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For Whom the Cell Tolls—The Ethics of Human-Derived Cell Lines

Introduction/Background

Do your cells actually belong to you? Think again. Cell lines—cultures of infinitely-replicating cells of one uniform type—are crucial for replicable scientific research. Bioengineers use these cells to produce medicine, study genes, and test drug safety. The ideal cell line will both mimic the human cellular environment and replicate indefinitely, but this is rarely the case. Instead, scientists must weigh the issues with using non-human mammalian cells and artificially-immortalized cells as proxies for human cells. The gold standard is human cancer cells, both human and immortal; however, the backlash from collecting and profiting from these cells threatens to destroy the entire industry itself. Henrietta Lacks in 1951 and John Moore in 1990 represent two landmark cases of cell lines derived from patient tumors, prompting billions of dollars in lawsuits. The two main ethical questions concern whether the patient is entitled to consent and royalties. Using Ibram X. Kendi's framework of antiracism, each point of contention should be rejected. Patients should not be entitled to informed consent if researchers obtain their tumor cells from storage, because the benefits to humanity from a cell line outweigh the harm to the patient from the unknowing usage of their cells. Patients should also not be entitled to royalties, since royalties serve to encourage innovation, which does not apply to cancerous mutations.

The Technology

Cell lines are incredibly diverse in terms of source, usage, and customization. One collection has recorded over 3,600 cell lines sourced from over 150 different species (Kaur 2012). Two traits of any ideal cell line are similarity to human cells and longevity, and researchers strive for these goals by using the cells of other mammals and genetically modifying them to reproduce forever. Chinese hamster ovary (CHO) cells represent a classic mammalian cell line to produce proteins in an environment that mimics the human cell while avoiding the ethical challenges of using human cells directly. Mammalian cells can be engineered to produce drugs, but they attach their own sugar molecules to the final product (Dumont 2016). CHO cells can make insulin, but they will modify the product in a different way than our body's insulin. The human body may not recognize an insulin molecule produced by a CHO cell, triggering an immune response (Dumont 2016). Non-human cells will also not respond to toxins or metabolize drugs precisely the same as human cells.

Ignoring the problems with mammalian cells, researchers cannot simply take a skin cell from an animal and grow it in a lab forever. Every time a cell replicates, it loses a small portion of DNA at both ends of each strand. These end regions, called telomeres, are not necessary for cells to function. However, when the telomeres are depleted, and the important coding DNA suffers damage, the cells stop replicating (Wronski 2015). Scientists engineer cell lines to indefinitely reproduce with two main methods: turn off tumor suppressor genes, which prevent

cells from shutting down replication, or turn on telomerase genes, which produce a protein that restores telomeres after each replication (Wronski 2015). However, these genetic modifications make the cell increasingly more different from the human cells that they intend to mimic. The gene edits are also often applied unpredictably or unequally to the cell population (Wronski 2015). Between issues with non-human and artificially edited lines, the gold standard is naturally-occurring cancer cells from humans. However, using human cancer cells has raised a storm of retaliation from patients who demand informed consent and royalties to use parts of their own body.

Ethical and Societal Issues

Two cases epitomize the ethical dilemmas arising from the use of naturally-occurring human tumor cells to engineer commercial cell lines, each case sparking debates over patient consent, compensation, and confidentiality. The epicenter of the issue lies in the case of Henrietta Lacks. In 1951, Lacks succumbed to cervical cancer in Baltimore. Her doctors later discovered that her cancer cells held the necessary genetic mutations to replicate endlessly in lab conditions. They named them HeLa cells and rapidly shared them with biobanks around the country. It is difficult to overstate the impact of the Lacks case on the ethical debate. A best-seller outlining the issue, *The Immortal Life of Henrietta Lacks*, has sold over 2.5 million copies since 2018 and occupies the reading programs of over 250 communities and educational institutions (Michel 2018). The vast majority of informed people believe that the non-consensual usage of her cells, while legal at the time, violated her ethics. Furthermore, an informal poll found that nearly two thirds of people believe that companies that use HeLa cells for profitable discoveries owe her family reimbursement (Gibney 2023). Naming the cells after Lacks clearly violated her privacy and would now be illegal. While the issue of naming the cells after Lacks is uncontroversial, the debate over the anonymity of cells in large-scale biobanks and genetic databases is ongoing. For example, Henry T. Greely, chair of the Steering Committee of the Center for Biomedical Ethics at Stanford, argues that biobanks must create novel methods of informed consent to ethically obtain cells from patients without violating their privacy (Greely 2007). A patient's genetic data can reveal sensitive information about their health and identity, so researchers must avoid leaking this information into the wrong hands.

