Immortal Cells, Enduring Issues

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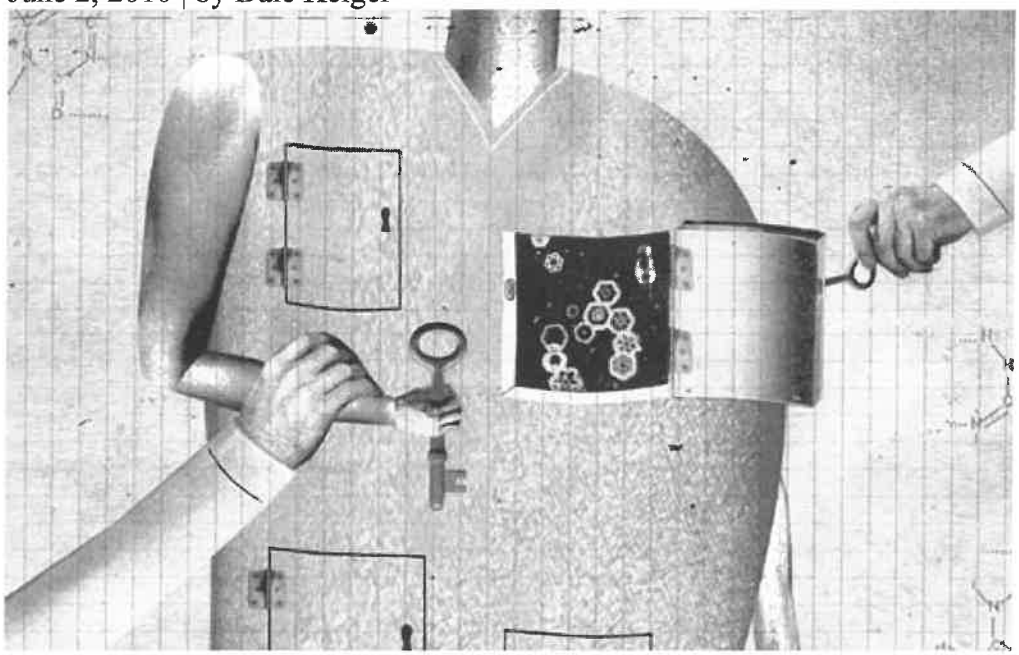
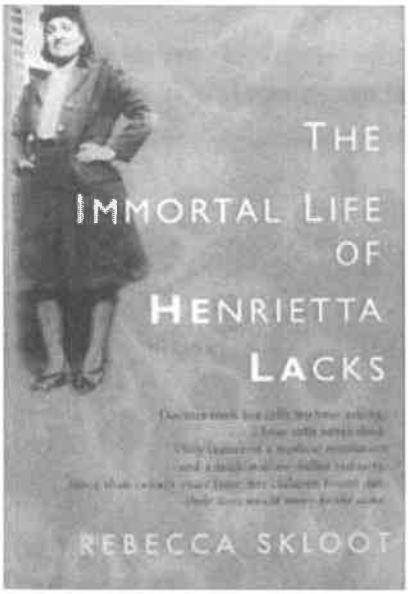


Illustration by David Plunkert

A young lab assistant attended an autopsy at the Johns Hopkins Hospital morgue on October 4, 1951. The assistant was Mary Kubicek. The autopsy was of a woman who had died at 31 from the metastasized cervical cancer that had so ravaged her there was scarcely an organ in her body not riddled with malignancies. Kubicek had never seen a corpse before and tried to avert her gaze from the face to the hands and feet. That's when she was startled by the deceased woman's chipped red toenail polish. Kubicek later told writer Rebecca Skloot, "When I saw those toenails, I nearly fainted. I thought, 'Oh jeez, she's a real person.'"

The real person was Henrietta Lacks. Much of the American public knows at least the outline of her story since publication of Skloot's best-selling book *The Immortal Life of Henrietta Lacks*. When Lacks came to Hopkins for treatment of her cancer, a surgeon sliced away small samples of the malignancy and Lacks' healthy cervical tissue for George Gey, the director of tissue culture research at Hopkins. By 1951, Gey was nearly 30 years into a quest to culture "immortal" cell lines: human cells that would reproduce endlessly in test tubes to provide a steady supply of cells for medical research. Gey had experienced little but failure when a Hopkins resident dropped off the pieces of Henrietta's tissue. Soon after the malignant cells, labeled "HeLa," were placed in culture medium by Kubicek, who was Gey's lab assistant, they began to reproduce, doubling within 24 hours. They have never stopped. They now live by the uncountable trillions in laboratories and the inventories of biologics companies throughout the world, still robust after 60 years and perfect for all sorts of research. The HeLa cell line has been the foundation of a remarkable number of medical advances, including the polio vaccine, the cancer drug tamoxifen, chemotherapy, gene mapping, in vitro fertilization, and treatments for influenza, leukemia, and Parkinson's disease.



