Primer

HeLa Cells & HPV Genes: Immortality & Cancer Module

by Katayoun Chamany Updated July 2018

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11. Yeampierre, E. Session 2: Building the Relationship: Citizen and Community Engagement. NIH Workshop to Explore the Ethical, Legal, and Social Implications (ELSI) of Citizen Science. (10:31min) Link
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13. Johnson, G. 2011. Rapid Visual Inventory & Comparison of Complex 3D Structures. *YouTube. Science*. Link
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15. Bohan, M.2005. Checkpoints and Cell Cycle Control. Harvard Molecular and Cell Biology-HHMI Outreach Program. Link
16. University of Michigan. 2005. Stem Cells Explained: An Interactive Tutorial. Link
17. **Learning Resource:** Learn Genetics. Epigenetics. University of Utah. Link
18. Providing Researchers with WI-38 Cell Cultures. Web of Stories. Link
19. Duguid, C. 2010. Video: Cell Culture. EuroStemCell. (Producer Kate Doherty) (6 minutes). Link
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21. **Animation:** HPV OncoTect Animation.mp4. *YouTube*. Animation Link
22. Thirteen/Education Broadcasting Corporation (Producer.) June 25, 2010. Religion & Ethics Weekly: Informed Consent and Medical Research. (7:22 min) Link
23. **Film:** Curtis, A. 1997. Modern Times: The Way of All Flesh. Aired on BBC. Modern Times Series, Editor Stephen Lambert. (52 minutes). Link
24. **World Stem Cell Summit Video Conference Session**: Sugarman, J., Zoloth, L. & Hempel, C. October 4 2010. FullviewMedia. The Immortal Life of Henrietta Lacks - lessons for stem cell researchers and patients. World Stem Cell Summit, Pasadena, CA. (Time Stamp 38:00min- 50:00min) Link
25. March 15, 2010. The Immortal Henrietta Lacks. CBSnews. Link
26. Snyderman, N. March 15, 2013. A Mother's Fight. Rock Center with Brian Williams. NBCnews. (Producers, Amy Schmitz and Stacey Naggier).(7:56min) Link
27. NBC. March 15, 2013. Man Starts Organization to Compensate Bone Marrow Donors. Rock Center with Brian Williams. NBC.com. (1:39') Link
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29. **Podcast:** Rogers, A. June 2011 Podcast. Breast Milk. Storyboard. (19:41min) Link
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31. 31. Podcast: Feb 16, 2016. Remembering Anarcha, Lucy, and Betsey: The Mothers of Modern Gynecology. HiddenBrain. NPR. (26 min) Link
32. Film: HBO and Harpo Films. April 2017. The Immortal Life of Henrietta Lacks Trailer. Director, George Wolfe. Link

Note that the yellow highlighted areas refer to media or the accompanying HeLa Primer PPT.
Note that the pink hightlights refer to the infographics available on the SCAC website

Introduction:

In 1951, cervical cancer cells from Henrietta Lacks, an African-American woman being treated in the "colored" ward of Johns Hopkins Hospital in Baltimore, were the first grown outside the human body in a Petri dish. This is the most widely used cell culture in biomedical research yet, for decades, her family was marginalized by the very health care system that her cells support. Now, many years later, the biomedical research community is revisiting the story of Henrietta Lacks, the establishment of the HeLa cell line, and the role of community in biomedical research studies. What lessons can be learned from this case? Can we challenge the normative assumptions surrounding biomedical research to support more just and informed participation in shaping healthcare practices and policies? What roles can individuals and communities play in directing research that serves their needs?

This primer addresses these questions through an historical overview of biomedical research and an exploration of contemporary practices and policies surrounding research with human subjects to advance basic scientific knowledge and biomedicine.

Section I reviews the emergence of biomedical research highlighting both the excitement and caution that accompanied this burgeoning field. This section uses two historically important proposals, *Science: The Endless Frontier,* which advocated for government investment in basic science, and the World Health Organization's proposed definition of health. Both of these proclamations, made in 1945 and 1946 respectively, were perceived to promote social well-being in a post-WWII era. This section also introduces the biomedical and social models of health and reviews approaches that seek to create inclusive environments that account for variance in physical and cognitive abilities within the human population. A social justice framework is used to analyze health equity through three specific approaches: *distributive justice,* which seeks to provide universal access to the knowledge and goods produced through research; *procedural justice* which involves the actions of multiple stakeholders in health policy decision making; and *responsive justice* which requires research and policy to be informed by community input. A review of books and resources that further this dialogue is also included.

Section II reviews the history of biology as it relates to our understanding of cell structures and organization into tissues and organs, with special attention to bioecological niches.

Section III presents the basic principles and concepts of cell biology such as cell division, cancer, and the role that "immortality" plays in the establishment of the first human cell lines. This section also emphasizes the need for cell lines as biological tools of study and highlights the unique features they bring to research. This biological address is necessary in trying to unpack the ethical issues associated with human subjects research.

Section IV reviews the historical trajectory of the first two human cell lines, HeLa and WI-38, and explores issues of commercialization, dissemination, and commodification. Section IV also touches on the social implications of separating cells from the body, and the ways in which such disassociation raises questions concerning ownership, privacy, and commodification.

Section V reviews the techniques and practices associated with cell culture, cell banking, and cell identification. This section also uses an intersectional analysis to highlight the interplay of biology, race, class, and gender in shaping the meaning of "cell line contamination," both within, and outside, the scientific community.

In **Section VI**, the relationship between human papilloma virus (HPV) and cancer is clarified, with specific attention to the role of telomerase and genomic instability in the establishment of the HeLa cell line, the

emergence of new diagnostic tools for HPV infection and cancer, and our increased understanding of stem cell niches.

In **Section VII,** practices regarding the participation of human subjects in research is reviewed, including an historical overview of informed consent and various policies regarding risk and harm to subjects.

Section VIII reviews the changing landscape of human subjects research, paying close attention to the evolution of laws and guidelines to recast privacy and ownership of human tissues, cells, and DNA within the context of emerging biocapital.

Section IX presents contemporary case analyses regarding ownership, recognition, and compensation in the context of bone marrow donation (Flynn v. Holder), egg procurement (New York and California policies)

Section X presents cases where altruistic donation of human tissue and DNA are being used in contexts without adequate informed consent and for profit including genomic banks (Havasupai v. Arizona State University), umbilical cord banks, and milk banks.

Note: Bracketed references in italics throughout the text refer to the HeLa Primer Powerpoint, and are linked to the SCAC website where that Powerpoint can be downloaded.

I. How Have Human Tissues and Cells Been Used for Biomedical Research?

Biomedical research, or experimental medicine, is a combination of basic and applied research done in the interest of promoting a healthy population. The World Health Organization's (WHO) definition, issued in 1946, implied a normative connotation when describing "healthy" as a "state of complete physical, mental, and social well being" (WHO, 1946). Later definitions continued to reference "the absence of disease or infirmity" as an indicator of a healthy state, thereby relegating people living with disease and disability to an "unhealthy" category. Using these definitions, one can only be part of a healthy population if their disease/disability is treated, or cured, which first requires diagnosis.

Thus, an individual's health is assessed using diagnostic tests that measure physical and cognitive abilities in a changing environment and comparing these results to a reference standard. When reduced ability, or disease, emerges, researchers use these cases as opportunities to investigate possible causes. The approach can be medical, seeking to understand, or address, the molecular processes that contribute to disease or disability. Alternatively, the approach can be social, investigating how our current and future environments are hindering some persons from contributing to society and living a full life, without social barriers. In some cases, the social model attempts to address the oppression felt by those living with impairment as a result of discriminatory practices (Shakespeare, 2002). A contemporary approach looks at the intersection of the biomedical and social models of health by investigating how social factors such as stress, poverty, and racism hijack molecular processes resulting in chronic disease/disability and increased mortality (Eisenberg, 1999; Galea et al., 2011; Radley et al., 2011).

Combining biomedical and social approaches to health aids in our understanding of disease, informs practices that prevent their occurrence, and addresses social discrimination associated with disability. Some of the earliest leaders of social medicine include Rudolph Virchow, an important figure in the history of cell biology, and Louis Pasteur, a pioneer in microbiology and communicable disease prevention (Pridan, 1964; Ullman, 2007). Health policies associated with prevention of disease and disability include air pollution standards, laws regarding occupational workplace safety, guidelines for nutrition and exercise, and mass screenings using diagnostic medical tests. A socio-biomedical approach can also ameliorate the negative effects of living with disease and disability through the development of biomedical therapies, assisted devices/technologies, and the creation of inclusive environments that accommodate variance in ability such as the installation of ramps and the incorporation of sign language. A healthy individual is then defined as one that has the "ability to adapt" to a changing environment, and a healthy environment is one designed to support the life activities of individuals with a diverse range of abilities. This history and approach is succinctly summarized in the *Lancet* editorial titled "What is health;The ability to adapt" (Anonymous, 2009).

The field of epigenetics bridges the medical and the social models of health by clarifying the molecular mechanisms involved in responding to the macro-scale environment in which we live (Bronfenbrenner, 1979; Kubicek & Tolpa Studios, 2011; Slide 3: Bioecological Model). Epigenetics also investigates local micro-environmental effects on cells, tissues, and organs, to determine which environmental signals are responsible for influencing cells to divide, differentiate, move, or die (Powell, 2005) (Slide 4: Cell Signaling and Cell Fate).

Infographic: Kubicek, S. 2011. Infographic: Epigenetics - A Primer. The Scientist. Link

Examples of the vital role that environmental factors have in human development include maternal factors in the womb that influence the developing embryo (Slide 5 & 6: Embryonic Development), extracellular matrix (ECM) components responsible for wound repair (Slide 7 & 8: ECM and Making Body Parts), metabolic by-products that alter gene expression, and bacteria and viruses that live on, and in, our bodies influencing our physiology (Fountain, 2012). This natural process of DNA reprogramming is what allows different cells in our

body to possess the same genome but behave and act differently, depending on which regions of the genome are programmed to be active

Nuclear Reprogramming ZoomGraphic

Video: Singh, V. Sept 17, 2012. Extracellular Matrix. New York Times Channel. (4:23 min) Link

Additionally, living organisms have evolved to react to stress by reprogramming their DNA and changing their gene expression. Stressors can take the form of dehydration, malnutrition, or infection. Stress can also be the by-product of social interactions that make a person feel threatened, such as situations involving discrimination (Radley et al., 2011; Cossins, 2015; Seppa, 2015).

Slide Show. Chaddha, R. July 7, 2007. A Tale of Two Mice. NOVA PBS Slide Show. Link

Though epigenetics has regained popularity in the scientific community, the concept has been intimately tied to the study of cancer for some time. Early studies in the 1950s sought to determine whether our genetic material or environment was responsible for the onset of cancer. Researchers quickly realized that this was not an "either/or" proposition and that gene-environment interactions are responsible for 90% of cancers. These same interactions prove important for understanding tissue regeneration in the context of injury and aging. There are also cases of individuals who have managed to halt some aging processes all together. The bodies, genes, and physiology of these individuals present researchers with an opportunity to identify genetic variations that might contribute to this unusual state, as well as illuminate which molecular processes are involved with regeneration and cancer.

[Video: Maclean's. Mackenzee Wittke:The Girl Who Never Ages. Link] (Slide 9: Aging and Immortality)

Much of the early work on cancer was dependent on tissue samples and cell cultures established from clinical biopsies, collected without consent for research, thereby circumventing conversations about privacy, ownership, and compensation. In the post-WWII fervor to bring science into the open, attention was shifted from the Big Science Physics of the Manhattan Project to Big Science Biology supporting medical research.

Timeline10: Biomedical Research

This shift refocused society's attention from external threats associated with wartime propaganda to threats located in our own bodies and genes. In the United States (US), the response was the publication of "Science The Endless Frontier" in 1945. The report, authored by Vannevar Bush, Director of the Office of Scientific Research and Development, equated scientific progress with social and economic development and proposed a national investment in biomedical research (NSF,1945; Crow, 2005; Cozzens, 2005; Pielke, 2010).

> "Progress in the war against disease depends upon a flow of new scientific knowledge. New products, new industries, and more jobs require continuous additions to knowledge of the laws of nature, and the application of that knowledge to practical purposes. Similarly, our defense against aggression demands new knowledge so that we can develop new and improved weapons. This essential, new knowledge can be obtained only through basic scientific research." (Bush, 1945)

Riding the wave of success in the development of antibiotics and vaccines to address infectious diseases, a national pride emerged with many citizens seeing their contribution as part of the larger social good. Soon after Bush's proposal was presented, the National Science Foundation (NSF) and the National Institutes of Health (NIH) alongside increased funding for biomedicine, led to developments in cell biology, immunology, and genetics, with the dual aim of maintaining a healthy workforce and creating marketable products. These

developments were then touted in campaigns to stimulate public interest in continued investment and expansion of this emerging field. The success of the international smallpox vaccine campaign spurred other large-scale efforts. Around the same time that smallpox was eradicated, Mary Lasker, a philanthropist and activist for biomedical research, propelled the first large-scale studies to address cancer, what was then considered an epidemic without a cause.

Video: Rosenbaum, J. Nov 4, 2013. The Long War on Cancer: From Nixon to Now. *Retro Report.org* (12:52min). Link

The "War on Cancer" and the National Sickle Cell Act announced by President Nixon in 1971 and 1972, respectively, led to fundraising efforts for biomedicine and broad dissemination of diagnostics. The buy-in from non-profit organizations, private philanthropy, and activist groups such as the Black Panthers resulted in mass collection of biological samples that then served as bioresources for research (Nelson, 2011). Thus, between 1950 and 1980, American citizens believed it was their civic duty to contribute to the public good by "finding cures" for a myriad of ailments and injuries and to comply with the standard practice of tissue biopsy and blood sample banking.

The investment in biomedical research was not the only consequence of WWII. War tribunals revealed that unethical medical research was conducted on individuals who were declared "unfit" in the name of science. These research subjects included orphans, those living with disabilities, prisoners, and, in the case of Nazi Germany, many ethnic groups considered impure.

Timeline0: History of Human Subjects Research

Because it was believed that they represented maladaptation, policies were put in place to limit their ability to reproduce, as they were considered to have genomes that did not confer biological fitness (the ability to survive in the current environment). In later years, more egregious practices were uncovered around the world, and by 1964, the first international effort to devise guidelines for ethical biomedical research using human subjects was issued as the Declaration of Helsinki. Though the declaration clearly stated that human research subjects be informed about the benefits and risks associated with research, and participate voluntarily with free will, it did not consider the downstream ethical issues associated with biological samples obtained from human subjects. The Declaration's focus on respect for the body as it pertains to personhood and dignity, does little to consider the ownership, compensation, or privacy dimensions of tissues, cells, and blood.

These disembodied pieces of bodies, be they organs, eggs, embryos, genetic sequences, blood components, or cells, continue to present bioethical challenges. Without an international consensus on what can be traded in global markets, used for research, or analyzed as evidence in courts of law, a patchwork of laws pertaining to methods of collection, biobanking, access, experimentation, and patents has emerged. Moreover, without clear ideas about where the connection to the body ends, issues of ownership, permission, and identity are also put into question (Knoppers & Laberge, 1995; The Body and the State, 2011). The case involving deCode and Iceland's Data Protection Authority illustrates how advances in science and technology can circumvent legal regulations regarding genetic data and further limit access down the road (Kaiser, 2013).

Some argue that this murky situation has led to the emergence of legitimized markets for biomaterial and cell therapies whose access is restricted to particular groups of privilege (Greene, 2006). This is particularly problematic when biomaterial is acquired from persons who continue to be marginalized, or exploited, through a biomedical research model that does not uphold distributive or procedural justice (Nelson, 2011; Chamany, 2011; Chamany, 2015). Distributive justice refers to access to knowledge and therapies produced from biomedical research, while procedural justice refers to participation in the shaping of the direction of biomedical research as a human research subject, policy maker, or scientist. Critics of the biomedical model approach claim that this approach neglects the systemic and/or structural injustice that creates health inequities and by

doing so, positions those on the downside of inequities as bioresources, exacerbating their exposure to health risk and reifying their risk status. Thus, a strictly biomedical approach to health inequity will maintain that the people who serve as sites of experimentation, or bodily goods, are the same people that will suffer from lack of access to drugs, technologies, and legal protections that could improve and protect their lives (Shakespeare, 2002; Goodwin, 2007; Washington, 2006; Democracy Now, 2010; Benjamin, 2013; Benjamin, 2014).

Video: Benjamin, R. Feb 5, 2015. From park bench to lab bench. What kind of future are we designing? TEDxBaltimore. YouTube.(21:25 min) Link

Mark Greene, a bioethicist, returns to the principles of distributive and procedural justice in "To Restore Faith and Trust: Justice and Biological Access to Cellular Therapies." According to Greene, biomedical therapies should be available to people of all ethnicities and, thus, diversifying the samples in biobanks is of high priority. By including under-represented minorities in the process of biospecimen collection (procedural justice through representation), the biobank can serve as a resource for medical therapies for this population (distributive justice through access). Greene offers a proposal for an ethnically weighted biobank created through additional public funding to support the health of under-represented minorities that can serve as a practical public expression of apology for past discrimination in health research (Greene, 2006). Seema Mohapatra and Michelle Goodwin, who specialize in health law, also propose plans using incentives to encourage donations to biobanks (Mohapatra, 2013; Goodwin, 2007; Trotter, 2006). Their proposals are designed to address the lack of diversity in these banks, which reduce the chances of immunological matching of blood transplants that would disproportionately impact specific communities. Additionally, Goodwin presents these proposals as an alternative to existing unregulated markets for bodily goods (Goodwin, 2007). Widdows and Cordell remind researchers that they must recognize the unique nature of each community and the goods that they provide. They warn researchers that to view community as a monolithic entity can lead to dangerous and unethical practices and a sense of distrust (Widdows & Cordell, 2011). To provide guidance and expertise to communities and individuals that provide vital information and biological resources to these growing large-scale datasets, David and Richard Winikoff have proposed a "Charitable Trust Model" which is being adapted by some states and countries (Winikoff & Winikoff, 2003). In this model the community and individuals within it, are expected to be dynamically involved in a tiered informed consent process and can influence the direction of research directly.

Video. Goodwin, M. 2011.Whose Values and Principles in a New Biopolitics. Tarrytown Meetings. YouTube. (10:48 min) Link

As biomedical research continues to advance, society needs to address issues of social justice within the context of differing value systems, and question models that support economic capital at the expense of social capital (Shanks, 2010b; Ikemoto, 2009). A review in *The Scientist* highlights the lack of public discourse surrounding issues of biobanking as it relates to ownership, compensation, and privacy (Fahy & Nisbet, 2013). The authors, bioethicists who analyzed social media related to the publication of Rebecca Skloot's book *The Immortal Life of Henrietta Lacks*, report that most discussions centered on informed consent. Although the informed consent process is designed to educate research participants about health risks and potential benefits associated with a research study, the expansive nature of biomaterial collection in a clinical setting introduces other ethical concerns such as privacy, ownership, compensation, and acknowledgement of contributions (Fahy & Nisbet, 2013; Ehrlich, 1997; Perriello, 2010; McLaughlin, 2010; Slide 10: Congressional Records).

Slide Show (49 slides): McLaughlin, T. May 31, 2010. An Epitaph, At Last. SoVaNow.com. Link

This focus on informed consent is central to the film adaptation of Skloot's book produced by Oprah Winfrey and broadcast on HBO. In line with Fahy and Nisbet's earlier analysis of public discourse, those who attended film screenings questioned the lack of consent, but also extended the conversation to issues of identification

and acknowledgement. This was particularly true for those who walked away from the film or the book believing that biomedical researchers were stealing tissues and samples only from African Americans (Personal Communication, April 24, 2017).