A similar case occurred in the latter half of the twentieth century. In 1976, John Moore visited the UCLA Medical Center seeking treatment for leukemia (Nott 2020). He consented to a surgery to remove his spleen. However, researchers David Golde and Shirley Quan noticed a potentially useful property of his cancer cells to overproduce a certain immune system protein (Nott 2020). Without Moore's knowledge, they established a cell line from his tumor, secured a patent, and struck deals with pharmaceutical companies (Nott 2020). They also ignored Moore's privacy when they named it the Mo cell line (Nott 2020). When Moore discovered his doctors' actions, he sued the University of California. More recently, the estate of Henrietta Lacks also filed a lawsuit against Thermo Fisher Scientific, a biomedical research giant. Both lawsuits highlight the conflict between patient rights and scientific progress. While they ignored the issue

of patient privacy, both lawsuits attempted to completely overturn current practices on informed consent and royalties.

Previously-Proposed Solutions

Given the ethical quagmire of these cell lines, an alternative source for cell lines appears attractive. The two primary alternatives are non-human mammalian cells and normal human cells that are engineered to replicate in perpetuity. Both bring their own ethical debates. Developing non-human mammalian cell lines, such as CHO cells, does not involve humans, but does require scientists to hold unwilling mammals in captivity, potentially induce tumors in them, and harvest the cells without providing medical care at a human standard. Engineering perpetual human cell lines from non-tumor cells would elicit the same ethical concerns of consent, ownership, privacy, and royalties as simply developing a cell line from human cancer cells. These two alternatives to human cancer cells do not sidestep ethical debate. Furthermore, the fact that biotechnology companies overwhelmingly prefer to use HeLa and similar human cell lines in spite of lawsuits demonstrates the sheer scientific superiority of human cancer-derived cell lines over these alternatives. Because the two other options are inferior scientifically and equivalent in ethical controversy, they cannot adequately replace cells derived from human tumors, such as those of Lacks or Moore.

Henrietta Lacks and other cases have sparked a wide range of federal protections for patients known as the Common Rule. The regulations require both informed consent and approval from an institutional review board when obtaining data from human subjects (Beskow 2016). Most sources, including Lacks's own hospital Johns Hopkins, believe that these new laws would have prevented Lacks's cells from being used as they were. However, Dr. Laura Beskow, Director of Research Ethics of the Vanderbilt Center for Biomedical Ethics & Society, points out that these new laws would still allow her case to transpire the same, only with a different name for the cell line (Beskow 2016).

The crucial details lie in how and why the doctor collects the cells. The Common Rule protects "human subjects," which the Office for Human Research Protections defines as "a living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual" (OHRP 2019). The law protects patients if doctors directly collect cells from them for research purposes. The law does not protect patients if doctors collect their cells from storage, since the doctors do not interact with a human subject. Beskow observes that in Lacks's case, the doctors saved her pancreatic cancer cells for clinical purposes, and from there researchers could use the cells as they wish (Beskow 2016). Therefore, current laws are insufficient to require informed consent in cases like that of Henrietta Lacks.

In 1984, after a chain of suspicious forms and surgeries, John Moore had enough. He sued the University of California, the researchers, and the involved pharmaceutical companies, claiming that he was owed informed consent and a portion of the profits made from the cells (Nott 2020). Judges initially dismissed the case, but the California Court of Appeal reversed the

decision, ruling that Moore had some level of property rights over his own tissue (Nott 2020). The Supreme Court of California then reversed this shocking reversal. The justices ruled that, while Golde and Quan did not adequately inform Moore of their intentions to harvest his cells for commercial purposes, Moore had no claim on the cell line (Nott 2020). The opinion likened his tissue to a donated organ and cited the dampening effect that more extensive informed consent requirements would cast on medical research (Nott 2020). When faced with an ethical decision between explicit and frequent consent and unhampered medical research, California chose to put the science first.

The recent lawsuit against Thermo Fisher Scientific on behalf of the Lacks estate signals a stark shift away from this priority. Citing the history of mistreatment of minorities by the medical system and the struggle of Henrietta Lacks's descendants, the estate asked for the entire profit that the company has obtained using HeLa cells—billions of dollars (Chen 2021). Lawyer Ben Crump conjures images of slavery, arguing that "Thermo Fisher Scientific treats Henrietta Lacks' living cells as chattel to be bought and sold" (Chen 2021). The suit also demands Thermo Fisher request permission from the family to use the cells in the future (Chen 2021). Crump's appeal to history and comprehensive demands display a staunch preference for the ethics of the patient, regardless of the law at any point in time. Thermo Fisher Scientific reached an undisclosed settlement with the family, a surprising victory given Moore's defeat and the suit's ambitious demands (Falconer 2023). A week after the settlement, the family launched another similar lawsuit against biotechnology firm Ultragenyx Pharmaceuticals (Falconer 2023). Crump believes that their mere usage of the cells represents not just a moral injustice, but "concrete harm" on the Lacks family (Falconer 2023). If the Lacks family and Crump continue to succeed, their suits may foretell a profound reversal in the ethical viewpoint of the public and lawmakers in favor of patients. Curiously, the lawyer does not emphasize the violation of privacy caused by the proliferation of Lacks's DNA, indicating that privacy is not as great an ethical concern compared to informed and possibly continuous consent and financial compensation. Their current lawsuit is proceeding at this very moment.