The Immortal Life of Henrietta Lacks by Rebecca Skloot

Though the science and history in Skloot's book are fascinating, they are not what has made it a national best seller. What has resonated with readers are the interwoven narratives of Henrietta Lacks' sad life and her daughter Deborah's pursuit of knowledge about the mother she never knew. And there is one more thing. Text on the front cover of Skloot's book reads, "Doctors took her cells without asking." The inside flap continues, "Henrietta's family did not learn of her 'immortality' until more than 20 years after her death, when scientists investigating HeLa began using her husband and children in research without informed consent. And though the cells had launched a multimillion-dollar industry that sells human biological materials, her family never saw any of the profits." A significant segment of the public harbors a deeply rooted mistrust of medical research. They do not trust physicians and scientists to be open and honest with them. They fear that the privacy of their medical records will not be respected. They believe that someone somewhere is making a lot of money off of drugs and biological products that were developed using pieces of tissue from people who now are entitled to a piece of the profits. *The Immortal Life of Henrietta Lacks* speaks to that skepticism, and above all is the vivid testament of how the Lackses feel they've been treated by physicians, researchers, journalists, and corporations. The book will not reassure those already suspicious that they are being used. Skloot says, "The thing that I hear more than anything [from readers] is, 'We want to know what's going on. We don't want to feel like someone is doing something behind our backs.'" People want their individual humanity acknowledged and respected. Physicians and scientists and ethicists know this. They also know that doing the right thing, which can seem so straightforward to the public, gets more complicated all the time.

WHEN LACKS CAME TO Johns Hopkins complaining that she had "a knot" on her womb, she entered the "colored ward" in the only major hospital in Baltimore that would treat an African American. She received treatment that did not succeed but was state of the art in 1951.

Simultaneous with her care, researchers at Hopkins and elsewhere were searching for better ways to diagnose cervical cancer, which was killing 15,000 women per year. They wanted a method of growing cervical cancer cells in the lab. That dovetailed with George Gey's quest to create an immortal cell line. He received tissue samples from every cervical cancer patient who came through Hopkins' door, including Lacks. Skloot states in her book that no one asked Lacks for permission to take some of her tissue for Gey's research. Documentary evidence of what was said at her bedside is scant and can be taken either as supporting Skloot's assertion or arguing against any retrospective moral judgment. Joann Rodgers, senior adviser for science, crisis, and executive communications at the School of Medicine, says, "People I've talked to here have told me that physicians and scientists did talk to their patients if they wanted to take tissue, if they wanted to have them participate in research." But Skloot has seen the consent form for Lacks' treatment, and it does not include any mention of taking tissue for research. Howard Jones, who was Lacks' gynecologist at the hospital, told Skloot that he never sought consent for tissue samples. Present-day researchers at Hopkins acknowledge that in the 1950s, the very concept of

informed consent as it's now known was not on researchers' minds. Daniel Ford, vice dean for clinical investigation at the School of Medicine, observes, "In that era, researchers got a little carried away with science and sometimes forgot the patient, and physicians treated patients the same way clinically—it wasn't shared decision making." David Nichols, vice dean for education at the school, adds, "It was a relationship that was utterly imbalanced with respect to power and privilege. There's a lingering sense, even today, of this imbalance, which has deep historical roots."

Before a procedure at Hopkins, patients now sign a consent form that includes this clause: "Johns Hopkins may dispose of any tissues or parts that are removed during the procedure. Johns Hopkins may retain, preserve, or use these tissues or parts for internal teaching or other educational purposes without my permission, even if these tissues or parts identify me. However, Johns Hopkins may only use or disclose tissues or parts that identify me for research with my permission or with approval of a review board governed by federal laws protecting these activities. If the tissues or parts do not identify me, Johns Hopkins may use them for scientific (research) purposes without my permission or action by a review board."