The collection of tissues and cells inevitably means that DNA is also collected, the latter of which can be used to identify the origin of the material. When Lars Steinmetz and colleagues at the European Molecular Biology Laboratory in Heidelberg Germany published the genomic sequence of the HeLa cell line online for the first time, some in the scientific community raised concerns about privacy because permission to publish the sequence was not secured from the Lacks family (Brainard 2013; Callaway, 2013a; Skloot, 2013; Hudson and Collins, 2013).

Video: Sparkman, S. 2013. The HeLa Cell Genome Published, Causes Privacy Controversy. Newsy./ Dailymotion Link

Following publication of this genomic sequence, two researchers were able to identify the source of the cell line using information from recreational genealogy databases. This alarming chain of events highlights the need not only for informed consent, but also, de-identifying mechanisms that protect the identities of donors and biospecimen providers (Hayden, 2013a; Hayden, 2013b). In 2013, as another research team prepared to release more data on the HeLa genome, Francis Collins, director of the NIH, saw an opportunity to involve the Lacks family in shaping the protocols for scientific access to genomic data entered into the Genotypes and Phenotypes Database on a case-by-case basis (Callaway, 2013b). That two members of the Lacks family now participate as members on the "HeLa Genome Data Access" working group may be viewed by some as a move in the right direction, but there are concerns that this sort of personal gate-keeping may prove challenging (Chamany, 2015). This approach is in stark contrast to prior decisions made by institutional review boards (IRBs) that dissuaded clinicians from placing research directives in the hands of patients or providing acknowledgement or compensation to their family members (Troug et al., 2012).

Video. Picht, M. Aug 7, 2013. Henrietta Lacks' Family Finally Gets Say in Genome Research. Newsy/ Dailymotion. (2:47 min) Link

In line with this shift in shared responsibility to negotiate privacy, ownership, and compensation related to biospecimens, proposals to improve current regulations and practices regarding human subjects have emerged (See section on **What Policies Are in Place for Regulating Research with Human Subjects**?). The International Society for Stem Cell Research (ISSCR) Registry of Human Embryonic Stem Cell Lines Provenance and the US National Stem Cell Registry address the ethical provenance of stem cell lines excluding cell lines that are not in compliance with contemporary rules and guidelines regarding biospecimin procurement (Knoppers & Isasai, 2010; Wadman, 2013). The authors of *Achieving Justice in Genomic Translation: Re-Thinking the Pathway to Benefit* evoke a responsive justice framework to call on researchers to take greater responsibility in protecting subjects and communities, specifically addressing redistribution and recognition with respect to underserved communities (Burke, et al. 2011; page 3-20 in Google Books). Some of these approaches mimic the benefit-sharing models created by the biotechnology and pharmaceutical sectors to secure indigenous knowledge and bioresources that are mined for the development of novel drugs. However, few of these benefit-sharing models are seen as sustainable or just, as reviewed by Harry and Kanehe in their chapter "The B.S. in Access and Benefit Sharing" published by the Edmonds Institute and Corey Hayden's book titled *When Nature Goes Public* (Harry and Kanehe, 2005; Hayden, 2003).

Most of the criticism regarding benefit-sharing agreements arises from unequal power relations regarding memoranda of understanding (MOUs), because one party lacks the language and procedural knowledge to negotiate for benefits within a legal, biotechnological, or business framework. In the case of the HeLa cell line and the publication of genomic data, questions regarding compensation to the family were addressed by the Supreme Court case dismissing patents on naturally occurring genes, with the language being narrowly

constrained around DNA sequences (Zimmer, 2013; Callaway, 2013b; Hudson and Collins, 2013). What was perhaps not made clear to the family is the ways in which this court decision leaves open the possibility of continued commercialization of products informed by these data as they could be based on RNA, chimeric proteins, or other inventions that are dependent on those DNA sequences but, remain patentable. It is also not entirely clear whether the HeLa genome would be considered something occurring in nature because genomic analyses reveal that the cell line has extensive chromosome shattering not seen in nature, but most likely induced by lab culture conditions (Landry et al. 2013).

For a deeper analysis of the ways in which the collection, use, banking, and marketing of human tissue and blood have become points of conflict, we can turn to a number of critical race theory, feminist, disability, and social justice scholars and activists. They highlight the ways in which a narrow focus on biomedicine and profit has both eclipsed the social model approach to health and wellness and exacerbated existing health inequities. Collectively, they use an intersectionality framework, namely a theoretical framework positing that multiple social categories (e.g. race, ethnicity, gender, sexual orientation, ability, socioeconomic status) intersect at the micro-level of individual experience, to reflect multiple interlocking systems of privilege and oppression at the macro, social-structural level (e.g. racism, sexism, heterosexism, ableism). (Bowleg, 2012), (Slide 11: Women and Minorities).

Rebecca Skloot's book *The Immortal Life of Henrietta Lacks* demonstrates how biology and social justice were intimately intertwined in establishing and marketing the HeLa cell line (Skloot, 2010). Her focus in the book is on distributive justice, with respect to who benefits from the applications of research, and who is marginalized by biomedical research policy because of shifting societal values and inequities with respect to race, class, ability, and gender. Although the book has exposed an important narrative regarding Henrietta Lacks, it is but one narrative. As Rebecca Kumar, a first-year college writing instructor, points out in her open letter to other colleges and universities, to use this book without incorporating a deeper analysis of intersectionality and alternate narratives is problematic (Kumar, 2012). She urges her colleagues to expand the class discussion to include larger views into systemic oppression and injustice. President Obama issued a similar statement with respect to the case of Trayvon Martin, the young African-American killed in 2013 due to racial profiling by a civilian. In a national address he stated, "I think it's important to recognize that the African-American community is looking at this issue through a set of experiences and a history that doesn't go away." (Obama, 2013). His comments are in response to the 2005 "Stand Your Ground" law in Florida that permits legal possession and use of a gun in self-defense, at a time when the nation continues to struggle with racial discrimination. Though the Trayvon case is not a biomedical one, it highlights the ongoing lack of inclusion of racial minorities in procedural justice with respect to construction of guidelines and laws (Rucker and Eilperin, 2013).

Ruha Benjamin's book *People's Science: Bodies and Rights on The Stem Cell Frontier* specifically addresses procedural justice with respect to who participates in life science research, either at the lab bench or as a research subject, policy maker, activist, or lobbyist (Benjamin, 2013b). Her case analysis centers on the political process behind the establishment of the California Institute of Regenerative Medicine (CIRM) and reveals the complex network of stakeholders behind this initiative. She challenges the notion that health inequity is the by-product of a competitive edge, and ends the book with a proposal for a more equitable way forward that simultaneously promotes biomedical innovation and equity.

Other resources that address health inequities in biomedical research and provide a trajectory for how racial minorities were often used as research subjects in biomedicine, or excluded from health services, include: Michele Goodwin's 2013 book *Regulating Contestable Commodities in the Global Body Market: Altruism's Limits*; Dorothy Roberts' 2011 book *Fatal Invention: How Science, Politics, and Big Business Re-create Race in the Twenty-first Century*; Alondra Nelson's 2011 book *Body and Soul: The Black Panther Party and the Fight Against Medical Discrimination*; Harriet Washington's 2008 book *Medical Apartheid The Dark History of Medical Experimentation on Black Americans from Colonial Times to the Present*; Miguel Melendez's Chapter "The Hijack" in his book *We Took the Streets: Fighting for Latino Rights with the Young Lords*, which describes

the movement to expand access to TB screening for Latinos living in East Harlem; Ana Maria Garcia's documentary film "La Operación", which reviews female sterilization practices in Puerto Rico in the context of reproductive justice; the Case Study on the Tuskegee Syphilis Trial by Fourtner et al.; and Charnell Covert's 2012 theatrical work *"Healing"*, in which one of four case analyses is centered on Henrietta Lacks.

Although these are contemporary works, they follow an earlier definition of health proposed by Georges Canguilhem in his book *The Normal and the Pathological* (Canguilhem, 1945). Canguilhem recognized that health is dynamic and varies depending on the circumstances of the individual and community. He argued that health care requires a working relationship between health providers and individuals in which autonomy is in the hands of the individual. It follows that, if individuals are marginalized and excluded from processes that influence the direction and practices of biomedical research, this will have a negative impact on their circumstances. Lack of access to health care, stress associated with poverty, and discrimination based on ability, race, class, gender, and sexual orientation can all serve as environmental factors that remodel the biology of these individuals. Recent studies in the field of epigenetics suggest that, as a result of these environmental accosts, entire communities may live with elevated levels of chronic metabolic disease, cancer, and neurological pathology. (Radley, et al., 2011; Bollati, et al., 2010; Oberlander, et al., 2008; Thayer & Kuzawa, 2011; Seppa, 2015).

Video: Ted TALK: Burke Harris, N. Feb 17, 2015. How Childhood Trauma Affects Health Across a Lifetime. Link

It is precisely these states of disease and disability that the field of stem cell research seeks to address. Stem cell transplants have been administered since the 1950s to treat blood-related disorders such as sickle cell anemia and leukemia. More recently, stem cell biology has moved beyond transplantation to providing vital information about how our bodies interact and adapt to changing environmental conditions. By studying human cells in a laboratory environment, researchers create a model for screening novel drugs to address the negative health outcomes of adverse circumstances. Additionally, researchers can conduct experiments that reveal which environmental factors result in cell toxicity, and thereby inform environmental health policies that would avoid these circumstances altogether. Lastly, by creating cell cultures that represent the diversity of the human population, researchers can compare cell behaviors from individuals living in varying social conditions, lending biological data to support the social model of health.

In the short presentation below, Elizabeth Yeampierre, of the community-based environmental justice non-profit UPROSE, emphasizes the need for researchers to be mindful of the health and environmental injustice that has its origins in colonization, oppression, and slavery. This presentation was one of many hosted by the NIH Workshop to Explore the Ethical, Legal, and Social Implications (ELSI) of Citizen Science, designed to inform the US Privacy and Trust Principles that accompany the changes to the Common Rule regulating the use of human research subjects and biospecimens.

Video: Yeampierre, E. Session 2: Building the Relationship: Citizen and Community Engagement. NIH Workshop to Explore the Ethical, Legal, and Social Implications (ELSI) of Citizen Science. Link. (10:31min)

II. What Is A Cell? What is Cell Research?

Cells are defined as the smallest functional biological unit of all organisms, capable of autonomous replication and dynamic interaction with changing environments. They may exist as forms of independent life, as in the case of bacteria and other unicellular organisms, or be a subunit of multicellular organisms contributing to specialized functions that allow the organism to perform as a whole (Slides 12-19: History of Cell Biology). A commonality to all cells is the chemical composition of carbon, nitrogen, oxygen, hydrogen, phosphorous and sulphur. These chemical units can organize to form water, among other compounds, which makes up 70-90%

of the total cell volume. These chemical units are also organized into larger molecular polymers that have specific forms and functions, called macromolecules.

There are four types of macromolecules (lipids, nucleic acids, proteins, and sugars). They collectively make up all the components of a cell and allow cells to interact and respond to their environment (Slide 20: Macromolecules). Fat macromolecules, or lipids, form membranes that create a barrier with the outside environment and form specialized compartments inside the cell. One such compartment is the nucleus, which houses macromolecules called nucleic acids, otherwise known as DNA and RNA. DNA is the genetic material that is passed on from generation to generation, and serves as an information depot for the synthesis of other macromolecules called proteins. Proteins can be subdivided into categories based on function (Slide 21: Proteins).

Some proteins provide a structural role to the cell that is akin to our skeletons, giving the cell membrane integrity and strength, and are collectively termed cytoskeletal proteins (cyto- meaning cell). Other proteins are involved in transporting material to and from various compartments within the cell and to the outside environment. Still other proteins "communicate" with the outside environment in the form of signaling pathways. A signaling pathway involves many proteins that interact in a specific sequence, in response to an initial signal outside of the cell (extracellular environment). Often this pathway includes a receptor protein that straddles the cell membrane, allowing it to undergo conformational changes upon binding this external signal. This change in conformational shape allows the receptor protein to make new interactions with molecules and proteins inside of the cell. This cascade of interaction elicits a change in cell behavior by triggering protein synthesis, protein activation, and/or protein reorganization resulting in cellular shape changes required for cell division, cell death, cell movement, or cell specialization. To synthesize proteins, a cell responds to an external signal and uses the information in its DNA to build the appropriate proteins for that specific environment. To accomplish this, the cell uses energy, which is created by a collection of proteins called enzymes that break down another macromolecule type, called sugars, to generate molecular energy in the form of Adenosine Triphosphate (ATP).

Cell biology is the study of cells as single units and also as organized collectives, referred to as tissues and organs. One of the most important aspects of cell biology is the role of the extracellular matrix (ECM), which is the material that surrounds cells in multicellular organisms. The ECM is a scaffold of structural proteins and sugar complexes that serves as a depot for extracellular signals such as growth factors. Cell behavior, structure, and organization are influenced by the composition and structure of the ECM, which varies among different tissues and organs. The ECM structure and composition can also be influenced by aging, trauma, and injury, all of which may halt or stimulate cell regeneration and specialization.

Video: Singh, V. Sept 24, 2012. Extracellular Matrix. *New York Times Video Science*. Link

This specialization can lead to dramatically different cell structures, internal compositions, and organizations that retain the ability to respond to the environment dynamically and quickly. The 2011 International Science and Engineering Visualization Challenge People's Choice 1st Prize in Video "Rapid Visual Inventory & Comparison of Complex 3D Structures" by Graham Johnson et al., illustrates how mouse pancreatic cells rapidly respond to sugar exposure by altering the synthesis and relative distribution of various organelles, which act as specialized sub structures within cells(Slide 22: Scale and Dynamics).

Video: Johnson, G. 2011. Rapid Visual Inventory & Comparison of Complex 3D Structures. *YouTube*. Link

In the human body, there are approximately 200 types of specialized human cells constituting the 10 trillion cells of our body and trillions more bacterial cells and viruses. Thus, the human body is an ecosystem situated within a larger ecosystem that includes our built and social environments, sometimes referred to as the bio-ecological model. Russian-born American psychologist Urie Bronfenbrenner, in his book *The Ecology of*

Human Development: Experiments by Nature and Design published in 1979, first proposed this model (Bronfenbrenner,1979). (Slide 23/Slide 3: Bioecological Model)

As early as the 1600s, scientists studied cells in living tissues and in isolation from their natural ecosystems, often employing microscopy and visualization techniques to label or dye particular compartments, or organelles, in the cell. (Slide 24 & 25: How Do We Visualize Cells). As technological and scientific advances were made, cells were not only studied in isolation or in pure liquid culture, but in complex three-dimensional environments that mimicked their natural environments (Slide 26: Moving from 2D to 3D). One of the most essential technological breakthroughs for biomedical research was the ability to propagate human cells indefinitely in the laboratory, otherwise known as cell culture.

For a deeper history on cell culture we can turn to Boyce Rensberger's excellent trade book *Life Itself: Exploring the Realm of the Living Cell* (Rensberger, 1996), Jane Maienschein's book *Whose View of Life? Embryos, Cloning and Stem Cells* (Maienschein, 2005), and her related multimedia learning resource The Embryo Project. In addition, Willy Lensch and Christine Mummary provide a review of cell culture techniques as they relate to contemporary stem cell research and, like Maienschein and the NIH report "Regenerative Medicine," evoke the Greek legend of Prometheus to highlight the ethical controversies associated with "culturing life" (Department of Health and Human Services, 2006; Lensch & Mummery, 2013). Hannah Landecker extends this analysis in her anthropological view of the evolution of cell culture research in *Culturing Life: How Cells Became Technologies* (Landecker, 2010).

III. How Does Tissue Culture Technology Contribute to Stem Cell Research (SCR)?

History of Cell Culture
Cell culture techniques began in the 1800s, but the ability to keep a cell alive in culture was the accomplishment of Ross Harrison, who in 1907 cultured a nerve cell for several weeks using the "hanging drop method." Over the next forty years a number of inventions and discoveries led to further advances in cell culture. Thomas Montrose Burrows discovered the medium of chicken embryo plasma clots as being essential for propagation of cells in culture, and coined the term "tissue culture," Alexis Carrel was the first to establish sterile technique for cell purity, George Gey in 1933 was the first to invent the cell culture roller, which provided adequate air flow, and Wilton Earle in 1943 established the first continuously growing culture of mammalian cells, and later established the first clonal mouse immortalized cells, known as the L cell line (Maienschein, 2005). (Slide 27: Be Still My Beating Heart)

A cell line is a collection of cells that can grow outside the body, while a cell strain is a clonal population of cells that arises from a single cell or small group of cells that have been propagated, or cultured, in a Petri dish. In the early days of "cell culture," cell lines were heterogeneous, but as purification methods improved, the term "cell line" become synonymous with "cell strain." As the *lineage* of cells in this culture can be traced back to the original single cell used to propagate the culture, the word "line" refers to this lineage and the clonal relationship of the cells, because they were generated through cell division from the original cell. Because the cells are growing outside of the body and in a Petri dish, we refer to any experiments done with these cells as being done *in vitro*, referring to the historic nature of cell culture using glass test tubes (*vitrum* is Latin for glass). Each cell line originates from living tissue or cells that grow *in vivo*, be they animal or human. Thus, each cell line represents the unique characteristics of that organism and that specific individual from which it originated (NCBI, 2014). (Slide 28 & 29: ATTC)

Video EuroStemCell. Cell Culture. Link (6 min)]

Cell Transformation and Immortalization
Nevertheless, it seems that cells in culture were not always identical to their original source, and rather appeared to be "transformed." In the case of the L cell line, Earle showed that these cells, if injected into a

mouse, induced sarcomas, which are a form of cancer. These results suggested that cells capable of growing in culture were transformed, either by their very genetic constitution or the environmental factors present in the culture conditions. The transformation allows these cells to divide continuously, and with the addition of additional growth media and space they replenish the cell culture.

Much of what we know about cell biology we have learned from the exceptional cases of cancer cells that have been transformed into an "immortalized" state. Immortalized cells are able to grow indefinitely in cell culture allowing for their observation and manipulation in the laboratory. Unlike non-cancerous cells, which under highly specialized conditions can be cultured for a limited number of divisions before they exit the cell cycle of growth and eventually die, cancer cells divide an indefinite number of times, surviving long after the original cell donor in the form of "immortal cell lines." Furthermore, cancer cells ignore "contact inhibition" and have fewer requirements for growth factors. Whereas non-cancerous cells divide only as much as the culture space allows and will stop when growth factors are depleted, cancer cells keep growing and create mounds of cells in a Petri dish, as opposed to a single, thin layer. Thus, in the body (*in vivo),* as well as in a laboratory environment (*in vitro)*, cancer cells are characterized by their ability to proliferate uncontrollably and incessantly in an unregulated manner.

Controlled Cell Proliferation in the Body and Stem Cell Niches

To better understand how cells in culture behave differently from cells in the body we can turn to human development, which includes all of the processes from fertilization to death. In humans, cells must grow and divide for the purposes of development, maintenance, and replenishment of tissues. Cells are endowed with genetic instructions for their own growth and division, which ensure that they proceed through this cycle in a controlled and timely fashion. The control, or regulation, of cell division is dependent on environmental cues that interact with cellular genes and proteins (Slides 31-33: Cell Cycle and Check Points).