Recommendations

Resolving the ethical and legal issues surrounding cell line development is critical to both patients and biotechnology firms. Hospitals must implement a clear set of guidelines that clearly inform patients of the rules, with the goals of patient understanding, legal harmony, and unimpeded scientific research. Furthermore, as Lacks estate lawyer Ben Crump evinces, the issue of patient consent and ownership is inextricable from the issue of racism and medicine, so a solution must include the perspective of Black patients.

To address the needs of Black patients, society should adopt the consequentialist framework of antiracism scholar Ibram X. Kendi. In *How to be an Antiracist*, Kendi defines a racist policy as "any measure that produces or sustains racial inequity between racial groups" (Kendi 2019). He expands on the definition of policy to include "written and unwritten laws, rules, procedures, processes, regulations, and guidelines that govern people" (Kendi 2019). By

Kendi's definitions, any process from a codified law to a common habit falls under the purview of racist or antiracist policy. Furthermore, we should not evaluate a policy on its intention or supporters, but purely on its effect on racial inequity. Using this perspective, patients should not be entitled to higher standards of informed consent beyond the Common Rule, and that patients should not be entitled to royalties from commercialized cell lines derived from their cells.

Researchers should not be required to ask patients for informed consent if they use their cells from storage. We already abide by this value when requiring newborns, students, and soldiers to be vaccinated, valuing common health over individual choice. Ben Crump's alleged "concrete harm" inflicted on patients is challenging to identify. Lacks, Moore, and any other patient in their shoes does not lose anything in their possession nor anything valuable to them when researchers utilize their cells from storage. On the other hand, the benefits reaped from the resulting research are immeasurable. HeLa cells alone have appeared in over 110,000 scientific publications and have contributed to three Nobel Prizes (NIH 2022). A standard of all-encompassing informed consent has undoubtedly noble intentions, but would spell disaster for nearly everyone, especially Black patients. Many diseases disproportionately afflict Black patients: sickle-cell anemia, HIV/AIDS, COVID-19, and more. HeLa cells provided crucial breakthroughs for every one of these examples. Scientists studied a now-approved anti-sickle-cell drug Hydroxyurea on HeLa cells (NIH 2022). Doctors used a unique resistance of HeLa cells to HIV/AIDS to discover a critical cell surface receptor that the virus uses to enter human cells (NIH 2022). Others later discovered a similar receptor used by COVID-19 (Jackson 2020). One Nobel Prize was awarded to Dr. Harald Zur Hausen for identifying a viral source for and potential vaccine for cervical cancer, precisely the type of cancer that afflicted Henrietta Lacks (NIH 2022). To require repeated, informed, and comprehensive approval to use HeLa cells—which Moore failed to achieve, but the Lacks estate currently is proposing—would without question hamstring research into these diseases and exacerbate the gap in health outcomes between Black and White patients. One individual or family should not possess the power to invalidate one hundred thousand scientific papers. Such a policy must be rejected from an antiracist perspective. On the contrary, our hospitals should affirm the Common Rule and be emboldened and encouraged to harness the life-saving potential of cells collected in hospital biobanks.

My recommendation against royalties for patients like Moore and Lacks is similar. Such royalties would stymie medical research, leading to worse health outcomes for all groups, especially Black patients. Royalties and profits for inventions exist to encourage researchers and companies to innovate at the pursuit of wealth. However, a patient cannot be encouraged to mutate the next breakthrough cell line with royalties, so the royalties do not serve their purpose. While Moore sued for a portion of the profits derived from his cell line, the Lacks estate has asked Thermo Fisher for 100% of the net profits incurred from HeLa cells. A company can still innovate while returning a portion of the profits to the progenitor of the cells. However, if a company cannot make any profit, then it has no reason to use the cells to develop therapeutics, leaving any life-saving discoveries unexplored. If we adopt the ethical standards toward royalties

for human-derived cell lines that the Lacks family and Crump propose, the vast majority of research on these cell lines would halt. Since these cell lines uncover numerous medical advancements against diseases that disproportionately harm Black patients, a royalty system would counteract progress in closing the racial health outcome gap.

These cell lines are a miracle of bioengineering. What else do you call the feat of turning cancer—a death sentence—into an avatar of ourselves? Cell cultures are more profound than test dummies for toxins or factories for medicines. They represent the very essence of our biological selves that will long outlive their progenitor. The alternatives—Chinese hamster ovary cells mutated to replicate indefinitely—can hardly compete with the real thing in predicting the human body's response to new molecules. Still, is the benefit worth this ethical maelstrom that could topple the pharmaceutical research industry? Do the Baltimore doctors that treated Lacks deserve to be recast as villains? These cell lines transcend the ownership of the individual who randomly mutated them and should be recognized as the human good that they are.

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