Three things make consent a more complicated matter than simply reading a clause like that and initialing the form. First, in some cases a patient may be asked to provide a biospecimen—tissue, a DNA swab, a blood sample—for a specific research project that has been approved by an institutional review board (IRB) and that requires specific consent. More often, though, researchers accumulate biospecimens for future use in research that cannot be specified at the time of collection. In 1951, someone could have told Henrietta Lacks or her husband that they wanted cells from Henrietta's cervix to research a better means of diagnosing her cancer. They could not have told her that someday science would want her cells for research on the effects of zero gravity in outer space, or for the study of leukemia or lactose intolerance or longevity or the mating of mosquitoes, all of which has happened. Chi Van Dang, the School of Medicine's vice dean for research, points out that scientists can't possibly anticipate many types of future research. He says, "Do we have the trust of the public to say, 'Look, we have your cells. What we'll do with these cells, I can tell you to some extent now, but five or 10 years from now they could be used in a completely different way. With your permission, we need to have that flexibility.'" Scientists worry that stringent regulations requiring specific consent for any future uses of biospecimens could hamstring research.

But a recent court case demonstrates that Dang's hoped-for flexibility on the part of the public cannot be assumed. Arizona State University recently settled, for $700,000, a lawsuit brought by Havasupai Indians after they learned that blood samples donated for a study on diabetes among tribe members were also used for research on schizophrenia and inbreeding. The Havasupai hold sacred ancestral stories about their origins in the valley they still inhabit, and they were particularly offended to learn that their samples were used in research about the migration of ancient peoples from Asia. They had not been asked if their blood could be used for those additional purposes, and they sued. Joan Scott, director of Hopkins' Genetics and Public Policy Center in Washington, D.C., and a research scientist at the Berman Institute of Bioethics, says, "People see bits and parts of themselves as bits and parts of themselves, you know? We find that in the research we've done there really is a strong altruistic vein in the American public, in particular individuals who have diseases. That's their way of helping someone not go through the same things they did. [But] what they do expect is transparency and full disclosure about what's going to be

done with the sample." Skloot has interviewed plaintiffs in lawsuits over tissue research: "Over and over again they say, 'If they had just asked us, we'd have said yes.'"

The second thing that makes informed consent complicated is the "informed" part. Scientists making a conscientious effort to secure informed consent must wrestle with translating complex issues for a lay audience. A section of *The Immortal Life of Henrietta Lacks* describes Hopkins researchers, including renowned geneticist Victor McKusick, Med '46, taking blood samples from members of the Lacks family in 1976. McKusick and his assistant at the time, Susan Hsu, were searching for DNA markers that could identify HeLa cells in any lab sample. They could not recall for Skloot how well they had informed Deborah Lacks about why they wanted some of her blood. But years later Lacks told Skloot that she believed she had submitted to a test for cancer. Hsu recalled for Skloot giving David Lacks, Henrietta's husband, a technical explanation of why she wanted to draw blood, using terms like "HLA androgen [sic]," "genetic marker profile," and "genotype." David had a fourth-grade education. Did Hsu inform him, or baffle him? Says Skloot, "People get this stuff if you can explain it to them clearly. There is a science literacy problem, but there's a bigger problem with a lack of communication from the scientists. If you go to a hospital and you don't speak English, you're going to get a translator—French, Spanish, whatever. If you walk in and you don't speak science, they're not going to call in the science translator who says, 'Let me help explain this to you.'"

Finally, current consent regulations cover only studies done by researchers who have firsthand contact with tissue donors. If you are a scientist working with anonymized tissue samples taken from a repository, that is not considered research on a human subject and no informed consent is required.

Ruth Faden, director of the Berman Institute, raises one more ethical issue: when to ask for informed consent. Is it proper, when patients are about to undergo surgery and have to deal with consent for the operations, to present them with another set of decisions regarding what might be done with their tissues? Faden recently had surgery to repair her shoulder's rotator cuff; she notes that like anyone, she has a finite amount of emotional energy, and in this case wanted to apply it to thinking clearly about her impending procedure, not what might be done with some of "the gunk," as she puts it, that was cleaned out of her shoulder. Says Scott, "How much are people going to be paying attention? They're under stress from their condition, then you've got this other thing that you shove underneath their noses."