Animation: Bohan, M.2005. Checkpoints and Cell Cycle Control. Harvard Molecular and Cell Biology-HHMI Outreach Program. Link

Cells in a developing embryo respond to growth factors in the mother's reproductive tract and divide rapidly in the first few days after fertilization to produce the cells that will eventually become the fetus and placenta. Cells in the developing embryos are referred to as embryonic stem cells (ESCs) and those in the fetus as fetal stem cells. While cell division is rapid and uniform during embryogenesis, as the organism develops, cells become specialized for different functions. Once the organism is born, some cells stop dividing and maintain their specialized state, while others in the adult maintain the ability to undergo regulated cell division when an appropriate environmental signal is present (Slide 5: Embryogenesis). These cells in the adult that maintain their ability to remain less specialized are referred to as adult stem cells (ASCs).

Animation/Tutorial. University of Michigan. 2005. Stem Cells Explained: An Interactive Tutorial. Link

Adult cells that are constantly exposed to environmental damage, such as those in our skin, gut, and hair follicles, reside in stem cell niches that provide environmental cues to signal ASCs to either remain quiescent, or undergo cell division and regenerate aging and damaged tissues (Slide 34: Cells Communicate and Coordinate). Similarly, some areas of the body possess cells that can respond to environmental trauma signals and undergo cell division as part of wound healing. Exploring the environmental and genetic interplay in these stem cell niches is the focus of stem cell research, which may help us understand how our bodies regenerate, age, and heal. Similarly, understanding how niches become disrupted, leading to rapid and uncontrolled cell division, can help us understand how cancers develop (Powell, 2005) (Slide 35: Microenvironments and Stem Cell Niches).

Cancer, Genes, and Immortalization
A collection of proteins in the stem cell niches of adult bodies control cell division. If the genes that code for these proteins are damaged, or changed, the cellular proteins become dysfunctional, increasing cell division rates in the niche. With continued uncontrolled cell division, cancer can develop. Unlike non-cancerous cells in the adult body that work in a cooperative, restrained, and organized fashion to maintain the orderly function of the tissues of the body, cancer cells divide without restraint, crossing boundaries and altering cell and tissue functions. An individual will typically experience cancer later in life, because its development requires the culmination of many different genetic alterations taking place over an extended period of time.

Genetic alterations such as gene mutations can be the result of oxidation events associated with cell metabolism or the result of environmental factors such as chemical interactions (carcinogens in food or cigarettes), physical damage (UV light or radiation) or DNA rearrangements caused by viral infection (viral integration). These mutations result in changes in the DNA sequences that code for the regulatory proteins involved in cell division. Cells with these malformed or missing proteins, ignore environmental cues and undergo aberrant and uncontrolled growth and division. In addition to DNA mutations, epigenetic modifications to the DNA or the proteins that organize DNA (histones, condensins, and cohesins) result in changes in the activities of cell division regulatory proteins, causing some to be upregulated and others to be downregulated (Kakui and Ullman, 2017). This in turn creates the opportunity for more genetic mutations and epigenetic changes that can contribute to the development of cancer (Stark, 2010).

Learning Resource: Learn Genetics. Epigenetics. University of Utah. Link

IV. The First Human Cell Lines: HeLa and WI-38

It should come as no surprise that, given their proclivity for rapid cell division, both cancer cells and fetal stem cells served as excellent starting materials to establish the first human cell lines used in biomedical research.

Derivation, Dissemination, Ownership, Privacy, and Profit
The first human cell line, HeLa, was established in 1951 using cells from the cervical cancer tissue biopsy of a young black woman and mother of five. Henrietta Lacks was being treated in the “colored” ward of Johns Hopkins Hospital in Baltimore for a particularly aggressive case of cervical cancer. Her health quickly deteriorated after her cells arrived in the lab of cell culturist George Gey. Although his research team had been trying to establish a stable human cell line for some time, most of these cells stopped dividing after one or two cell divisions. However, when Henrietta’s cells were placed in Gey’s signature growth medium of chicken blood, calf embryos, and human placental blood, they continued to divide. Gey’s assistant, Mary Kubicek, carried out the original culture. She named the cell line “HeLa” using the first two letters of the patient Henrietta Lacks’s first and last name, as was the custom for naming cell lines at the time. Gey distributed the cells at no charge to researchers around the world, creating a new field of cell biological research. To aid researchers in their work, many companies emerged to provide reagents and equipment for cell culture. Human tissue culture led to the birth of an enormous profit-making industry. Henrietta died of her cancer shortly after the biopsy was removed, but her cells live on to this day and a vial of HeLa cells can be purchased through the American Tissue Culture Collection (ATCC) by non-profit researchers for $359 (Skloot, 2010). (Slide 36 & 37: Henrietta Lacks, HeLa as Commodity)

For many years neither Henrietta nor her surviving family received recognition or compensation for use of her ground-breaking cells, but the cell line itself became known to biologists worldwide and led to countless discoveries and breakthroughs in cell biology, genetics, and oncology (the study of cancer) (Slide 38: The Way of All Flesh Film; Curtis, 1996). The cell line was so robust, became so well known and so widely used, that it came to contaminate and overgrow many subsequently created cell lines. Though the family never received financial benefits from derivation of the cell line, they did experience a loss of privacy when Henrietta’s image was released to the public in an article written by journalist Michael Rogers in *Rolling Stone* magazine, and

more recently when researchers released the genomic sequence of the cell line in 2013 without permission from the family (Rogers, 2011; Hayden, 2013; Callaway, 2013) .

The derivation of the first non-cancerous human cell line, WI-38, was also mired in ethical issues. Leonard Hayflick established WI-38 in 1962 using fetal lung tissue. The successful line was derived using tissue from a therapeutically aborted fetus obtained from a Swedish hospital, where abortions were legal at that time.

Fetus.Fetal Tissue.In Vitro.ZoomGraphic.

Though the HeLa cell line was named after the person from whom tissue was removed, WI-38 was named after the Wistar Institute in Philadelphia, where Hayflick was employed. Ethical conduct regarding the derivation of the cells has been questioned by the pro-life stance against fetal tissue research, and the distribution of the cells has led to challenges regarding equitable ownership and financial benefits for all stakeholders.

The fetal origin of WI-38 continues to plague pharmaceutical companies that use it to propagate rubella vaccines. Anti-abortion activists have publicized its origin and advocate strongly against the rubella vaccine, which is cultured in these cell lines (Children of God for Life). The 1960s was the height of the rubella epidemic, affecting 1% of all births in Philadelphia General Hospital. Due to the severe developmental defects associated with fetal infection, some women would terminate their pregnancy to avoid this consequence (College of Physicians Philadelphia). Stanley Plotkin, the scientist who developed the rubella vaccine, says "I am fond of saying that the rubella vaccine has prevented thousands more abortions than have ever been prevented by Catholic religionists." Debbi Vinnedge, the executive director of *Children of God for Life*, advocates against using a fetal cell line to propagate the vaccine. Her position is in line with the Vatican, which recommends that if no alternative exists it is "lawful" for the parents to have their children immunized with vaccines made using WI-38, in order to avoid health risks to their children and the population. However, the Vatican also encourages that faithful Catholics "employ every lawful means in order to make life difficult for the pharmaceutical industries" that use cell lines derived from fetuses (Wadman, 2013).

With respect to ownership and profit, the WI-38 line has a complicated history that provides lessons for contemporary cell line derivation and banking. Shortly after Hayflick derived the cell line, he accepted a contract by the federal government to disseminate the cells, distributing them to other researchers for a nominal shipping cost ($15). As Hayflick prepared to take a new faculty position, discussion concerning the transport and location of the cell line ensued. The NIH and his home institution, the Wistar Institute, decided to renegotiate the terms of the contract and split the original frozen cell line stocks among the three stakeholders. Hayflick felt pressured to agree, but instead "absconded with the cells" and continued to distribute them to researchers working in the non-profit and commercial sectors, placing any money received in a "Cell Culture Fund" until ownership could be rightfully ascertained. By May 1975, the fund totaled $66,000, and as a consequence of an NIH investigation, Hayflick's name was released, tarnishing his reputation. Hayflick retaliated and sued the government and ultimately the case was settled out of court (Wadman, 2013; Azvolinsky, 2015).

Video: Providing Researchers with WI-38 Cell Cultures. Web of Stories. Link

Hayflick, in a letter to the editor of the journal *Science,* reminds the scientific community that ownership of the WI-38 cell line was determined by important legal and social relationships within the biotechnology sector as it relates to government support. He mentions several significant events that contributed to this victory: the Supreme Court ruling that biological material can be patented; passage of the Bayh-Dole Act, which states that federally funded research is not the sole ownership of the government and that royalties can be shared with institutions receiving federal funding; an executive order issued by President Reagan in 1983 that permitted the private sector to hold patent rights on inventions developed under federal contracts and grants; and the

emergence of a biotechnology industry that was built on federally funded, basic scientific research (Hayflick, 2013).

That fetal cells and cancer cells were both used to establish the first human cell lines sheds some light on a natural phenomenon as well. In the 1990s, there were some anecdotal evidence that fetal cells could be responsible for extending the lives of women who had been pregnant, and in some cases address diseases of degeneration. Studies in mice have revealed that fetal cells migrate to their mother's tissues, creating fetal microchimerisms. Because of their high regenerative power, fetal cells can not only promote health in pregnant women, but they could also promote cancer, based on the "immortality" phenotype (Boddy et al., 2015; Zimmer, 2015).

Immortality: Telomerase, HPV, and the Hayflick Limit
With two different kinds of human cell lines established, scientists could identify the factors responsible for the immortality property. Prior to establishing WI-38, Hayflick had cultured fetal cells and found that they would divide 50-70 times in cell culture, and adult cells only about 40-60 times, before halting cell division. This cap on the number of times a non-cancerous cell will divides is termed the Hayflick Limit, a theoretical proposition that Hayflick put forth in 1961 based on the hypothesis that something related to aging was responsible for this limit (Slide 39: Hayflick Limit). The term "senescence" is used to describe the molecular processes that contribute to the cessation of cell division, resulting in eventual cell death (Azvolinsky, 2015).

Though there are many molecular processes involved with cell aging, a particularly important one is the protection and maintenance of vital DNA information. Cells protect sequences of DNA from loss by adding a "bumper" of non-coding DNA to the ends of chromosomes (Slide 40: Telomerase Activity). These bumper DNA sequences are referred to as telomeres (the prefix "tele" in Greek means far off or at a distance). Without these non-coding bumpers, cells gradually lose DNA with every round of cell division, due to the nature of DNA replication processes. The existence of such bumper DNA was hypothesized by Hermann Muller and Barbara McClintock in the 1930s, and in 1982, Elizabeth Blackburn and Jack Szostak identified the bumper sequence. In 1984, Blackburn's student Carole Greider discovered the enzyme responsible for maintaining the bumper DNA sequence and called it "teloVmerase." In 2009, the three scientists received the Nobel Prize for these discoveries that demonstrated that vital DNA information that codes for proteins is not lost as cells replicate their DNA during multiple cell divisions, as DNA loss only occurs in the telomeric region, which does not code for protein. An illustrated overview of these discoveries and processes can be accessed from the Nobel Prize Website where an Illustrated Presentation reviews molecular steps involved in this fundamental mechanism of DNA maintenance.

Video: Cellular Reprogramming (iPSC). Stem Cells Across Curriculum. Link

Telomerase activity is highly controlled and is only present in cells that need to undergo continual cell division, such as those of the developing embryo, fetus, and adult stem cells in regenerating tissues like bone marrow, gut, skin, and liver. Most cells of the body inactivate telomerase, and this is one reason that our tissues become less efficient as we age, because not all tissues are capable of regenerating cells indefinitely. Telomerase is also active in cancer cells, and its activation is considered one of the hallmarks of cancer progression (Hanahan & Weinberg, 2011). Telomerase activation can be induced by viral infection, as is the case with the HeLa cell line, which is known to be infected with many copies of Human Papilloma Virus 18 (HPV18) (Ambros & Karlic, 1987).

Not surprisingly, the addition of genes such as hTERT that encode molecular components necessary for telomerase function can increase the efficiency of DNA reprogramming ten-fold when creating induced pluripotent stem cell (iPSCs) (Malik, & Mahendra, 2013). hTERT can be used to derive iPSCs from adult body cells that have been reprogrammed to be non-specialized through induction, or exposure to genetic or environmental inducers (Malik, & Mahendra, 2013). iPSCs can undergo rapid cell division providing stem cell

researchers with a source of material for regenerative medicine that does not involve the ethically contentious termination of embryos, and can be more immunologically appropriate, as the donor and recipient can be the same person. In more recent research, hTERT has been found to be activated in 73% of cancers and, in some cases, as a result of promoter methylation, suggesting that the promoters can no longer bind to repressor proteins leaving the gene active (Anonymous, 2017, Kakui and Ullman, 2017; Barthel et al., 2017).

As mentioned earlier, activation of telomerase and telomere lengthening is essential for stem cell maintenance, however, macro environmental factors, such as stress, diet, and exercise can influence the rate of telomere shrinking. Based on this work, Blackburn and others have founded a company, Teloyears, that measures telomere length in circulating blood cells. Because hematopoietic stem cells reside in the bone marrow and give rise to a fresh supply of blood cells, telomere length in these cells can serve as biomarker for "biological" age, and by inference the activity of telomerase in this stem cell population. More recent studies have suggested the exercise and meditation can prevent telomere shortening and Teloyears is designed to be used to monitor how life experiences affect telomere length.

V. HeLa Cultures and Contamination: The Intersection of Biology, Race, Class, and Gender

Cell Culture and Cell Banks

Today, thousands of cell lines have been established using refined methods of tissue culture. The first human cell lines, much like HeLa in 1951, were established by placing freshly removed human tissue in a growth medium containing animal cells, or human fetal cells. These "feeder" cells provide the newly transplanted cells with the appropriate growth factors and extracellular matrix (ECM) to establish the environmental conditions necessary to sustain growth for this new cell lineage, or cell line.o promote cell viability, cell lines must be incubated at the right temperature, humidity, and CO_2 levels. The cell lines are maintained by human researchers who "split the cells" daily. Splitting involves washing the cells and reducing their numbers by distributing (splitting them up) them over numerous Petri dishes. This process of splitting removes waste, dead cells, excess cells, and old culture media and provides cells with fresh media containing growth factors and adequate space to ensure continued cell division (Slide 29: What is Cell Culture).

Because researchers split the cells daily, great care must be taken to ensure a sterile environment. In order to limit contamination by cells either shed from the body of the person performing cell culture or present in the environment a tissue culture hood is used. The tissue culture hood uses air flow to pull air up and out away from the cultures, keeping the working environment sterile. Laboratories using human cell lines are designated as Biosafety level 2 (BSL2) and require special ventilation and air flow rates, as well as sterile biosafety cabinets and sterilizing equipment. Thus, human tissue culture experimentation is a costly endeavor, but one that can produce a wealth of knowledge and a range of biomedical products. Cells can be cultured short-term to serve as sites of experimentation for screening toxins and environmental chemicals, or for the development and testing of drugs and vaccines. They can also be used as biological factories to create humanized proteins for therapeutic outcomes. Cell lines can also be frozen at -80°C for long-term storage and thawed out when needed, allowing researchers to start and stop time with respect to the life of the cell line. A short video produced by EuroStemCell presents a "walk- through" of a cell culture lab, highlighting some of the most important aspects of cell culture. (Duguid, 2010)

Video: Duguid, C. 2010. Video: Cell Culture. EuroStemCell. (Producer Kate Doherty) (6 minutes). Link

In the story of *The Immortal Life of Henrietta Lacks*, written by Rebecca Skloot, the notion that time can be frozen and a cell line resurrected is revisited throughout the narrative. Because cells can be thawed, placed in in the optimal growth conditions, and divide, it means that cell lines "live" past the typical human life span. In the case of the Lacks family, this caused some family members to pause and consider the spiritual and cultural ramifications of such manipulations (Skloot, 2010).

As the title of Cynthia Verspaget's artwork suggests, such cells are exhibiting a type of "anarchy," either refusing to stay connected to the individual from whom they originated or, perhaps, reaffirming this human connection. In this work, Verspaget fused her own cells with HeLa cells to create what she calls a new "artistic cell line." Her work questions the notion of ownership and cell memory that can be rendered obsolete through laboratory manipulation, and poses philosophical questions regarding kinship and ontology (Verspaget, 2004). (Slide 41: Anarchy Cell Line). Helen Wilson-Roe seeks to redress this loss of familial connection through a collective work, "A Brush With Immortality," in which she painted portraits of individual Lacks family members and exhibited these alongside photographs of HeLa cells caught in various stages of cell division (Wilson-Roe, 2013). Adele Senior, has written about other bioartists who have used HeLa cells and the narrative of their derivation to highlight the human connection, and RadioLab conducted an extra segment on the evening of the premiere of the film adaptation of Skloot's book (Senior, 2011; Radiolab; Wolfe, 2017)

Anthropologist Hannah Landecker explores further what the ontology of cell culture means to society, and writes in the introduction to her provocative book *Culturing Life: How Cells Became Technologies*:

> Despite its relative novelty in historical terms, this state of life has quickly become normal, imbuing scientific objects such as cell lines with the aura of inevitability or, ironically enough, with an air of natural existence. How is it that life, once seated firmly in the interior of the bodies of animals and plants, came to be located in the laboratory? At what point did living matter get extracted from and stripped of the individual forms of organisms? Further, why did the cells of humans become incorporated in the research biomass along with those of other organisms, and how do the lives of such human-derived objects affect the concept of the human subject? How did life, including human life, take this contemporary disembodied, distributed, continuous form? The question of where tissue culture came from is not only one of origins but also of conditions - of what makes it possible for these biotechnical things to exist in these detached, and transformed ways. (Landecker, p. 4, 2007).

She goes on to investigate the ways in which the freezing of cell lines plays an important role in creating a new temporality and commodity. By freezing and cataloguing cell lines, researchers can store, ship, and exchange cell lines with one another.

As cell culture techniques expanded, a new industry emerged, supplying researchers with reagents, media, and materials as well as the cell lines themselves. Thus, although George Gey, with his firm belief in the free exchange of scientific knowledge, supplied researchers worldwide with the HeLa cell line at no cost, much like Leonard Hayflick did with WI-38, present practices often involve the purchase of cell lines through national or international clearinghouses.

As cell line expert John Masters of University College London puts it, "Much of what we know today and much of what we do tomorrow depends on the supply of HeLa…" HeLa was used to study infectious agents, including polio, making it possible for Jonas Salk to develop the life-saving polio vaccine in 1952 (Masters, 2002). Salk, like Gey and Hayflick, operated on the unwritten rule that if scientific results are published, scientists are obliged to share their work freely with other scientists to promote scientific knowledge and to advance human health. To that end, HeLa cells were grown in space to test the effects of zero gravity and radiation on human tissue, and were exposed to countless drugs and toxins on earth for drug development purposes. Even in today's modern research, HeLa is still the most widely used human cancer cell line. To trace its provenance and use, Walbaum created an infographic for a short article authored by Erin Biba for *Wired Magazine* (Biba, 2010). (Slide 42: HeLa Everlasting)

To produce the vast quantities of cell lines needed to conduct this work, scale-up techniques were developed. Walter Nelson Rees, the researcher who discovered through use of genetic markers that HeLa cells had

contaminated other cell lines, co-authored an historical perspective entitled “Henrietta Lacks, HeLa Cells, and Cell Culture Contamination” published in the *Archives of Pathology and Laboratory Medicine Online* just before his death in 2009 (Lucey, 2009). The perspective outlines a rich history, and describes the inventions, such as the bioreactor, that produced the enormous quantities of cells needed for such clearinghouses. Two major repositories are the ATCC and the European Collection of Animal Cell Cultures (ECACC), which provide international access to a variety of cell lines that have been tested and had their histories documented. This standardization assists experimental reproducibility and regulatory approval procedures. Using the ATCC online database, one can review information about the creation of the cell line, the genetic and biological characteristics of the cells, and any additional genetic characteristics unique to the cell line such as HPV 18 DNA and the presence of genomic instability M regions (ATCC CCL2 accession number). Both of these genetic characteristics contribute to the immortality phenotype.

