable, additional guidance will be provided regarding how the unique properties of different types of biospecimen research will be reconciled with the default standards applicable to other types of human research (eg, the right of withdrawal).

After 6 years of debate, the ultimate disposition of research with deidentified specimens has yet to be settled. However, the ethical component of this analysis, between the property and privacy interests of contributors and the public beneficence and justice interests of future patients who might benefit, remains critical. Evolving governance models must reflect the diversity of the many variants of biospecimens and empower research by anticipating unintended consequences of additional regulations. Continued deliberation and analysis is necessary for the benefit of both life-saving research and the contributors that enable it.

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Table 1.**Differences Between Cell Line Research and Fixed Biospecimen Research**

Fixed Biospecimens	Cell Lines
Procurement	
Consent can be requested at a later time for banked specimens	Consent should be requested prior to generation
Generation	
Immediately capable of supporting research	Must be created before research can begin
Evolution	
Fixed or frozen	Mitotically active and “alive”
Sharing	
Finite and may be commercialized	Renewable and replenishable, often shared at cost

Table 2.

Contributor Interests in Cell Line Research vs Fixed Biospecimen Research

Fixed Biospecimens	Cell Lines
Property and Related Autonomy Interests	
Researchers using biospecimen taken directly from contributor	Researchers must create the medium with which they work
People have moral, religious, or cultural concerns in the use of biospecimens	Higher level of dynamism and manipulation
Privacy	
Possible (although rare) to reidentify via genetic sequencing	Risk of reidentification lower