IN THE JANUARY 30, 1976, issue of Science, McKusick co-authored a paper, "Genetic Characteristics of the HeLa Cell." That paper published the analysis of the blood drawn from Deborah Lacks and others in her family and listed 43 genetic markers found in the Lackses' DNA. The paper identified Henrietta and listed family members as "Husband," "Child 1," and "Child 2." Your DNA reveals who you are in the most fundamental sense—your genetic abnormalities if you have any, your predisposition to certain diseases such as breast cancer, whether your parents are really your parents or your sister is really your sister. Today no ethical researcher would publish the sort of genetic information complete with identifiers that McKusick published in 1976.

The Immortal Life of Henrietta Lacks reports other examples of violations of the Lackses' privacy. For example, someone, presumably at Hopkins, gave Henrietta's medical records to journalist Michael Gold, who quoted from them in his 1985 book *A Conspiracy of Cells: One Woman's Immortal Legacy and the Medical Scandal It Caused.* According to Skloot, no one in the Lacks family had ever seen those records or given permission for their release. Gold included a stomach-churning description of Henrietta's autopsy. He later told Skloot that he recalled unsuccessful attempts to contact the family; she quotes him as telling her, "And to be honest, the family wasn't really my focus. . . . I just thought they might make some interesting color for the scientific story."

The privacy of medical information remains an ever-growing concern as biomedical research, both academic and commercial, has burgeoned. In 1999, RAND Corporation estimated, in a monograph titled *Handbook of Human Tissue Sources*, that 307.1 million human tissue samples were stored in various repositories throughout the United States. No doubt that number is significantly larger today. The term "biobank" has entered the lexicon. A biobank is a collection of human tissue, like a living database of human cells. National biobanks now exist in Estonia, Canada, Japan, Latvia, Singapore, Sweden, Iceland, and the United Kingdom. Biobanks have been created by disease advocacy groups, commercial research companies, and academic centers such as Howard University, which founded the National Human Genome Center to foster genomic research on African Americans and African diaspora populations. "Recently, there's a biobank on every corner," says Scott. "That may be a slight exaggeration, but not by much."

Geneticists are excited by the prospect of new research made possible by linking genetic samples in these biobanks to clinical information contained in digitized medical records. This raises new privacy concerns. Some laboratories and biobanks have procedures that strip the identifiers from specimens, so that no one knows from whom they came. But linking those samples to the information contained in medical records databases, while scientifically useful, may erode some of the privacy safeguards that depend on biospecimens being truly anonymized. Ford recalls a researcher in Arizona who did an experiment on a 1,000-person public biodatabase that included genetic and clinical data on each person. "It was said to be de-identified," Ford says—all identifiers stripped out. "That means it did not have to be approved by a review board and anybody could access it—detective, lawyer, whatever, OK?" The researcher took 50 entries selected at random and by cross-referencing the data with other public information was able to match a person's name to 47 out of 50.

Medical and genetic records have long lives. Henrietta Lacks' medical records were made public again as recently as September 2009 by the authors of an article that appeared in Archives of Pathology and Laboratory Medicine. One of those authors was Grover Hutchins, a professor of pathology at the School of Medicine.

AS GENETIC MEDICINE, genomic science, and bioengineering become bigger fields, they generate more opportunities for profit by commercial enterprises. The public understands that human biospecimens may be used by scientists purely for the advancement of knowledge and the development of new medical therapies, but they're also used by business to generate profits; through technology transfer, they have the potential to generate profits for universities as well. Few reviews of The Immortal Life of Henrietta Lacks or stories about its author have failed to mention that while Johns Hopkins has never sold, licensed, or patented HeLa cells, a number of commercial firms have sold them and continue to do so, and none of the

proceeds have ever gone to Henrietta's descendants. There seems to be no precise accounting of how much money has been made from HeLa; the near-meaningless figure of "multi-millions" has been in circulation since publication of Skloot's book. But the amount is assumed to be substantial. In the afterword, Skloot writes, "Today, tissue-supply companies range from small private businesses to huge corporations, like Ardais, which pays the Beth Israel Deaconess Medical Center, Duke University Medical Center, and many others an undisclosed amount of money for exclusive access to tissues collected from their patients." Meanwhile, the public asks: If a corporation used my tissue sample—a piece of my body—to develop a product that now generates profits, why am I not entitled to a share of those profits?