A closer look at the genomic instability information reveals a common phenomenon in cell culture, which is the power of evolution. Cells in a Petri dish are competing for resources such as growth media and space. Any genetic changes that would allow a cell to utilize resources more efficiently or quickly, will be at an advantage. Cancer cells often have DNA mutations in genes that code for proteins that control mutation rate, or DNA repair. Thus, they tend to accumulate mutations at a faster rate than non-cancerous cells, and often these mutations take the shape of large DNA rearrangements. So not surprisingly, many cell lines are established from cancerous tissues because these cells have genetic mutations that allow them to create more mutations. These frequent DNA rearrangements are described as genomic instability, because entire regions of chromosomes are fragmented, translocated to other chromosomes, deleted, or duplicated. Thus, as cells compete for limited space and resources in the Petri dish, they undergo rapid cell divisions due to continuous exposure to growth factors and accumulate genetic mistakes or mutations at a quick rate. The HeLa cell line, being one of the oldest cell lines in culture, can contain cells in its Petri dish with up to 80 chromosomes, rather than the typical 46 that appear in our bodies. Given this rather dramatic difference in genetic content, some researchers have proposed that the HeLa cell line represents a species distinct from human. Evolutionary biologist Leigh Van Valen and his colleague Virginia Maiorana suggest renaming HeLa as *Helacyton gartleri*; cyton, from the Greek *cytos*, reflecting the neutral gender of the cells; and gartleri after geneticist Stanley Gartler, the researcher who documented the cells’ evolutionary fitness advantage over other cell lines (Oliwenstein, 1992).

Feminist scholar and scientist Lisa Weasel points to the irony of demoting HeLa to a microbial species, despite its ability to survive in multiple environments. She considers the inconsistency to be rooted in both sexist and racist thinking. She explains how race, class, sexuality, and gender intersect in this attempt to reclassify HeLa cells as a new species because of their inability to breed with humans.

> “The route from human carcinoma to novel microbe was not one uniformly accepted in evolutionary biology, calling into question the researchers’ designation of HeLa cells within the kingdom Protista, which somehow implied that evolution could take place backwards, retroactively transforming a complex metazoan into a primitive protist … And so the story comes full circle, the madly proliferating cells, now verging on becoming a separate and inferior species, linked at least in some readers’ minds to the unbridled, infectious sexuality of a black woman from Baltimore. Is this mere coincidence? After all, the HeLa cell line could just as easily have been derived from a lung carcinoma from Herbert Langston, a middle-class bank teller from suburban New Jersey, or from the prostate cancer of Henrik Larson, a Scandinavian immigrant living in the Midwest, or from any other number of individuals whose first names began with the letters “He” and last names with “La” and were host to a pernicious cancer proliferating wildly within their confines. Then we might read the story differently, or might not tell it at all (Weasel, p 187, 190, 2004).

Though Weasel explains that the HeLa cells’ proliferative power is a result of infection with the sexually transmitted HPV 18, she does not unravel how the very nature of viral infection is caught up in the intersection

of biology, race, class, and gender. Henrietta Lacks, unlike the laundry list of theoretical male cancer patients she brings forth, was an African-American woman who did not access healthcare early on due to her social and built environment. In the 1950s, John Hopkins Hospital served as a Charity Hospital and was one of the only hospitals serving African-Americans during this time. Given her responsibilities to raise children in a patriarchal community that had a deep mistrust of the medical establishment, due to centuries of practice during which African-American slaves were used as experimental subjects, she postponed what might have been perceived by others as routine care. Because of her race, class, and gender she arrived at John Hopkins Hospital with late-stage cervical cancer.

The aggressive nature of Henrietta's cancer was partially due to this delay to seek medical care as well as a compromised immune system. Being infected with multiple sexually transmitted diseases taxed her immune system. Thus, immune cells that address virally infected cells and clear them from the body,were not efficient, resulting in multiple copies of HPV18 genomic DNA being inserted in more of her cervical cells' genomes. Had the cancer been detected in its earliest stage, the number of insertions would be far less, leading to a less aggressive cancer phenotype. In 1951, the Pap smear was not yet available in the United States, making cervical cancer a challenge to diagnose and prevent. Cervical cancer screening via the Pap commenced in the late 1950s, increased rapidly after 1960, and grew steadily until 1973, when it stabilized. These statistics are applicable to Caucasian women who had access to healthcare, but does not address the African American community that remained marginalized and fearful of the medical establishment. It should be noted that the unethical Tuskegee Syphilis Trial conducted on African American men was not terminated until 1972.

As Rebecca Kumar states in her Open Letter to the faculty at universities and colleges, to teach the story of Henrietta Lacks without giving close attention to the social and political context in which these cells were brought into the biomedical arena disregards the systemic injustice that has occurred in the African-American community, and does nothing to remedy the health disparities that continue to challenge marginalized societies today (Slide: 43: Open Letter). Kumar writes:

> " I confess that I too have given blood for HPV vaccine research so I could get $75 to help supplement my grad school stipend; I did it so that perhaps one day less women will suffer from HPV, but I admit, shamelessly, I did it for the money as well. When I went to give my blood, the office was populated primarily by African-American women, Latina women, and students. Skloot's narrative is therefore part of a much longer history that intimately ties quantifiable "knowledge" to eugenics and the female body….Thus, I am of the opinion that the "immortality" to which the title of the book refers is as much a reference to the racism behind the first cut that took Lacks' cells as it is to Lacks' cells themselves. (Kumar, 2012)

Charnell Covert, artist, actor, activist, and health justice scholar, echoes Kumar's view in her theatrical production "They called me HeLa," which provides viewers with a counter narrative about the provenance of the HeLa cell line.

Video Slide Show: Covert, C., Chamany, K. and Elie, C. 2013. They Called Me HeLa Educational Slide Show. Stem Cells Across the Curriculum/Media. Link.

Ruha Benjamin, a sociologist interested in scientific innovation and equity, challenges us to be more forward thinking and to learn from our mistakes of the past. She challenges the the biomedical community to be critical of approaches that result in study designs that are ill matched to community context and needs. In a TedX Talk she discusses the derivation of a profitable cell line in the face of health and economic inequities (Benjamin, 2014).

Cell Line Contamination

Undergirding the exciting discoveries and innovation that accompanied the development of cell culture techniques is one of the most challenging issues plaguing biologists over the past 50 years, namely cell line contamination. Because a cell line is defined as a collection of cultured cells derived from one specific tissue in a single donor, its provenance is of importance. While the ability to divide indefinitely is certainly the most essential quality of a cell line, the specificity of the cells' origin from a single tissue type and from a single donor is a crucial aspect of the research conducted using this tool. For example, a potential stomach cancer drug would need to be tested specifically on human stomach cancer cells, not lung or other tissue origins. Similarly, for stem cell transplant therapies, most often the donor and the recipient should be one and the same, to reduce graft rejection due to immune incompatibility. In these instances, cross-contamination of cell lines (where a more aggressive cell line take over the culture) becomes an issue, as the validity of the study or the efficacy of transplant therapy depends on knowing the very specific origin of the cells (Masters, 2002).

After HeLa was developed in 1951, scientists were able to culture other human cancers using Gey's technique, and soon after the issue of contamination emerged. As scientists started culturing non-cancerous human cells, they noticed that their cells "spontaneously transformed" in culture to divide rapidly and continuously like cancer. Not long after, scientists began finding evidence of interspecies contamination among cell lines. As early as 1957, researchers were using immunological and karyotyping techniques (observation of chromosomes) to determine species of origin and detect cross-contamination between lines of different species. The use of fluorescent antibody detection in the early 1960s furthered such discoveries. This led scientists to wonder whether cross-contamination was occurring for cultured cells within a species as well.

In 1967, Stanley Gartler made an astonishing discovery that was deeply disturbing to biologists working on human cell lines (Culliton, 1974). Using isoenzyme analysis (a technique comparing enzymes that vary within a species), Gartler showed that two separate human enzymes, G6PD and PGM, which were known to vary within the human population, were identical for each cell line in his survey of 18 human lines sampled from the ATCC. The statistical odds of all 18 cell lines sharing identical phenotypes for these two proteins are nearly impossible. There were only two explanations: either all cell lines reverted to this phenotype in culture, or the cell lines were identical, a result of contaminating overgrowth by an aggressive cell line (Oliwenstein, 1992; Masters, 2002).

In the 1950s, there were a limited number of cell lines and most were established from tissues obtained from Caucasians. Thus, the frequency distribution of two variants of the gene coding for the G6PH enzyme was utilized as a means of identifying the HeLa cells line as Black. The "A" variant is the result of a genetic mutation that reduces the efficiency of the enzyme, but is believed to provide a protective effect against malaria, reducing infection rates by 46-58% (Ruwende et al., 1995). This variant is more *common* in individuals of African descent given their continued environmental exposure to mosquitoes harboring the protozoa *Plasmodium falciparum* responsible for malaria. Over time, African populations living in endemic malaria zones evolved to carry this gene variant as it improved survival.

The race-based analysis of the HeLa cell line was only possible given the small number of cell lines at the time and the limited population sampling represented in these lines. Because there were only 18 cell lines in existence and all but Henrietta's were derived from Caucasians, generalizations about the distribution of gene variants among populations allowed the tracing of a cell line's provenance back to HeLa. Additionally, it was known that cell lines do not revert to this phenotype but maintain the phenotype of the original donor. Collectively these data suggested that HeLa cells had infiltrated the other cell lines. This cross-contamination explained why it was suddenly possible to culture non-cancerous tissue types when they "spontaneously transformed" after a short time in culture. HeLa was the elusive "transformation factor," and the other lines had been overrun early during the culture process and were actually HeLa (ErinC, 2009).

The notion that cells can be defined as Black goes against research that demonstrates that race is socially constructed and not biologically based. It is of note that population genetics is based on frequencies that describe general trends and that traits are not discontinuous in human populations such that one population carries a genetic variant at the exclusion of all other variants. The distribution of G6PH genetic variants is the result of environmental factors that placed selection pressure on the population and, thus, altered the frequency of the A variant in different human populations; this is similar to the explanation of the emergence of haplotypes that vary in frequency among human populations (Online Mendelian Inheritance of Man). So though the genetic structure of human populations corresponds to stressors specific to geographic locations, this structure does not support essentialist conceptions that racial categories are discrete or informative. A project developed with funding from the National Science Foundation and the American Anthropological Association entitled "Race: Are We so Different?" provides a deeper analysis of race and genetic variation, as does the PBS series "Race: The Power of Illusion." Given the inclination of society to carry essentialist notions concerning genes and race, it is of import to contextualize the narrative of the HeLa cell line within a larger socio-political context. If given cursory address, the discussions regarding cell contamination and race can reify essentialist beliefs regarding race by suggesting that there is an entitativity (characterizing groupness) dimension in this sort of thinking (Donovan, 2013; Donovan, 2015).

In her book *Culturing Life*, Landecker remarks on the ways in which the boundary between the scientific community and the lay public became blurred around discussions of cell line contamination by HeLa cells (Landecker, 2010). That cell lineage was being described in race-based language, and associated with terms like "contamination" and " aggressive" presents a particularly unique challenge to scientific communication. Though "contamination" in the lab refers to lab practices and is a result of poor sterile technique, the term carries with it a negative connotation, not unlike the ways in which "contamination" is referenced in non-scientific communities.The term "contamination" was often used during the eugenics movements of the US and Nazi Germany. The prefix "eu" implies purity and is applied to describe the pure genetic lineage of those considered "fit" enough to reproduce. Thus, those individuals who were considered "unfit" were prevented from "contaminating" the gene pool of these "pure" populations through policies that regulated reproduction as well as elimination of those individuals deemed unfit (Brignell, 2010a; Brignell 2010b). This rationale of maintaining a true-breeding population of humans goes against all scientific evidence. Evolutionary theory is based on the fact that hybridization produces genetic diversity in populations allowing them to survive environmental changes.

Additionally, the notion that a cell line derived from an African-American woman was being referred to as "aggressive," and that the immortality characteristic was attributed to a sexually transmitted viral infection, led to a conflation of the cell line and the person from whom they were derived. The use of "aggressive" was similarly problematic, given the social history of labeling African American women as "angry black females."

At times it was difficult to know whether the conversation was about the cell line or Henrietta herself when terms like "promiscuous" were used. For scientists, promiscuity refers to a cell line's ability to take up DNA from its environment and grow more rapidly. However, for the general public, all of these descriptive terms to linked to societal prejudices (Landecker, 2010). During the height of the Social Darwinism movement, the term "unfit" was often used in conjunction with "promiscuity." More recently, James Watson, co-discoverer of the structure of DNA has, on more than one occasion, remarked that people of color have an elevated sexual appetite. Watson's ideas echo those who showcased Sarah Baartman, known as the Hottentot Venus, in public venues as a highly sexualized African woman during the 1800s. So though using words like "contamination" and "promiscuous" may seem benign in the lab, it may unintentionally register differently in the minds of students and, be linked to these other discriminatory remarks that have a deep and troubled history.

Interestingly, the scientific community on the whole does not seem ready to address this social implication nor the issue of contaminated cell lines in general. Gartler's work was extended throughout the 1970s by Walter Nelson-Rees of the Cell Culture Laboratory at UC Berkeley. For more than 10 years, Nelson-Rees collected

information from 144 publications identifying cross-contaminated cultures and compiled a list of 279 contaminated lines, more than 40 of which were HeLa. Both Gartler and Nelson-Rees were shunned for exposing cell line contamination. Acknowledging it would devalue years of research, commercially available products, and long-held paradigms about how cells behave in response to environmental toxins, drugs, vaccines, and reprogramming factors. In the 30 years since Gartler and Nelson-Rees presented their findings, little attention has been given to the issue of cell culture contamination and its consequences for biomedical research (Lucey, 2009).

Video: Duguid, C. 2010. Video: Cell Culture. EuroStemCell. (Producer Kate Doherty) (6 minutes). Link

With the advent of molecular techniques for identifying cell lines, the issue of cross-contaminated cell lines has resurfaced. John Masters has published widely about the extent to which cell lines appear to be mixed populations, and despite an entire session devoted to the topic in the 2009 American Society for Cell Biology conference, there has been little response to rectify this situation (Masters, 2002, Ouellete & Nardone, 2009)

The most up-to-date list of cross-contaminated cell lines that has been published includes 360 lines, 106 (9%) of which are HeLa. This list, compiled by Capes-Davis (of CellBank Australia) and a team of researchers from other major international cell banks, was generated through the PubMed database, references within articles relating to the topic, and websites of five major cell banks: ATCC, DSMZ (Germany), ECACC (Europe), JCRB (Japan), and RIKEN (private, Japan) (Slide 44: HeLa Contamination). The authors hope that the list will be included in a new initiative improving access to authentication data in the form of a free database, and more recently the lead author, Amanda Capes-Davis, a physician and researcher, has taken to annotating publications in PubMed that contain incorrect cell line identities (Capes-Davis et al., 2010; NCBI, 2014)

The percentage of contaminated cell lines found in collections has apparently decreased, from the initial 100% contamination of ATCC stocks reported by Gartler in 1967, to present-day estimates for various collections of 18%. However, this decrease may be the result of expansion of collections, and not due to more rigorous methods of derivation and storage. When Gartler found that 100% of lines were contaminated with HeLa, there were very few other lines existing, and methods for immortalizing cells were not yet invented. In Nelson-Rees's time, more cell lines had been created, but not nearly as many as exist today. The fact that recent studies report significant contamination (10-18%) is disturbing, because we now have highly efficient methods for identifying cell origins (Katsnelson, 2010; Masters, 2012; Del Carpio, 2014; Marrow, 2015; Grens, 2015).

The DSMZ cell bank in Germany has played a large role in exposing the issue of cell line cross-contamination, and has been a pioneer among cell banks in practicing measures to improve their collections. It routinely performs multi-parameter (DNA typing, cytogenetic and immunophenotypic) authentication.

Purchasing cells from cell banks instead of sharing among colleagues would help to reduce the misidentification of cell lines, although this may squelch the collaborative and collegial practice of scientific investigation. Others critics suggest that government and private sponsors should require authentication of cell lines when receiving submissions for grants and contracts. In fact, the FDA has adopted this mandate, as has the National Cancer Institute (Chatterjee, 2007; Nardone, 2008).

Although the cross-contamination issue is one that should be addressed by the cell biology community, stem cell researchers learned early on that verifying newly established stem cell lines is essential. The very nature of stem cell research requires a researcher to be able to demonstrate that a specialized cell is capable of adopting a wide set of cell fates without cell fusion or contamination by other cell lines. This was a particular sticking point when the first putative adult stem cell lines were reported, because they were cultured on embryonic feeder cells. Later studies demonstrated these adult cells were able to adopt multiple cell fates as a consequence of cell fusion between the cell line in question and the mouse embryonic feeders. For this reason, more recent studies have taken great care to keep cell lines pure, and include repeated monitoring of

lineage-specific characteristics for that cell line, using molecular techniques to ensure that no cell cross-contamination has occurred (NCBI, 2014; Anonymous, 2015; De Los Angeles et al., 2015)

VI. Cervical Cancer, HPV and TERC: Prevalence and Diagnostics

Cervical cancer is a cancer of tissue from the cervix, an organ that connects the vagina to the uterus or "womb", and is the second-most common cancer for women of reproductive age, disproportionately affecting those with inadequate access to healthcare. There are approximately 530,000 cases of cervical cancer each year, half of which result in death and 98% of which occur in resource-poor settings. Harald zur Hausen made the first link between HPV and cervical cancer, postulating his hypothesis in the late 1970s and discovering the HPV DNA in the human genome in the 1980s. He was recognized for this work with Nobel Prize in Physiology and Medicine in 2008.

Illustrated Presentation: Nobel Prize in Physiology and Medicine 2008.

Later studies confirmed that the HPV virus acts as a cancer promoter and is associated with 99% of all cervical cancer biopsies. More recently, HPV has been linked to other cancers of the urogenital region and oropharyngeal cancers (WHO; NIH; Scudellari, 2013).

Early-stage cervical cancer often appears asymptomatic, because the cervix is an internal tissue not readily visible to the eye. With introduction of the diagnostic Pap smear in the late1950s, cervical cells could be analyzed, providing earlier diagnosis and treatment and a subsequent drop in cervical cancer death rates in North America and Europe. Pap smears involve microscopic analysis of cells scraped from the cervix in order to detect cellular abnormalities that might progress to cancer. Abnormal or "dysplastic" cells detected though a Pap smear are often described in stages of progression towards cancer. These stages are cervical intraepithelial lesions level 1, 2 or 3 (CIN1, CIN2, CIN3), or low to high-grade squamous intraepithelial lesions (LSIL or HSIL). Cells classified as LSIL are more likely to regress, whereas HSIL cells are more likely to persist or progress to cancer. Cervical screening using the Pap smear was integrated into the US and UK in the 1960s resulting in dramatic reduction in mortality rates associated with this type of cancer. Early detection triggers more frequent screening and if abnormal cells are detected, they can be removed via micro laser surgery or cryotherapy.

In resource-poor settings, the technological requirements for Pap smears are not tenable. In these settings, a similar procedure, Visual Inspection Analysis (VIA) does not require a microscope extended health training, nor specialty labs to process samples. VIA screens for cervical abnormalities using a combination of acidic solution and iodine to visualize cell abnormalities on the surface of the cervix and can be performed by anyone after two days' training. The sensitivity and specificity of VIA approximates that of the Pap, averaging 82% and 87% respectively, with results received the same day. This short turnaround time is crucial for reducing loss of patients due to long callback times, and allows for immediate follow-up diagnostics and treatment. These attributes of VIA make it a particularly useful diagnostic for rural populations where individuals must travel long distances to obtain cervical screening (Monsonego et al. 2003).

However, given that HPV infection in most cases is cleared by a healthy immune system, screening to reduce cancer progression presents challenges. Over 20 million people are infected worldwide by one of over 100 possible HPV strains. However, only a subset of HPV strains can infect the urogenital and oralpharyngeal tissues, and only a subset of these have been associated with cancer, or considered oncogenic promoters. So an effective diagnostic would be one that can distinguish who of this very large population of HPV+ will go on to develop precancerous lesions that need to be removed.

Just as advances in science led to more sophisticated cell culturing and cell identification techniques, they also led to a range of diagnostic techniques that can capture cervical cancer susceptibility long before any

cancerous characteristics emerge. Additionally, vaccines to prevent infection altogether have also been developed. These techniques are based on basic scientific knowledge about the relationship between HPV and the host, and specifically genomic changes that promote oncogenesis.

HPV awareness has increased with the development of vaccines that provide 100% immunity to two of the most oncogenic strains (HPV16 and 18) and multivalent vaccines are being used in clinical trials in an effort to provide coverage for additional strains (Luxenbourg et al., 2015). When the actor Michael Douglas announced that he had throat cancer, the news lit up the blogosphere illustrating how lifestyle behaviors (smoking and drinking) may have elevated his risk of cancer (Jaslow, R., 2013). Similarly, when Melissa Mark-Viverito, City Council Speaker of New York City, revealed that she was undergoing surgery to address her HPV-related cervical cancer, her twitter feed exploded (Editorial Board, 2014). These announcements were made in an effort to reduce the stigma associated with HPV infection and increase awareness for screening and vaccination. However, with only the cervical and anal Pap smears available to those under the age of 30, the sensitivity and specificity of this approach results in repeated screening for those that test positive, an unclear prognosis moving forward, and stigma when they reveal to partners (Shire, 2014). In some cases, those under 30 are recommended to obtain an additional diagnostic, the Dihybrid Gene Test, but as described below, this test does not reveal how the human body is responding to HPV infection and thus leaves many in a fearful state and inappropriately blaming partners of infidelity. This challenge is the result of the complex HPV-human co-evolution that has taken place over centuries, resulting in a benign symbiotic state in most HPV+ individuals.

When HPV enters human cells it can exist in one of two states: either the viral DNA remains separate from the host cell nuclear DNA in the cytoplasm as a circular genetic element, or the viral DNA linearizes and integrates into the host genome. The former state tends to result in benign infection, with most individuals mounting an immune response that clears the virus with no further cellular abnormalities. In some cases, people will remain HPV+ with no pathological symptoms. However, in some individuals when the virus integrates into the host genome, the production of viral proteins can sequester and destroy host tumor suppressor proteins, leaving the person more vulnerable to cancer progression over time (Ambros & Karlic, 1987). (PPT Slide 44: Infection and Progression)

Young people with robust immune systems are often able to clear HPV infections before the age of thirty, while older individuals, those with other infections or compromised immune systems, and those who are designated high-risk for cancer development may be unable to clear the infection. When HPV infection persists, individuals are monitored and tested for the presence of oncogenic variants of HPV using genetic diagnostic analysis (Digene Hybrid Capture II). In addition, the host cellular response is also monitored in the form of a Pap smear. (PPT Slide 45-53: HPV and Cancer Diagnostics)

However, these two diagnostics, although important to the pubic health system, occupy two ends of the spectrum of HPV infection. An HPV DNA test is considered an early stage viral infection diagnostic. The DNA test provides information about the presence of viral DNA, and is only capable of detecting the 13 most oncogenic strains. As mentioned above, it is not the presence of HPV DNA that is important, but rather the intracellular location. If the HPV DNA is not integrated into the human genome but exists on its own in the cytoplasm, there is little medical concern. The HPV DNA test detects initial stages of the viral-host interaction but is not the best predictor of oncogenic development, because it provides no information on the integration status of HPV DNA. On the other hand, the Pap smear is a late stage diagnostic that depends on host pathology, as it tests for the host's response to HPV infection in the form of cellular abnormality. The Pap reveals the host cell changes that have already occurred long after the HPV DNA has integrated. Still with the Pap, we have no definitive way to predict who will progress to cancer among those with an early-stage cellular abnormality. It has been reported that 10% of individuals who test for low-grade cellular abnormality will progress to high-grade, 60% will regress or clear the infection, and 30% will maintain low-grade abnormality.

Therefore, combining the HPV DNA test with Pap testing does not provide adequate predictive power, requiring individuals who are HPV$^+$ and Pap$^+$ to undergo multiple, frequent HPV and Pap screening to determine if viral clearance, viral maintenance, or disease progression is occurring. (PPT Slide 44-53)

To address this gap in diagnostic testing and better predict who among the HPV$^+$, and Pap$^+$ population will progress to cancer, two new diagnostics have emerged that specifically address human cell responses to HPV infection and can be categorized as intermediate stage diagnostics. The following animation provides an overview of the impact of cervical cancer, the molecular pathology leading to oncogenesis, and the ability to determine which HPV+ individuals are most likely to have disease progression.

Animation: HPV OncoTect Animation.mp4. *YouTube*. Animation Link

The first category of diagnostics to evaluate the status of human cell response to HPV infection indirectly detects whether viral integration into the human genome has occurred by testing for HPV RNA. Viral RNA will only be produced if the viral genome has integrated into the human host genome. This RNA serves as a template to build viral proteins that can sequester human tumor suppressor proteins. By binding to the tumor suppressor proteins, the viral proteins prevent these proteins from doing their natural job of tumor suppression. Diagnostics that test for HPV RNA include Pretect Proofer and APTIMA, the latter of which has been approved in the U.S. but is not in wide spread use. These tests detect the presence of E6 and E7 viral mRNA, indicating that viral DNA has integrated into the host genome, is being transcribed by the host cell machinery into RNA, and that this viral RNA is actively being used to synthesize viral proteins (E6 and E7) that will hijack the cell's tumor suppressor pathways (p53 and RB).

The second category of diagnostics evaluates the outcome of HPV DNA integration on human genome integrity. oncoFish cervical, detects host cervical cell genomic instability, or the rearrangement of genomic sequences as a consequence of viral DNA integration (Ikonisys; Zhao & Yang, 2012; Cuzick et al., 2013). When HPV DNA integrates into the host genome it can cause genomic instability, a process by which large regions of human chromosomal DNA are duplicated and inserted into random locations in the host genome, often on other chromosomes. What results is a case of "too much of a good thing." One of the most common regions to be duplicated and inserted is the TERC human genomic sequence, which codes for an essential RNA component for telomerase activity. Multiple copies of TERC on multiple chromosomes, results in elevated telomerase enzyme activity, allowing these cells to divide indefinitely or to become "immortal." As these transformed cells undergo cell division they continue to accumulate genetic mutations that could contribute to cancer development (Hesselmeyer-Haddad, 2005). One of the earliest hallmarks of cancer progression is gene rearrangements, or large-scale gene duplications, which can be visualized using molecular biology and microscopic techniques (Hanahan & Weinberg, 2011).

Because humans typically receive 23 chromosomes from each parent, for a total of 46 chromosomes in each cell of the body, diagnostics that visualize specific regions of DNA on the chromosomes can be instructive in the case of HPV infection. Using a fluorescent DNA probe capable of binding to TERC duplications within the genome allows physicians to determine the number of TERC duplications suing a simple visual screen. Since humans should receive one copy of TERC from each parent. Each cell should exhibit two such DNA sequences. If the DNA probe identifies more than two, it suggests that the genome is unstable.
The TERC sequences codes for an essential telomerase RNA factor. The more duplications a person has in their genome, the more TERC is made available for telomerase to function. With telomerase active, these cells are essentially "immortal," no longer recognizing the environmental cues that would regulate cell division.

Animation: Bohan, M. 2005. Checkpoints and Cell Cycle Control: Normal and Abnormal Cell Division. President and Fellows of Harvard College and MCB- HHMI Outreach. Animation Link

Thus, the oncoFish test quantifies the number of TERC duplications in host cells. If the number of repeats is higher than two (i.e. one from each parent), this suggests that the genome is unstable, and a higher repeat number means a higher risk for cancer development. Currently, oncoFish technology has been approved by the FDA to detect susceptibility for breast and bladder cancers, by detecting DNA duplications that are specific to those cancers, and as of the date of this publication the technology is only in the test phase for cervical cancer in the U.S. Ikonisys, the manufacturer of the oncoFish cervical test, has established a clinical laboratory in the U.S. that has been certified by the Clinical Laboratory Improvement Amendment (CLIA) and works with partner health clinics to market this diagnostic choice directly to women and their clinicians (Ikonisys).

Ikonisys claims to have solved one of the greatest challenges in cervical cancer screening. oncoFish cervical can distinguish between individuals who are infected, but not harmed by HPV. Their unique approach to visualizing the human cervical cell response to viral DNA integration indicates who is at higher risk of progressing to cancer. Through DNA probes detect one of the early hallmarks of oncogenesis, namely genomic instability, or the shattering and recombination of chromosomal segments in the genome. This ability to distinguish the small minority of individuals who persist with HPV infection and develop pathology will reduce the total number and frequency of cervical cancer screenings for those who test negative with oncoFish, and provide close monitoring for those whose tests are positive.

Journalists, scientists, and clinicians will comment that no one really knows why Henrietta Lacks' cells were capable of growing outside the body, when all other human tissue samples proved unsuccessful. Perhaps their responses are the result of using only one disciplinary lens. If an intersectional analysis is applied, it is not hard to see how a culmination of social and biological factors resulted in an aggressive case of cervical cancer in which immortalized cells flourished. In 1951, Pap smears were not yet available in the US. Additionally, because African Americans were struggling for equal rights, there was no opportunity for regular healthcare, and what healthcare had been provided left fear in this community. Women were also struggling for equal rights at this time, and most felt constrained by gender roles that did not allow them to question their partner's sexual habits, which in the case of Henrietta involved multiple sex partners. So you have a situation where a young wife contracts multiple sexually transmitted diseases, one of which is capable of promoting cancer if not monitored. She does not seek medical care until the cancer has reached late stage, because of past medical abuses against African Americans and no local hospital serving this population. At diagnosis, her cells are found to be infected with multiple copies of the HPV virus, and her genome is recognized as fragmented and unstable. That HPV related cervical cancer today accounts for over 280,000 deaths per year with 98% in under resourced areas, suggests that immortalized cells are the endgame for many who do not have access to regular screening and healthcare and who live in societies where women still struggle to have voice.

VII. What Policies Are in Place for Regulating Research with Human Subjects?

Advances in science and technology, and an increasingly complex network of stakeholders, have led to a range of national responses to the international call for ethical biomedical research. Countries have operationalized and expanded the directive of the Declaration of Helsinki in various ways. In most cases, the establishment of regulatory bodies and rules was in response to news that unethical practices had occurred.

Nuremberg and The Declaration of Helsinki
During WWII, Nazi Germany industrialized medical research,using prisoners as test subjects. Their practices extended to the most marginalized and persecuted, and included orphans, the mentally ill, and those of ethnicities deemed unfit by their ideology. The uncovering of these practices led to an international effort to curtail harms to those captured during war, but also extended protections more generally to all medical research subjects. A brief overview of the history leading to policy and practice regarding human research subjects is outlined below.

> The voluntary consent of the human subject is absolutely essential. The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.-*Nuremberg Code 1948*
>
> After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent.-*Declaration of Helsinki 1964*
>
> Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them.-*Belmont Report 1979*
>
> Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative.-*The Common Rule 1981*

Belmont Report and The Common Rule

In the US, The National Research Act of 1974 and the Belmont Report of 1978 require that human research subjects be informed of risk-benefit ratios, have autonomy in decision making, and have the ability to discontinue participation at any time. These regulations emerged when it was revealed that the US Public Health Service engaged in the Tuskegee Syphilis experiments of 1932-1973. The Tuskegee Trial prevented African-American men from acquiring antibiotic treatments even after the drugs became available in the 1940s. The rationale for the study was to study the disease progression in African American males over the course of their lifetimes. The Act has since been updated to provide special provisions for vulnerable populations including women, children, and prisoners (Code of Federal Regulations title 45).

In 1991, the Act was extended from the Department of Health and Human Services to the Food and Drug Administration (FDA) and fourteen other federal agencies, and is now known as the “Common Rule.” In this capacity, the Common Rule requires institutions to formulate an Institutional Review Board (IRB Guidebook) to oversee federally-funded research practices involving human subjects. IRB committee composition is designed to reduce conflicts of interest, and includes members from the institution who span a wide array of disciplines and practices, as well as members from the community and other institutions or organizations. All researchers supported by federal funding and using human subjects must apply for IRB approval, regardless of whether the research subjects reside in the US or other countries

Human Subjects Research Timeline

In 2010 more discoveries of the USPHS studies abroad prompted President Obama to request for a review and redress of the code of conduct regarding research using human subjects (Obama, 2010). These egregious practices included federally funded research that included forced sterilization of women in the name of reproductive medicine, deliberate infection of individuals in Guatemala to study sexually transmitted diseases, and DNA research that questioned the heritage of the Havasupai without their permission (Presidential Commission for the Study of Bioethical Issues, 2011a; Presidential Commission for the Study of Bioethical Issues, 2011b; Anonymous, 2012; Garrison, 2013; Lehrman, 2013).

Video: Thirteen/Education Broadcasting Corporation (Producer.) June 25, 2010. Religion & Ethics Weekly: Informed Consent and Medical Research. (7:22 min) Link

In response to the President’s executive order to minimize harm and increase effectiveness of research with human subjects, The Office of Management and Budget convened a working group titled Advance Notice of

Proposed Rule Making (ANPRM). In addition, the National Bioethics Committee and the National Academies of Sciences (NAS) issued reports documenting needed improvements in the system (Emanuel et al., 2011). Collectively, these committees and working groups proposed revised standards that address advances in science and technology and increased education and awareness. To that end, the National Bioethics Committee published a Study Guide titled "Ethically Impossible" for educators (Presidential Commission for the Study of Bioethical Issues, 2012). In addition to this guide, the Commission created an Education Link with several other teaching tools with many available in Spanish.

Unlike the original Common Rule, the proposed changes address ethical issues concerning privacy, compensation, and ownership that extend beyond the body of the human subject and include tissues, cells, and DNA of the individual, otherwise referred to as biospecimens. The proposals also emphasized a participatory action research model, in which communities are involved in directing and informing research practices and benefits to the community outweigh harms. Although some welcomed these proposals, were stalled until January 2017, due to concerns that such intensive management would stunt research efforts (Chamany, 2015; Anonymous, 2013a). In the interim, some researchers became wary of using clinical samples in population-based research (Emanuel et al., 2011).

In 2017, after an extensive review including 2100 public comments, the Common Rule was revised. In an effort to inform research subjects and avoid lengthy and jargon ridden language, the revisions require a concise summary of benefits and risks to research subjects. Additionally, identifiable specimens can be secured under broad consent, while de-identified specimens, as was previously done, do not require informed consent and IRB review. This last provision came under great scrutiny, given the media coverage of the HeLa cell line and its derivation alongside other case examples of dual use. Dual use in this context refers to specimens acquired for diagnosis and/or treatment and also for research. Though the proposed revisions had intended to require consent in these circumstances, many researchers felt it would halt research and, thus, this aspect of the rule was not revised.

Like the US, the United Kingdom has also implemented policies to uphold the ethos of the Declaration of Helsinki. These policies extend beyond the national healthcare system to include research practices and new technologies. The UK is considered a leader in this regard with a universal health care system and the establishment of the Human Tissue Authority (HTA) and the Human Fertilisation and Embryo Authority (HFEA). These bodies regulate practices surrounding collection and banking of biospecimens and issue licenses to those seeking their use in research. The UK has, in an unusual move, also addressed the balance between benefit and risk for research subjects by constructing a no-fault insurance fund for unintended medical harm suffered by research subjects within the context of research (VanderWalde & Kurzban, 2011). In order to address benefits more directly, the HFEA has additionally instituted an egg-sharing policy in 1993, which allows individuals seeking assisted reproductive technologies to obtain additional cycles at reduced cost, if they donate 50% of their eggs to biomedical research (HFEA Egg Sharing Schemes)

Given the UK's dedication to regulating the collection, management, and access to biospecimens, the ANPRM regarding the Common Rule turned to the UK and more generally the EU for guidance and adopted similar proposals. These included requiring projects funded by private dollars to abide by the Common Rule, but in the same breath eliminating the need for broad consent for de-identified specimens. The European Union, which had taken a similar approach, reversed its position at the end of 2015 drafting legislation that would grant researchers access to data for which patients or research subjects provided broad consent (Feldwisch-Drentrup, 2015).

Both the ANPRM and the EU legislative processes allowed for public input, and in some cases, open letters influenced the final outcomes. In the EU the European Data in Health Research Alliance, which included the Wellcome Trust, pushed hard for the reversal using the URL "Datasaveslives.com." In the US, the National Institutes of Health funded a project to collect public opinion through surveys informed by a meta analysis of

patient and research subjects' views via the Consent, Education, Regulation, and Consultation (CERC) Working Group of the Electronic Medical Records and Genomics (eMERGE) consortium working group (Garrison et al., 2015).

Embryo.IVF.Extranumerary ZoomGraphic

Technological Advances and Policy Making
In many countries, the interpretation of human subject ethics in the context of generating national biobanks presents new challenges.

Iceland's deCode, a company purchased by Amgen, has come under fire for a study that seeks to triangulate data from human research volunteers, genomic databases, and family members' medical records. This is the second time that Kari Stefansson, founder of deCode, has run into problems when creating a "work-around" for informed consent as it relates to population studies. The Icelandic Data Protection Agency (DPA), ruled that the company must first obtain informed consent from each individual to be studied, and that health records can be not be treated as publicly available information (Kasier, 2013).

In the US, the 2010 Stem Cell Research Enhancement Act implemented a policy to increase cord blood banking. This policy was in response to a Government Accountability Office (GAO) report that highlighted the lack of diversity in public cord blood banks. Cord blood has in recent years become the preferred source of blood stem cells that are used during transplant therapies for blood-related disorders, due to its less immunogenic properties and less invasive collection method as compared to either blood stem cells collected from bone marrow or the peripheral blood supply. Despite efforts to increase awareness around donations post-birth, 97% of all cord blood is discarded as medical waste, with the majority of donations occurring in the private cord blood banking sector. Reasons for the low donation rate include general mistrust of the biomedical community, concerns regarding identity and privacy associated with the samples, and resistance to the creation of marketable goods that may subsequently be inaccessible for the donor (Mohapatra, 2013).

Adult. Adult Cell Source. Blood Stem Cells ZoomGraphic

Patents and Laws
As the number and types of biobanks increase so, too, have the number of court rulings associated with biobanking, resulting in a significant impact on the diversity of, and public access to, banked human tissues and cells. Court cases can be divided into those addressing the patenting of banking *processes* and those that address banked *products*.

In 2002, Pharmastem, a leader in cord blood banking, sought licensing fees from commercial umbilical cord banks using their collection, freezing, and storage technology. Ultimately, Pharmastem sued the commercial banks for patent infringement, threatening the livelihood of not only commercial cord blood banks but public cord blood banks as well. The cord blood banks argued that the technologies were ubiquitous in cell banking and thus, considered "prior art." In 2009, the courts decided that the Pharmastem patents were invalid because the companies were not buying or selling cord blood, but simply providing a paid service to families interested in banking their newborn's blood stem cells (Kurtzberg, J. et al. 2005).