Ethicists speak of a "common good model" in which tissue donors are not compensated because they donated pieces of themselves not in the hope of a future payday but to further science that contributes to the common good. In this model, the payoff is not in dollars but in better medicine that someday might cure your disease or repair your injury. All well and good, but two factors complicate the situation. The first is articulated by Faden: "The hitch with this vision, which ethically has so much to commend it, is the suppressed moral premise that everyone will benefit from the advances that will result from this shared agreement to let our biospecimens be used for science," says Faden. "This vision of the shared public good presupposes that all of us really benefit, with the emphasis on all of us. So in the absence of guaranteed access to a decent level of medical care, the moral justification for that structure breaks down." She adds, "One of the really tragic dimensions of the Lacks story is the fact that her children still experience enormous difficulty getting access to decent medical care." Says Skloot, "The truth is, not everyone does benefit. The people who benefit are people with money. The people it doesn't help are people like the Lackses, people who do not have money, minorities. People who historically have been hurt most by research done without their consent tend to be the ones who do not benefit."

Second, a biotechnology company or pharmaceutical company does not operate for the common good; it operates to enrich its investors. That suggests a different equation. If your labor as an employee contributes to the company's success, that company owes you a salary. Why doesn't the company owe you if it developed a lucrative product from a piece of your body? And regardless of its contributions to the common good, were a nonprofit medical center to generate revenue from selling your cells to a corporation like Ardais, wouldn't you be entitled to a share?

Researchers and ethicists understand the sentiment behind these questions, but they point out several complications. Ethicists warn of the commodification of human tissue and the dangers of creating a market for body parts, even the tiniest of body parts. Researchers note that Henrietta Lacks' story—a scientific breakthrough of immense importance that derived from the cells of a single person—is extraordinarily rare. Most often, advances in biomedical research involve hundreds if not tens of thousands of biospecimens, many of which may have been collected five, seven, 10 years ago. (Almost 60 years ago if they're HeLa.) How does a research center or a for-profit company track down all of those donors to pay a royalty or fee? Says Nichols, the Hopkins vice dean for education, "You can imagine a world in which the retrospective reporting and notification requirements become so onerous that one is not able to do science at all, and the potential benefits from discovery are withheld from future patients because science is forced to grind to a halt. On the other hand, patients have rights that have to be respected, particularly if there's commercial value." If the alternative is to pay for tissue samples at the time they are taken, in case someone might gain commercially from them in the future, will nonprofit

research centers be able to afford large-scale studies? The public wants its privacy guaranteed. How do researchers or companies know whom to pay retroactively if identifiers have been stripped from every specimen used in their research? As yet no one knows the answers to these questions. One solution, says Dang, is for consent forms to include a waiver of rights to any financial benefits.

JOHNS HOPKINS MAGAZINE wanted to include the Lacks family in this discussion, but Sonny Lacks, Henrietta's son, indicated by way of Skloot that they had spoken to enough journalists and were disinclined to speak to one more. Over the years some of the Lackses have complained about a lack of compensation, especially in light of their difficulties paying for health care. But various family members also have stated they have no desire to impede research, and they're proud of the contribution Henrietta has made to science. Much of their annoyance comes down to a lack of communication. They resent that for years no one told them about HeLa cells. They believe that they themselves were used in research without adequate informed consent. They are angry that no one asked before releasing Henrietta's medical records or the genetic markers that are as much theirs as Henrietta's. They would like to have been acknowledged decades ago by researchers as they have now been acknowledged by Skloot's book.

Acknowledgment is not just a courtesy, it's a basic human need and important in addressing the power imbalance that people still feel when illness or injury forces them to deal with medicine, science, and large institutions like hospitals, insurance companies, and the pharmaceutical industry. The needs of science or institutions can become decoupled from the needs of individuals. That's why the public still worries about informed consent, privacy, and who profits from their participation in research. Dang says, "We need to remind scientists, physicians, and businesspeople that we have a common goal and that the patient is waiting—for treatment, for a cure, for humanity, and particularly for hope. We often get lost in our own world when there is a disjunction of science and humanity—the self-interested drive for recognition and glory can lead us down the wrong path that crosses ethical boundaries."

Says Joann Rodgers, "When people come to a [medical] institution, they are vulnerable. If you're sick and you come here for care, we need to be sure there's always recognition of that vulnerability." The vulnerable want medicine and science to acknowledge and respect that they are people, and not need to be reminded of that, too late, by chipped red nail polish.

Dale Keiger is associate editor of Johns Hopkins Magazine.