In 2013, the US Supreme court decided that Myriad Genetics's *product* patents on BRCA1/2 DNA sequences were not valid, reversing twenty years of patenting in the biotech sector. The court, however, maintained the validity of *process* patents for techniques in which a drug or diagnostic is developed based on DNA sequence information. Following these earlier rulings, it would seem that tissue samples themselves can not be patented because they occur naturally in human bodies, making them a public good (Marshall & Price, 2013). Yet, any discoveries made using such samples would continue to be patentable and thus, marketable. This stance regarding tissues and cells is apparent in decisions to invalidate the Wisconsin Alumni Research Fund (WARF)

patents on the first human embryonic stem cell lines, which were created using private funding and extranumerary embryos that had been donated from fertility clinics (Wadman, 2005).

In all of the above instances, financial benefit could be bestowed to all stakeholders, except the individuals from whom tissue or DNA samples are acquired (Kominers & Becker, 2012). In the US, the Bayh-Dole act of 1980 permits development of marketable and patentable products using basic scientific research conducted by universities that are funded by federal money (Loise & Stevens, 2010). This policy has created the field of translational science, which involves moving basic science from the laboratory bench to the clinic.

In some cases, the perceived inequity of financial benefit to some stakeholders (biomedical researchers, universities, the pharmaceutical industry, or national governments) and not others (human research subjects) has resulted in patients who sue to protect their individual rights as they relate to ownership and compensation. In most cases, courts have declared loss of individual ownership for material that has been removed from the body in a therapeutic context.

To avoid such complications and reduce undue inducement associated with participation, France has restricted monetary payments to human research subjects. (VanderWalde & Kurzban, 2011). Meanwhile, many countries are utilizing opt-out policies in which all clinical samples can be used for research under the auspices of "presumed consent," with no financial benefit accruing to donors regardless of whether therapies or diagnostics are developed using their samples (Anonymous, 2013). This approach is already used in five countries in the realm of organ donation and is continuing to expand (Harman, 2009).

Video :Nov 11, 2015. The Challenge of Informed Consent In Times of Controversy. UC Irvine School of Law. Video footage is broken up by speaker and topic. Panels are tackle complicated issues. Radhika Rhao specifically addresses Henrietta Lacks and Deborah Laufer, playwright of Informed Consent site pushes back on biomedical ethics, while Marcy Darnovsky brings in issues of equity and social justice on Panel 2. Link

VIII. Altruistic Donor, Paid Research Subject, or Savvy Negotiator?

As biomedical research shifted from a general public good to a lucrative industry, public support and expectations regarding gifting and donation of bodily tissues also shifted (Knoppers & Laberge, 1995). In the 1930s, malnutrition, infectious agents, and environmental toxins were the cause of most human morbidity and mortality. The emergence of antibiotics was heralded as a medical miracle, entering the mainstream media in the form of the film *Dr. Ehrlich's Magic Bullet*. Public outreach was also accomplished through education media, in the form of public health campaigns using posters to promote the elimination of communicable disease (Dieterle, 1940; NIH Visual Culture and Health Posters). Similarly, the development of childhood vaccines stoked public interest in biomedical research, providing yet another success story. Therefore, when cancer was the next scourge to be attacked, most people willingly provided samples for research or volunteered themselves as test subjects. This kind of altruism can be seen most clearly in the documentary film *The Way of all Flesh* by Adam Curtis, where prison inmates are asked about their participation in a study involving subcutaneous injection of HeLa cells to determine if cancer is infectious. The inmates remark that they are compelled to do something for the public good and see their participation as a form of redemption. But what is perhaps not so clear, is that even these subjects most likely obtained some direct benefit, in the form of reduced sentences or early parole review.

Film: Curtis, A. 1997. Modern Times: The Way of All Flesh. Aired on BBC. Modern Times Series, Editor Stephen Lambert. (52 minutes). Link

Similarly, the depiction of altruistic research subjects by bioethicist Laurie Zoloth in the World Stem Cell Summit 2010 keynote address "Lessons Learned from Henrietta Lacks" is somewhat misleading

World Stem Cell Summit Video Conference Session: Sugarman, J., Zoloth, L. & Hempel, C. October 4 2010. FullviewMedia. The Immortal Life of Henrietta Lacks - lessons for stem cell researchers and patients. World Stem Cell Summit, Pasadena, CA. (Time Stamp 38:00min- 50:00min) Link

In her presentation, she presumes that if Henrietta Lacks had realized how many children's lives would be saved by the polio vaccine, she would not have wanted a cent for her part in creating the cell line that led to its development. She also describes a young Jimmy Sarkett, the boy in whom the polio virus was cultured, as a pioneer willing to act as a human incubator for the polio vaccine despite not being able to benefit from it himself. What was not revealed in these stories, as presented in this forum to promote "Cure," were the downstream effects of altruistic participation. The Lacks family has little to no access to healthcare, and Sarkett, who retired on a small disability income and social security, is unable to pay for a new set of crutches (Fabregas & Bails, 2005). Although in both of these cases the hospitals and researchers developing these biological tools and vaccine made no profit from their discoveries, they received no recognition. Jonas Salk was often referred to as the People's Scientist, yet the hospitals have celebrated these accomplishments with little recognition for the patients that made them possible. In the Lacks case, the family requested that a wing of John Hopkins Medical School be named after Henrietta, but there has been no such response as shown in the video below.

Video: March 15, 2010. The Immortal Henrietta Lacks. CBSnews. Link

Similarly, when the University of Pittsburgh School of Pharmacy developed learning tools for the 50th anniversary of the launch of the Salk polio vaccine, they did not include Jimmy Sarkett's contributions in the timeline associated with the awareness project and documentary titled "A Shot Heard Around the World." Ironically, Sarkett was interviewed for some of the promotional materials and upon learning about his situation, the University of Pittsburgh Medical Center and a local orthotics center donated new crutches to him (Fabregas & Bails, 2005).

As Palmer remarks in his editorial "Private Reparations" in the *Hastings Center Report*, philanthropic efforts, such as the establishment of Skloot's Lacks Foundation, does little to address the inequity that exists between researchers and human subjects (Palmer, 2010). Furthermore, most acknowledgement is reactive, an attempt to minimize threat to one's position and privilege once an injustice is revealed. The *Nature* editorial "Justice for All" highlights the need not just for acknowledgement, but legitimate recognition for harms committed in the name of scientific progress (Anonymous, 2012). This short editorial lists many cases in which financial reparations were secured for those who may have been harmed and/or unknowingly participated in biomedical research. These state and national orders to provide reparations are in some ways methods for biomedical science to "save face." This diversity of opinions is reflected within the Lacks family regarding compensation for speaking engagements versus acknowledgement and reparations on a systemic level (Hendrix, 2017).

Similarly, in viewing the congressional records regarding the Henrietta Lacks Case, in 1997 and 2010, it is understandable that policymakers would request such acknowledgement to maintain both their constituency base and economic growth as a result of biomedical research in their districts (Perriello, 2010; Ehrlich, 1997) (Slide 10: Congressional Records). Each request was made shortly after the public learned about Henrietta Lacks' story, first by Curtis' film on the BBC program *Modern Times* in 1997 (Curtis, 1997) and, subsequently, with the publication of Rebecca Skloot's book *The Immortal Life of Henrietta Lacks* in 2010 (Skloot, 2010). Notably, in the congressional records, the words "contribution" and "given" appear, though Lacks was never made aware that her tissue was being used in research.

Because human research subjects and biomedical researchers recognize the value of human biological material, much activism to address the value of this biocapital has emerged. As Lori Andrews remarks in her book *Body Bazaar,* a tissue movement seems to be emerging in which patients or human subjects are reigning in their rights to control what happens with their bodily tissues and DNA (Fahy & Nisbet, 2013). Such shifts are

apparent with the emergence of the trade journal *Guinea Pig Zero,* which adopts practices familiar to the labor movement to organize for autonomy and protections for human research subjects. Two cases are commonly used to highlight these efforts. The first is that of John Moore, a cancer patient who sued the Regents of the University of California for patenting a cell line made from his body without informing him of the value of such a cell line in the development of cancer therapies. Moore was repeatedly subjected to blood draws and clinical testing so that his physician could acquire more biological material to study, yet, the physician evaded discussions of the non-therapeutic nature of these studies with Moore. Moore, who reacted to his situation after learning of the true intent of his blood work, lost his case in 1990.

In the second commonly used case, Ted Slavin, a Hepatitis B patient, took steps proactively to protect his unique biological material. Slavin, upon learning the value of his biological samples for Hepatitis B antibody production, patented his own blood and began selling it to researchers on his own. He then donated the profits to non-profit research centers of his choosing. In an attempt to keep the information and material in the hands of patients, Slavin also formed *Essential Biologicals*, a company designed to collect and distribute blood that contained unique or useful biomarkers. By securing patent rights, it could be argued that Slavin prevented a monopoly of knowledge, and rather, contributed to the open access movement in science (Landecker, 1999; Skloot, 2010; Truog, 2012).

Though Moore and Slavin acted individually to shake up the status quo, by participating in the structures and systems that are in place to negotiate such terrain, race scholar Ruha Benjamin reminds us that some populations are choosing a different tactic, that of "organized ambivalence" (Benjamin, 2011). Her ethnographic work on stem cell therapies in communities that are disproportionately affected by sickle cell anemia suggests a need for community rather than individual actions, because

> "ambivalence-in-action [is] structured by three contextual strands: therapeutic uncertainties of the clinic, institutionalized conflation of healthcare and medical research, and political contests over scientific and medical investments." (Benjamin, 2011)

She posits that

> "organized ambivalence is an analytic alternative to individualized notions of distrust and as a framework for implementing more participatory research initiatives that better account for the multiple uncertainties characteristic of regenerative medicine." (Benjamin, 2011)

Because Benjamin's work emerges from her focus on stem cell research in California, a flurry of editorials and academic papers have proposed revisiting payments for research subjects, or donors, to incentivize participation and donation within the context of stem cell therapies and research (VanderWalde & Kurzban, 2011; Truog, 2012; Kominers & Becker, 2012; Hayflick, 2013). This is particularly true for those human tissues and cells that are capable of regeneration, or normally discarded as medical waste, such as umbilical cord blood. Mohapatra has highlighted the lack of altruistic donation for umbilical cord blood to public stem cell banks and has proposed that incentives such as tax credits, or reduced medical costs, be put in place to incentivize donations, especially in light of the lack of diversity in current cord blood units (Mohapatra, 2013). Most recently, Nicola Lacetera and others provided data to refute the notion that non-cash incentives decrease altruistic donation or reduce the quality of samples (Lacetera et.al, 2013 podcast)

IX. Paying Up Front for Human Tissue: Bone Marrow, Eggs, and DNA

Bone Marrow: Flynn v. Holder

Given a capitalist culture where everything can be commodified and corporations can act as individuals (Citizens United v. Federal Election Commission), it is paradoxical that the US federal government allows for the barter and sale of gametes (egg and sperm), yet, does not support the compensation of bone marrow

donations designed to diversify existing bone marrow stem cell banks (Flynn v. Holder). The National Organ Transplant Act of 1984 **(**NOTA**)** "prohibits the transfer of any human organ for valuable consideration for use in a human transplantation if the transfer affects interstate commerce." However, this act does not prohibit the sale of bodily reproductive tissue such as eggs and sperm, which is left to the private sector and market-driven economy.

In 2009, the US Attorney General, Eric Holder was sued for prohibiting payment for bone marrow stem cell donations by plaintiffs represented by the Arlington-based libertarian nonprofit Institute for Justice. The plaintiffs included California nonprofit MoreMarrowDonors.org (MMD), parents of children living with disease, and a physician. At the state court level, the case was decided in favor of the government based on the policies associated with NOTA. The plaintiffs took the decision to the US 9th Circuit Court of Appeals, where the decision was reversed in favor of the plaintiffs on December 1, 2011. The decision in Flynn v. Holder permits compensation for bone marrow donations via apheresis (peripheral blood draw) in the form of scholarships, housing allowances, and charitable donations, but not direct cash payment. Patients can now also ask their insurance providers to cover the costs of such compensation (Barnes, 2012)

Video: Snyderman, N. March 15, 2013. A Mother's Fight. Rock Center with Brian Williams. NBCnews. (Producers, Amy Schmitz and Stacey Naggier).(7:56min) Link

The stakeholders in this groundbreaking case were all interested in diversifying the bone marrow stem cell supply, but their approaches and philosophies differ. MMD is a nonprofit that seeks to broaden the diversity of existing hematopoietic stem cells (HSC), which are collected from bone marrow to treat a variety of blood and genetic disorders and reestablish blood cells following cancer. Because individuals from mixed-race populations are more genetically diverse, and the number of donors in the registry from mixed-race backgrounds is low, immunological matching proves challenging for non-Caucasian recipients (Brown, 1996; NMDP). Though the US National Marrow Donor Program (NMDP) is one of the most ethnically diverse in the world with over 11 million donors registered, it estimates that less than 3% of donors self identify as mixed race.

Video: NBC. March 15, 2013. Man Starts Organization to Compensate Bone Marrow Donors. Rock Center with Brian Williams. NBC.com. (1:39') Link.

Currently, those of mixed heritage can identify a bone marrow match about 25% of the time as compared to Caucasians who match 66% of the time.

Slide Show: BET July is African-American Bone Marrow Awareness Month. Bet.com. Link

The matches consider the presence of over 600 million possible combinations of HLA surface proteins on haemopoeitic blood stem cells (Brown, 1996; NMDP). For those regions with a scarcity of bone marrow donations from diverse backgrounds, MMD has proposed a pilot program to pay immunologically matched donors up to $3,000 in non-cash payments to promote donors of mixed-race backgrounds to provide bone marrow stem cells (Shay, 2010).

Though all plaintiffs sought to broaden the diversity of the pool of bone marrow stem cells as the current national registry only contains donations from 2% of the population, the involvement of the MMD and their proposed compensation program speaks to the larger notion of "just participant selection" and community based approaches designed to address health inequities in the US. With this proposed program, the donor and recipient both belong to the community of underrepresented minorities that lack representation in bone marrow stem cell banks. However, the $3000 compensation scheme could present opportunities for exploitation, which is a concern of the NMDP. That the program would provide donors with educational scholarships, housing allowances, or contributions to a charity of their choice also raises ethical concerns regarding paternalism. It

could be argued that the non-profit decided what is of value for the donor, but this may not be in line with the values of the donor or the community that they represent.

The idea of paying donors who possess HLA combinations that are not well represented in the current registry has also been deliberated by economists who use mathematical models to determine the probability of matches across races and countries. They argue that altruism alone may not be sufficient in addressing those populations in greatest need. The group most affected by low matches are African Americans because of the wide range of HLA genetic diversity within this racial group. Though their models are based on generalizations, they conclude that to meet the demands of the African American population, the US would need to increase donations from this group by tenfold. Bergstrom et al. are careful to point out that all races would benefit from increased participation in the registry, but that payment for donation should only apply for those populations in greatest need (Bergstrom et al., 2009).

Doreen Flynn, another plaintiff in the case, and mother of three daughters living with Fanconi Anemia (FA) believes that payment to all donors, regardless of race, is in order. Flynn is in a unique position as a mother, as she gave birth to one daughter with FA, but then conceived two more using IVF and PGD in hopes of birthing children without FA. Due to errors in her PGD diagnosis, both siblings also live with FA, but she has not had success in matching donors in the NDMP for her children. Flynn's argument is based on the use of new technologies that reduce risk and harm to the donor, but provide incentives to those with unique HLA profiles. Currently blood stem cells can be expanded *in vivo* through the administration of granulocyte-stimulating factor five days prior to donation. Due to the stimulation, an increased number of HSCs in marrow results in a larger number of stem cells migrating to the peripheral blood supply (PBSC) where they can be collected without the painful procedure of bone marrow aspiration (Cohen, 2012). Because 70% of bone marrow donations are currently collected from the peripheral blood supply, the plaintiffs argued that the prohibition of payment under NOTA violated the constitutional Equal Protection Clause, because donors could regenerate their own supply of bone marrow stem cells and would experience little harm through a procedure not dissimilar to sperm and blood donation (Barnes, 2012). Based on the precedent of this court case, a similar proposal regarding cord blood donation and incentives to diversify it was proposed by Seema Mohapatra (Mohapatra, 2013).

The NMDP and the Justice Department both expressed concern regarding exploitation of the impoverished and the vulnerable. The 9th District Court panel deliberated on the notion of "blood for money" exchanges in which very ill patients might be financially depleted in trying to secure a bone marrow stem cell match, but ultimately decided in favor of the plaintiffs (Williams, 2012). The decision in the case is in line with a trend in which economic rewards are used to motivate donations of bodily tissues (Lacetera et al., 2013; Klein, 2013). There are also several studies that suggest compensation increases the rate of provision for sperm, eggs, and blood (Ikemoto, 2009; Klitzman & Sauer, 2009; Egli et al., 2011). These policies are careful to avoid language that would indicate the purchase of a biological product and, rather, express a desire to recognize the efforts associated with *providing* a product or service. Though some argue that these policies place society on an ethical slippery slope, others present evidence for proposals that would move towards the payment for bodily goods, as appeared in a *New England Journal of Medicine* editorial titled "Made-To-Order Embryos for Sale – A Brave New World?" (Cohen & Adashi, 2013).

On March 28, 2012, rehearing the case on behalf of the government resulted in a unanimous vote to uphold the Appeals Court decision, and US Attorney General Eric H. Holder Jr. decided not to bring the case to the Supreme Court. Had the case gone to the Supreme Court, it would require analysis of the constitutional question of equal protection (Williams, 2012). The decision has led to much debate surrounding the buying and selling of living tissues and organs (Park, 2012).

Egg Procurement: NY ESSCB and CA Bonilla Bill

This decision echoes Ellison and Meliker's position paper regarding payment for oocyte provision, published in the *American Journal of Bioethics* in 2011 (Ellison and Meliker, 2011). They argue that paying people to provide

oocytes, despite the potential and unknown health risks, is not different from current practices of employment in which agricultural workers and miners are exposed to toxic materials. What their argument fails to account for is the disproportionate health risk that is being outsourced to marginalized populations for the benefit of those with privilege in agricultural, reproductive medicine, and energy markets. The "choice" to engage in labor that may harm one's health is not normalized across different socioeconomic strata. Ellison is a member of the Empire State Stem Cell Board's Ethics Committee that deliberated for over a year before arriving at the decision to provide people with up to $10,000 for oocytes provided for stem cell research purposes (ESSCB 2009).

Unlike other states, where decisions regarding oocytes in stem cell research were made through ballot initiatives, or other democratic means, New York declared this policy without public input. Much of the opposition to state initiatives for oocyte compensation centers on the informed consent process and the ways in which it may minimize, exclude, or provide unclear language about potential harm. In New York, the proposed informed consent forms underwent several rounds of revision by members of Ethics Committee before being approved (NYSTEM Model Consent Forms; Roxland, 2010; Roxland 2012). Some see the resulting form as a step in the right direction, because it highlights the lack of existing data on long-term health and lists the limited physical and psychological risks known to date. Additionally, a bill that would require pharmacists to distribute Lupron, an ovarian stimulation protocol drug, with the following warning label: "Caution: This drug could cause adverse reactions including, but not limited to heart attacks, diabetes, convulsions, excessive bleeding, and could lead to death" has been deliberated by both the NY Senate consumer protections and affairs committee and the higher education committee, with a decision still pending as of January 2012 (Open Legislation, 2012).

Robert Klitzman, bioethicist and NYSTEM Ethics Committee member, has argued that long-term health data for oocyte providers should be collected, and that compensation for participation in oocyte provision for stem cell research is socially just. He proposes that the NY provision permits underrepresented minorities, who are not typically recruited by privately run IVF clinics, the opportunity to receive the current rate of up to $10,000 should they choose to provide oocytes for state-funded stem cell research (Klitzman & Sauer, 2009).

In 2013, California Assemblyperson Susan Bonilla presented a bill that was sponsored by the American Society for Reproductive Medicine, seeking to compensate oocyte providers for their services. Although the billwas passed by the State Congress, Governor Jerry Brown vetoed the bill saying that "not everything in life is for sale, nor should it be." This decision was in line with provisions within the California Institute of Regenerative Medicine that prohibit compensation that is above reimbursement for medical expenses (Benjamin, 2013a; Lifscher, 2013).

Although these compensation policies can be contextualized within a responsive justice framework because they seek diverse and equitable representation of participants and stem cell products, it can be argued that these policies propagate injustice. Opponents of payment for tissues destined for stem cell research claim that the compensation schemes described here could reaffirm the very disparity they seek to minimize. They argue that by providing compensation for living tissues in a society with an inequitable distribution of resources, we remove the option of "choice" and create scenarios where the disadvantaged must sell their body parts to gain the same privileges as those who seek their bodies as sources of biological goods (Hyun, 2006; Ikemoto, 2009; Chamany, 2011; Park, 2012; Chamany, 2015).

X. "Altruistic" Donations for Profit or Unintended Use?

Even in situations where human tissue, cells, or DNA are donated, ethical issues of control over their use whether for research, or profit, are increasingly placing pressure on the "informed consent" process. In many cases the donor is completely unaware of how their tissues or DNA may be used. This is best illustrated in the case of the Havasupai Native American DNA study. The Havasupai reside on a reservation in the state of

Arizona, and experience disproportionate rates of diabetes and other metabolic disorders. Many of their health challenges are thought to arise from policies regarding water and land use on the reservation that have negative consequences for the Havasupai diet and physical activity. Although the Havasupai "donated" their DNA samples, they did so with the express interest of learning more about the community's propensity toward diabetes, making the donation part of an exchange of valued goods.

DNA Biobanking: Havasupai v. University of Arizona

Not only did the Havasupai gain no new genetic knowledge regarding diabetes from these investigations, Havasupai DNA from ancestral remains became the subject of extensive genome-wide analyses, for which the community did not provide informed consent. These analyses included searching for DNA identifiers characteristic of schizophrenia and studying human evolution, which called into question their cultural knowledge surrounding lineage, identity, and neurodiversity (Couzin-Frankel, 2010). The case of the Havasupai highlights the ethically fraught nature of biobanking, where samples can be used to study a variety of questions, not all of which were presented during the informed consent process. Settlement of the *Havasupai v. Arizona State University* lawsuit demonstrates the need for more standardized protocols surrounding informed consent as it relates to genomic data and the disembodied person (Ossario, 2011). However, as some warn, this issue goes beyond legislative procedures and requires cultural competence and acknowledgement of variance in world views; even if research subjects are fully aware of the research goal, they may not agree that the research questions hold value and there may be downstream effects of "informational harm" (Shanks, 2010a). Playwright Debra Laufer, a Sloan Fellow, showcased the specific case of the Havusapai and the lack of cultural competence, in her play "Informed Consent," which debuted in 2015 (Gawlak, 2015).

Video: Laufer, D. 2015. Informed Consent Highlights. (4:34min) Link

Video: Thirteen/Education Broadcasting Corporation (Producer.) June 25, 2010. Religion & Ethics Weekly: Informed Consent and Medical Research. (7:22 min) Link

To identify research questions of shared value, many researchers are now adopting the participant action research (PAR) model, in which human research subjects act as active participants in the research endeavor, shaping its direction and overseeing how information is shared with both the community being studied and those outside the community. This approach involves building trust and networks of stakeholders who can develop a common language and an authentic benefit-sharing model. Most importantly, community members will contribute valuable knowledge and experience and drive the research questions. In this way, the added value is more transparent, as can be seen in the shift of research questions from identifying gene variants for vulnerability to metabolic disease to lifestyle practices that protect individuals from developing these conditions (Garrison, 2013; Lehrman, 2013). The importance of this shift in approach is highlighted in the Presidential Address of the American Society of Human Genetics titled "Culture: The Silent Language Geneticists Must Learn—Genetic Research with Indigenous Populations" (McInnes, 2010).

To further these efforts, many research initiatives actively recruit bioethicists and social science scholars as members of research teams, to ensure inclusivity of all stakeholders and promote an accountability that speaks to all stakeholders. The Translational Genomics Research Institute (TGen), a non-profit company, has incorporated policy experts to oversee community outreach and legislative affairs and involved the community in every step of the research, which led to a $5 million contribution from the Salt Water River Pima-Maricopa Indian Community. Nanibaa Garrison, a trained Navajo geneticist who completed a post-doctoral fellowship at Stanford's Center for Biomedical Ethics, authored a paper on the Havasupai case that examines the role of IRBs and the responsibility of the NIH for federally funded research (Garrison, 2013). The Stanford center is one of six NIH-funded Centers for Integration of Research on Genetics and Ethics (CIRGE). Garrison is a contributing author of the online resource "Genetics Resource Center," which was developed by the National Congress of American Indians to educate communities about genomic research and issues of privacy and

ownership and provide model informed consent templates as well as an interactive decision guide (Lehrman, 2013).

Precision Medicine Initiative
The use of the PAR model will be tested with the launch of the US Precision Medicine Initiative (PMI), designed to amass the data of a million volunteers in an effort to advance research and support public health (CURE, 2015; Reardon, 2015). As individuals are increasingly asked to participate in such projects, patient autonomy within the practice of informed consent is evolving.

Early on in biomedical and genomics research, the risks and benefits presented as part of the informed consent process were confined to health side effects and therapeutic outcomes. More recently, with the advent of advances in biotechnology, supercomputing, and the construction of large-scale data sets, risk and benefit take on new meaning. In a country that is struggling to address national healthcare within the context of racial and economic inequities, analyses of risk and benefit must expand beyond traditional definitions. This is especially true as biomedical research has become increasingly dependent on human bodies, cells, tissues, and DNA.

Video: Oct 15, 2015. Kimberly Koss: Medical Researcher Advances Critical Research by Letting Her Own Cancer Grow.WCPO.com Youtube.(2:18 min) Link

Video:March 14, 2016. Dr. Kimberly Koss- Koss National Triple Negative Breast Cancer Research Foundation. (4:017 min). Link

An interesting example that is built on the history of the HeLa cell line is the story of Kimberly Koss. Koss is not a typical cell donor. She is a biomedical scientist who willingly chose to donate her breast cancer cells to research. Koss has a particularly aggressive type of cancer (triple negative for estrogen, progesterone, and HER-2 receptors) that disproportionately affects African American women. Koss even refused chemotherapy in an effort to keep the cells alive for culture. For Koss, this sacrifice and donation will not bring about personal benefit, but rather her altruistic actions could result in a benefit to society. Her ability to do so, is based on a deep trust and relationship with the researcher and community more broadly, a position that most in the public do not have (Loyola University Health System, 2014).

Today, healthy volunteers in clinical trials can gain financial benefit in the form of payment or compensation; contributors of genetic information must consider privacy and discrimination risk associated with release of genetic information; and patients must be aware of profits made from research on biospecimens collected as part of diagnosis, therapy, or altruistic donation. This is particularly true as the PMI intends to collect lifestyle and social information alongside genomic data.

Similarly, private genomics companies like 23andMe and research studies using Apple's Researchkit will be collecting data that can be used in both biomedical and social science research, and will be most useful when these data are used together to address epigenetic influences on health (Duhaime-Ross, 2015; Bushley, 2015; Servick, 2015; Grady et al., 2017). That biological data falls under the Common Rule, while environmental (built, social, and natural) data does not, seems counterintuitive to the goals of these interdisciplinary projects (Hudson & Collins, 2015). Interestingly many realize that in order to achieve the statistical power necessary for genome associate studies, large amounts of data must be collected from healthy individuals, who are not part of the clinical trial process. A new a nonprofit, social benefit organization "Unpatient" proposes a technological solution that allows biomedical data to be shared and traded as property at a very granular level, but that retains the privacy and security necessary for human dignity and in compliance with existing regulations (Kish and Topal, 2015).

Cord Blood International Markets

Moreover, with biobanking, the line between the public and private sector is becoming blurred and the role of informed consent is morphing from a form of ethical oversight to an organizational decision making tool or commercial contract (Hoeyer, 2008; Ikemoto, 2009). This can be seen most noticeably in international trade for umbilical cord blood units. A growing market for cord blood has emerged with as much as 40% of all publicly banked cord blood units being traded across country borders. The biocapital being generated is not insignificant, with some units trading for as much as $30K per unit, resulting in a $30million industry (Dickenson, 2013). The high cost is the result of some communities possessing low genetic diversity, such that those of mixed ethnic background find it more difficult to find an immunological match in existing national banks. Thus, the public banks trade among themselves to address this gap and, in some cases, have developed an export business to provide products for particular minorities. This export business not only serves an underserved population with goods, it provides a steady income to support the expenses of maintaining a public cord bank more generally (Dickenson, 2013).

Video :Cord Blood: Banking and Uses. StemCellChannel.National Stem Cell Foundation of Australia. (7 min). Link

Adult.Adult Cell Source. Blood Stem Cells.

Though many individuals are volunteering to donate umbilical cord blood, many private companies offer banking services that restrict access to family members. These companies charge approximately $1500 for collection and annual fees approximating $150 for storage. The standards for cord blood that enters the national or international public registries is much higher than that of the private family banks. Thus, though there are many donations, only 10% proves suitable for inclusion in these public banks based on criteria that involves counting the blood stem cell count (Petrini, 2014).

What becomes of the unsuitable donations should be of interest to altruistic donors. Often these units are used to derive platelet gel that can be sold for profit. Platelet gel is used to accelerate repair of cutaneous and bone tissue. Additionally, though the US national cord blood bank is subsidized by government grants and private donations, a good amount of the financial support comes in the forms of payments made by other banks in exchange for blood units of rare HLA types. In other words, an international trade market has emerged for blood units (Petrini, 2014).

Milk Banks for Profit

A similar altruistic based profit making mechanism is in place for breast milk banks. Prolacta is one of the most lucrative companies to capitalize on such a model. Prolacta solicits volunteer donations for breast milk, but then uses this milk as base material to create a fortified product that they sell to hospitals to support neonatal health for those babies in critical care. When asked why they don't compensate donors, Prolacta echoes the same rationale used by those that oppose the use of incentives for blood donation, namely that compensation would lower the quality of the pool, as it might attract unfavorable donors desperate for financial support (Dutton, 2011).

Podcast: Rogers, A. June 2011 Podcast. Breast Milk. Storyboard. (19:41min) Link

Originally, the Prolacta website was not forthcoming about its tactics, however, with media coverage, the company has had to explain their policies and practices to potential donors by placing these practices in the FAQ. More recently, they moved this information up in the FAQ after an investigative story revealed the concern of some donors who felt the company should be more forthright (Givens & Glorioso, 2013).

Video: Givens, A. & Glorioso C. Nov 15, 2013. I-Team: Donated Breast Milk Is Often Sold for Profit. (4:09min) Link

Cadaver Tissue for Profit

In addition to the commercialization of human fluids such as blood and breast milk, human tissues collected from cadavers for research and life saving treatments are in scarce supply due to demand emerging from pharmaceutical and regenerative medicine companies. As the case of Henrietta Lacks has revealed, people expect transparency with respect to how bodily tissues are going to be used. This is particularly true for those communities experiencing economic hardship, which ultimately leads to disproportionate health burdens.

> "This situation has created tension between the altruistic principles of hospital tissue banks and industry's profit-oriented principles. Meanwhile, industry lobbying and the political desire to promote the growth of biotechnology markets and jobs have led to increasingly business-oriented legislation controlling human tissue handling … This shift has now gone so far that in some legislations, the risk arises that the interests of industry could take precedence over the interests of patients and research." (Pirnay et al., 2015, p559).

Perhaps most startling is that the industry push is coming from companies that provide resources for non-essential tissue transplants used in cosmetic surgery.

> "In addition, some companies in the tissue engineering field cater to cosmetics rather than medical products. A striking example is the processing of human skin, the gold standard for the treatment of severe burns, into cosmetic products without medical indication, such as penis widening or lip enhancements, which fetch much higher prices than analogues for burn treatments. US burn centres were reportedly struggling to obtain skin because local tissue banks are committing all their donated skin to firms that market products for plastic and cosmetic surgery." (Pirnay et al., 2015, p 561).

Clearly, as technology and science advance so, too, will the ethical oversight regarding biospecimens and human subjects. Informed policy making will require an interdisciplinary approach that attempts to anticipate which communities and individuals are in need of protections, and how the right to health can be achieved in ways that promote scientific innovation as well as health and economic equity (Arias et al., 2015).

References

1. Ambros, P. and Karlic, H. 1987. Chromosomal insertion of human papilloma virus in HeLa cells detected by nonisotopic in situ hybridization and reflection contrast microscopy. *Human Genetics*. 77:251-254. http://www.ncbi.nlm.nih.gov/pubmed/2824333
2. Anonymous, 2009. What is health? The ability to adapt. *The Lancet.* 373(9666):781. http://www.thelancet.com/journals/lancet/article/PIIS0140673609604566/fulltext?rss=yes
3. Anonymous. 2012. Justice for all. *Nature.* 484 (7394): 287. http://www.nature.com/nature/journal/v484/n7394/full/484287a.html
4. Anonymous. 2013a. Culture of consent. Nature. 498:407. http://www.nature.com/news/a-culture-of-consent-1.13262
5. Anonymous. 2013b. Presumed consent. Nature. 499:6. http://www.nature.com/news/presumed-consent-1.13316
6. Anonymous. Sept 23, 2015. STAP revisited. *Nature.* 525 (7570): 426. http://www.nature.com/news/stap-revisited-1.18400?WT.ec_id=NATURE-20150924&spMailingID=49614214&spUserID=MjA1NzU5MzAyNwS2&spJobID=763182077&spReportId=NzYzMTgyMDc3S0
7. Arias, J., et al. Oct 29, 2015. Trust, vulnerable populations, and genetic data sharing. *Journal of Law and Biosciences*: 1-7. jlb.oxfordjournals.org/content/early/2015/10/29/jlb.lsv044.full
8. Azvolinsky, A. March 1, 2015. Of cells and limits. *The Scientist*. 29(3): (2 pages) Link http://www.the-scientist.com/?articles.view/articleNo/42256/title/Of-Cells-and-Limits/
9. Barnes, R. Jan 22, 2012. Government Fights Court Decision That Says Bone Marrow Donors Can Be Paid. *The Washington Post.* https://www.washingtonpost.com/politics/government-fights-court-decision-that-says-bone-marrow-donors-can-be-paid/2012/01/21/gIQA5L7LJQ_story.html
10. Barthel, F. et al. 2017. Systematic analysis of telomere length and somatic alterations in 31 cancer types. Nature Genetics. 49(3): 349-357. http://www.nature.com/ng/journal/v49/n3/full/ng.3781.html
11. Benjamin, R. 2011. Organized ambivalence: When stem cell research and sickle cell disease converge. *Ethnicity and Health.* 15(4-5):447-463. http://www.ruhabenjamin.com/a/wp-content/uploads/2015/08/Organized-Ambivalence.pdf
12. Benjamin, R. April 4, 2013a. Which Comes First the Women or Her Eggs? *HuffingtonPost.com.* http://www.huffingtonpost.com/ruha-benjamin-phd/which-comes-first-the-woman-or-her-eggs_b_3018415.html
13. Benjamin, R. 2013b. People's Science: Bodies and Rights on the Stem Cell Frontier. Stanford University Press. Stanford. http://www.sup.org/books/title/?id=20585
14. Benjamin, R. 2014. Race for cures: Rethinking the racial logics of 'trust' in biomedicine. *Sociology Compass*. 8(6): 755-769. Link
15. Bergstrom, T. et al. 2009. One chance in a million: Altruism and the bone marrow registry. *American Economic. Review*. 99(4):1309-34. https://www.aeaweb.org/articles.php?doi=10.1257/aer.99.4.1309
16. Biba, Erin. Jan 25, 2010. Henrietta Lacks Everlasting: 1950s Cells Still Alive Helping Science. *Wired.* Infographic by Walbaum. http://www.wired.com/magazine/2010/01/st_henrietta/
17. Boddy, A. et al. 2015. Fetal microchimerism and maternal health: A review and evolutionary analysis of cooperation and conflict beyond the womb**.** *BioEssays*. 37 (10): 1106-08. http://www.ncbi.nlm.nih.gov/pubmed/26316378
18. Bohan, M.2005. Checkpoints and Cell Cycle Control. Harvard Molecular and Cell Biology-HHMI Outreach Program. Learners TV https://lifesciencesoutreach.fas.harvard.edu/biology-cancer-animations
19. Bollati V. et al. 2010. Epigenetic effects of shiftwork on blood DNA methylation. *Chronobiology International*. 27:1093-104. http://www.ncbi.nlm.nih.gov/pubmed/20636218
20. Bowleg, L. 2012. The problem with the phrase *women and Minorities*: Intersectionality-an important theoretical framework for public health. *American Journal of Public Health.* 102 (7): 1267-1273. http://ajph.aphapublications.org/doi/abs/10.2105/AJPH.2012.300750?journalCode=ajph
21. Brainard, C. March 28, 2013. HeLa-cious Coverage: Media Overlook Ethical Angles of Henrietta Lacks Story. *Columbia Journalism Review.* http://www.cjr.org/the_observatory/henrietta_lacks_hela_genome_pr.php?page=all
22. Brignell, V. Dec 10, 2010. The Eugenics Movement Britain wants to Forget. *New Statesman*. Link (audio available at website; 2 ½ pages)
23. Brignell, V. Dec 10, 2010. When America Believed in Eugenics. *New Statesman*. Link (audio available at website; 3 1/2 pages)

24. Brofenbrenner, U. 1979. *The Ecology of Human Development.* Harvard University Press: Cambridge. 330. https://books.google.com/books/about/THE_ECOLOGY_OF_HUMAN_DEVELOPMENT.html?id=OCmbzWka6xUC&hl=en
25. Brown, J. December 1996. National Bone Marrow Program: Effectiveness in Retaining Donors. Office of the Inspector General. http://oig.hhs.gov/oei/reports/oei-01-95-00121.pdf
26. Bush, Vannevar. 1945. *Science The Endless Frontier*. Original letter from Roosevelt to Bush and his report. Focus on Letter Exchange (1-5) and Chapt 3 (9-13) (18pages) http://www.nsf.gov/about/history/nsf50/vbush1945_bush_letter.jsp
27. Bushley, R. May 28, 2015. 23andMe's Plan to Harness Data for Disease Treatments. *Biosciencetechnology.com*. Link
28. Callaway, E. March 27, 2013a. Hela Publication brews bioethical storm. *Nature.* http://www.nature.com/news/hela-publication-brews-bioethical-storm-1.12689
29. Callaway, E. Aug 7, 2013b. Deal done over HeLa cell line. *Nature.* 500:131-133. http://www.nature.com/news/deal-done-over-hela-cell-line-1.13511
30. Canguilhem, G.1943. *The Normal and the Pathological*. MIT Press. Cambridge. http://mitpress.mit.edu/books/normal-and-pathological
31. Capes-Davis, A. et al. 2010. Check your cultures! A list of cross-contaminated or misidentified cell lines. *International Journal of Cancer.* 127:1-8. http://onlinelibrary.wiley.com/doi/10.1002/ijc.25242/abstract
32. Chamany, K. Fall 2011. Introduction: Part II Buying and Selling the Body. *Social Research: An International Quarterly*. 78(3):823-827. https://epay.newschool.edu/C21120_ustores/web/product_detail.jsp?PRODUCTID=5498&_ga=1.232712095.1200864493.1358260774
33. Chamany, K. Nov 19, 2015. New Rules Proposed to Address Privacy and Trust in the Precision Medicine Initiative. Biopolitical Times. https://www.geneticsandsociety.org/biopolitical-times/new-rules-proposed-address-privacy-and-trust-precision-medicine-initiative
34. Chatterjee, R. 2007. Cases of mistaken identity. *Science*. 315(5814):928-931. http://science.sciencemag.org/content/315/5814/928
35. Cohen, G. Jan 26, 2012. Selling bone marrow- Flynn v. Holder. *The New England Journal of Medicine*. 266: 296-297. http://www.nejm.org/doi/full/10.1056/NEJMp1114288
36. Cohen, G. & Adashi, E. 2013. Made-to-order embryos for sale – a brave new world? *New England Journal of Medicine*. (368):2517. http://www.nejm.org/doi/full/10.1056/NEJMsb1215894
37. Cossins, D. Jan 1, 2015. Stress fractures. *The Scientist.* The Scientist.com. http://www.the-scientist.com/?articles.view/articleNo/41708/title/Stress-Fractures/
38. Couzin-Frankel, J. April 30, 2010. DNA returned to Tribe, Raising Questions About Consent. *Science.* 328(5978):558. http://science.sciencemag.org/content/328/5978/558.short
39. Cozzens, S. Social Sciences: Shunned at the Frontier. In Science the Endless Frontier: Learning from the Past, Designing for the Future. Highlights from a conference series held between 1994-1996. P101-105. https://cspo.org/legacy/library/090729F3GD_lib_BushconferenceHi.pdf
40. Crow, M. Beyond the Endless Frontier. In Science the Endless Frontier: Learning from the Past, Designing for the Future. Highlights from a conference series held between 1994-1996. P-114-118 https://www.nsf.gov/od/lpa/nsf50/vbush1945.htm
41. Culliton, B. J. 1974. HeLa cells: contaminating cultures around the world. *Science.* 184:1058-1059. Link
42. Curtis, A. 1997. *Modern Times: The Way of All Flesh*. Aired on BBC. Modern Times Series, Editor Stephen Lambert. (52 minutes). Link
43. CURE. Joe Handelsman: From the Laboratory to the White House. Link
44. Cuzick, J. et al. 2013. Comparing the performance of six human papillomavirus tests in a screening population. *British Journal of Cancer.* 108(4):908-913. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3590662/
45. Del Carpio, A. Spring 2014. The good, the bad the HeLa. *Berkeley Science Review*. Link http://berkeleysciencereview.com/article/good-bad-hela/
46. De Los Angeles, A. et al. Sept 23, 2015. Hallmarks for pluripotency. *Nature.* 525 (7570):469-78. Link
47. Dickenson, D. 2013. Your Birth Day Gift: Banking Cord Blood" *In We Medicine, Me Medicine: Reclaiming Biotechnology for the Common Good.* Columbia University Press. 84-112. Google Books https://books.google.com/books?id=z2oHLlgv8g4C&pg=PA89&lpg=PA89&dq=Your+Birthday+Gift+Banking+Cord+blood+Dickinson&source=bl&ots=Xf2D3XrZ_T&sig=BTGm9lz95Ds9pianbdUbQ6sOi_g&hl=en&sa=X&ved=0ahU

KEwif4IKr69TKAhWGFT4KHT7wDaMQ6AEIUjAD#v=onepage&q=Your%20Birthday%20Gift%20Banking%20Cord%20blood%20Dickinson&f=false
48. Duguid, C. 2010. Video: Cell Culture. EuroStemCell. (Producer Kate Doherty) (6 minutes). https://www.youtube.com/watch?v=0iQqOuINeZI
49. Donovan, B. 2013. Playing with Fire? The impact of the hidden curriculum in school genetics on essentialist conceptions of race. *Journal of Research in Science Teaching.* 51 (4):462-496. http://onlinelibrary.wiley.com/doi/10.1002/tea.21138/abstract
50. Duhaime-Ross, A. March 10, 2015. Apple's New ResearchKit: Ethics Quagmire or Medical Research Aid? *TheVerge.com*. Link
51. Dutton, J. May 17, 2011. Liquid Gold: The Booming Market for Human Breast Milk. *Wired. http://www.wired.com/2011/05/ff_milk/*
52. ErinC. Jan 30, 2009. The Story of Henrietta Lacks: A Lesson in Biology and Ethics. *23andMeResearchNews*. http://blog.23andme.com/news/the-story-of-henrietta-lacks-a-lesson-in-biology-and-ethics/
53. Egli, D. et al. 2011 Impracticality of egg donor recruitment in the absence of compensation. *Cell Stem Cell*. 9(4):293. http://www.cell.com/cell-stem-cell/abstract/S1934-5909(11)00383-3
54. Editorial Board. Aug 20, 2014. The City Council Speaker's Honesty. *New York Times*: A20. http://www.nytimes.com/2014/08/21/opinion/melissa-mark-viverito-candidly-discusses-hpv.html
55. Ehrlich, R. June 4,1997. In Memory of Henrietta Lacks. Congressional Record.143(75):E1109. Link
56. Eisenberg, L . 1999. Does social medicine still matter in an era of molecular medicine? *Journal of Urban Health*. 76: 164–175. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3455991/
57. Ellison, B., & Meliker, J. 2011. Assessing the risk of ovarian hyperstimulation syndrome in egg donation: Implications for human embryonic stem cell research. *The American Journal of Bioethics*. 11(9):22-30. http://www.ncbi.nlm.nih.gov/pubmed/21877969
58. Emanuel, E., et al. 2011. Reforming the regulations governing research with human subjects. *The New England Journal of Medicine.* 365:1145-1150. http://www.nejm.org/doi/full/10.1056/NEJMsb1106942
59. ESSCB/Empire State Stem Cell Board. 2009 Statement of the Empire State Stem Cell Board on the Compensations of Oocyte Donors. http://stemcell.ny.gov/node/227
60. ErinC. Jan 30, 2009. The Story of Henrietta Lacks: A Lesson in Biology and Ethics. *Spittoon Blog*. 23andme. http://blog.23andme.com/news/the-story-of-henrietta-lacks-a-lesson-in-biology-and-ethics/
61. Fabregas L. and Bails, J. April 3, 2005. A Lasting Link to Discovery. *Triblive*. Pittsburgh. Link
62. Fahy, D. & Nisbet C. July 2, 2013. Debating bioethics openly. *The Scientist.* 27(2):20 http://www.the-scientist.com/?articles.view/articleNo/36098/title/Debating-Bioethics-Openly/
63. Feldwisch-Drentrup, H. Dec 19, 2015. E.U. frees up data for science. *Science.* http://www.sciencemag.org/news/2015/12/eu-frees-data-science
64. Fountain, H. Sept 17, 2012. Damon Winter/photo. Human Muscle Regrown on Animal Scaffolding. *New York Times*: A1. http://www.nytimes.com/2012/09/17/health/research/human-muscle-regenerated-with-animal-help.html?src=recg
65. Galea, S. et al. 2011. Estimated deaths attributable to social factors in the United States. *American Journal of Public Health.* 101(8): 1456-1465. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3134519/
66. Garrison, N. March 2013. Genomic justice for Native Americans: Impact of the Havasupai case on genetic research. Science, Technology, & Human Values. 38(2):201-223. Link
67. Gawlak, E. 2015. Asking the Tough Questions with "Informed Consent" Playwright Deborah Zoe Laufer. Link http://stagebuddy.com/theater/theater-articles/interview-deborah-zoe-laufer-informed-consent
68. Givens, A. & Glorioso C. Noc 15, 2013. I-Team: Donated Breast Milk Is Often Sold for Profit. http://www.nbcnewyork.com/news/local/Donating-Breast-Milk-Prolacta-For-Profit-Companies-231799191.html
69. Goodwin, M. 2007. The body market. Race politics & private ordering. Arizona Law Review. 49(599). Minnesota Legal Studies Research Paper No. 38. Available at SSRN: http://ssrn.com/abstract=1660564
70. Green, M. Jan-Feb 2006. To restore faith and trust: Justice and biological access to cellular therapies. *Hastings Center Report*. 36(1): 57-63. http://www.jstor.org/stable/3528598?seq=1#page_scan_tab_contents
71. Grady, C. et al. March 2, 2017. Informed Consent. NEJM. 376(9):856-867. Link
72. Grens, K. Sept 2, 2015. The great big clean up. *The Scientist.* Link
73. Human Fertilization Embryology Authority. 1993. Egg sharing schemes. http://webarchive.nationalarchives.gov.uk/20111114231523/http://www.hfea.gov.uk/1411.html
74. Hanahan, D. & Weinberg, R. 2011. Hallmarks of cancer: The next generation. *Cell.* 144 (5): 646-674. http://www.cell.com/abstract/S0092-8674(11)00127-9
75. Harmon, C. 2009. Presumed consent: Yes we should. *Nature Reviews Nephrology*. 5:177. http://www.nature.com/nrneph/journal/v5/n4/full/nrneph.2009.47.html

76.Harry D. & Kanehe L. 2005. The BS in benefit sharing (ABS): Critical questions for indigenous peoples. In *The Catch: Perspective on Benefit Sharing. Ed (Beth Burrows). Edmonds Institute.* http://www.ipcb.org/publications/other_art/bsinabs.html
77.Hayden, E. Jan 17, 2013a. Privacy loophole found in genetic databases. *Nature.* http://www.nature.com/news/privacy-loophole-found-in-genetic-databases-1.12237
78.Hayden, E. May 3, 2013b. Privacy protections: The genome hacker. *Nature.* 497:172-174. http://www.nature.com/news/privacy-protections-the-genome-hacker-1.12940
79.Hayflick, L. September 14, 2012. Paying for tissue: The case of WI-38. *Science*. 337(6100):1292-1294. http://science.sciencemag.org/content/337/6100/1292.1
80.Hudson, K. & Collins, F. 2013. Biospecimen policy: Family matters. *Nature*. 500:141-142. Link
81.Hoeyer, K. 2008. The ethics of research biobanking: A critical review of the literature. *Biotechnology & Genetic Engineering Reviews.* 25:429-452. http://www.ncbi.nlm.nih.gov/pubmed/21412365
82.Hudson, K. and Collins, F. Oct 28, 2015. Bringing the common rule into the 21st century. *NEJM.org* Link
83.Hyun, L. 2006. Fair payment or undue inducement? *Nature*. 442:629-630. http://www.nature.com/nature/journal/v442/n7103/full/442629a.html
84.Ikemoto, L. 2009. Eggs as capital: Human egg procurement in the fertility industry and the stem cell research enterprise. *Signs: Journal of Women in Culture and Society.* 34:763-782. http://www.jstor.org/discover/10.2307/40272263?uid=3739832&uid=2&uid=4&uid=3739256&sid=21103243111551
85.Kakui, Y., & Uhlmann, F. (2017). Building chromosomes without bricks. *Science.* 356(6344): 1233. http://science.sciencemag.org/content/356/6344/1233.full
86.Kaiser, J. June 2013. Agency nixes Decode's new data-mining plan. Science. 340 (6139):1388-89. http://www.sciencemag.org/content/340/6139/1388.full
87.Katsnelson, A. June 2010. Biologists tackle cell's identity crisis. *Nature.* 465: 537. Link http://www.nature.com/news/2010/100602/full/465537a.html?s=news_rss
88.Kish, L and E. Topal. Sept 2015. Unpatients—why patients should own their medical data. *Nature Biotechnology*. 33(9):921-924. Link and link to organizational site.
89.Klein, K. 2013. Paying for blood, cockroach adaptation, the future of a long-running natural experiment, and more. *Science*. 340(6135):995. http://www.sciencemag.org/content/340/6135/995.2.full
90.Klitzman, R. & Sauer, M. 2009. Payment of egg donors in stem cell research in the USA. *Reproductive BioMedicine Online.* 18(5):603-608. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3667654/
91.Knoppers, B., & Isasi, R. 2010. Stem cell banking: Between traceability and identifiability. *Genome Medicine*. 2(10):73. (7 pages) Link
92.Knoppers, B. and Laberge, C. 1995. Research and stored tissues: Persons as sources, samples as persons? *JAMA.* 247(22):1806-1807. http://www.ncbi.nlm.nih.gov/pubmed/7500515
93.Kominers, S., & Becker, G. 2012. Paying for tissue: Net benefits. *Science.* 337 (6100): 1292-93. Link https://www.sciencemag.org/content/337/6100/1292.2.full
94.Kubicek, S. 2011. Infographic: Epigenetics – a primer. *Tolpa Studios, Inc*. http://www.the-scientist.com/?articles.view/articleNo/29546/title/Infographic--Epigenetics---A-Primer/
95.Kumar, R. An Open Letter to Those Colleges and Universities that have Assigned Rebecca Skloot's The Immortal Life of Henrietta Lacks as the "Common" Freshmen Reading for the Class of 2016. *Brown Town Magazine*. Link
96.Kurtzberg, J et al. 2005. Untying the Gordian knot: Policies, practices,a nd ethical issues related to banking of umbilical cord blood. Journal of Clinical Investigation. 115(10):2592-2597. http://www.ncbi.nlm.nih.gov/pubmed/16200191
97.Landecker, H. 1999. Between beneficence and chattel: The human biological in law and science. *Science in Context*. 12 (1): 203-225. Link
98.Landecker, H. 2007.*Culturing Life: How Cells Became Technologies*. Harvard University Press. Cambridge. http://www.hup.harvard.edu/catalog.php?isbn=9780674034761
99.Landry, J. et al. 2013. The genomic and transcriptomic landscape of a HeLa cell line. G3: *Genes/Genomes/Genetics:* 1-17. http://www.g3journal.org/content/early/2013/03/11/g3.113.005777.abstract
100.Lehrman, S. Jan 16, 2013. Shifting Roles and Shifting Research: Collaborative Genetic Studies with Indigenous Communities. SACNAS. Link
101.Lifscher, M. Aug 18, 2013. Egg Donor payment bill Vetoed by Brown. *LA Times.* http://articles.latimes.com/2013/aug/18/business/la-fi-capitol-business-beat-20130819

102.Loise, V. & Stevens, A. Dec 2010.The Bayh-Dole act turns 30. *les Nouvelles*. 185-194. https://www.lesi.org/les-nouvelles/les-nouvelles-online/2010/december-2010/2011/05/02/the-bayh-dole-act-turns-30
103.Lucey, B. et al. 2009. Henrietta Lacks, HeLa Cells, and Cell Culture Contamination. *Archives of Pathology and Laboratory Medicine Online*. 133(9):163-67. http://www.archivesofpathology.org/doi/full/10.1043/1543-2165-133.9.1463
104.Maienschein, J. 2005. *Whose View of Life? Embryos, Cloning, and Stem Cells*. Harvard University Press. Cambridge. http://www.amazon.com/Whose-View-Life-Embryos-Cloning/dp/0674017668
105.Malik, N. & Mahendra R. 2013. A review of the methods for human iPSC derivation. *Methods in Molecular Biology*. 997: 23-33. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4176696/
106.Marrow, J, May 1, 2015. Seeded by weeds. *The Scientist.* Link
107.Marshall, E. & Price, M. June 13,2013. U.S. Supreme court strikes down human gene patents. *Science*. 340:1387. http://www.sciencemag.org/news/2013/06/us-supreme-court-strikes-down-human-gene-patents
108.Masters, J. April 2002. HeLa Cells 50 years on: The good, the bad and the ugly. *Nature Reviews Cancer*. 2:315-319. Link
109.Masters, J. December 2012. Cell-line authentication: End the scandal of false cell lines. *Nature* 492:186. http://www.nature.com/nature/journal/v492/n7428/full/492186a.html
110.McInnes, 2011. 2010 Presidential Address: Culture: The Silent Language Geneticists Must Learn—Genetic Research with Indigenous Populations. *American Journal of Human Genetics.* 88(3): 254. http://www.ncbi.nlm.nih.gov/pubmed/21516613
111.McLaughlin, T. May 31, 2010. An Epitah, At Last. *SoVaNow.com.* http://www.thenewsrecord.com/index.php/news/article/an_epitaph_at_last/
112.Mohapatra, S. Fall 2013. Cutting the cord from private cord blood banking: Encouraging compensation for public cord blood donations after Flynn v. Holder. *University of Colorado Law Review.* 84: 944-983. http://lawreview.colorado.edu/wp-content/uploads/2013/11/10.-Mohaptra_703_s.pdf
113.Nardone, R. 2008. Curbing rampant cross-contamination and misidentification of cell lines. *Biotechniques* 45: 221-227. http://www.ncbi.nlm.nih.gov/pubmed/18816888
114.NBMP (National Bone Marrow Program). HLA Matching. http://marrow.org/Patient/Transplant_Process/Search_Process/HLA_Matching__Finding_the_Best_Donor_or_Cord_Blood_Unit.aspx#basics
115.NOTA. National Organ Transplant Act. (NOTA). 42 U.S. C. Sec. 274e, 301 (1984). https://en.wikipedia.org/wiki/National_Organ_Transplant_Act_of_1984
116.NCBI/National Center for Biotechnology Information. May 16, 2014. Spotlight on… Amanda Capes-Davis, Setting the Cell Line Record Straight. PubmedCommonsBlog. http://pubmedcommonsblog.ncbi.nlm.nih.gov/2014/05/16/spotlight-on-amanda-capes-davis-setting-the-cell-line-record-straight/
117.Nelson, A. 2011. *Body and Soul. The Black Panther Party and the Fight against Medical Discrimination*. Minneapolis: University of Minnesota Press. 312. http://www.jstor.org/stable/10.5749/j.ctttt9qf
118.NSF. July 1945.Science:The Endless Frontier. A Report to the President by Vannevar Bush. Director of the Office of Scientific Research and Development. http://www.nsf.gov/about/history/nsf50/vbush1945.jsp
119.Obama, B, 2010. Human Subjects Protection Letter. http://bioethics.gov/sites/default/files/news/Human-Subjects-Protection-Letter-from-President-Obama-11.24.10.pdf
120.Obama, B. July 19, 2013. President Obama: Trayvon Martin Could Have Been Me. WhiteHouse.gov. http://www.whitehouse.gov/blog/2013/07/19/president-obama-trayvon-martin-could-have-been-me
121.Oberlander T. et al. 2008. Prenatal exposure to maternal depression, neonatal methylation of human glucocorticoid receptor gene (NR2C1) and infant cortisol stress responses. *Epigenetics*. 3 (2):97-106. http://www.ncbi.nlm.nih.gov/pubmed/18536531
122.Ossario, P. 2011. Bodies of Data: Genomic Data and Bioscience Data Sharing. *Social Research.* 78(3): 907-932. http://www.jstor.org/stable/23347021?seq=1#page_scan_tab_contents
123.Ouelette, L. & Nardone, R. 2009.Cross-Contamination of Cell Cultures: A call for Vigilance and Authentication. *ASCB Newsletter*. http://www.ascb.org/files/0707newsletter.pdf
124.Oliwenstein, L. Dec 1, 1992. No Longer Human. *Discover.* http://discovermagazine.com/1992/dec/nolongerhuman171
125.Palmer, L. Nov–Dec 2010. Private Reparations. *Hastings Center Report.* 40 (6):49. Link
126.Park, A. Aug 28, 2012. Should people be allowed to sell their organs? CNN/*Time.com*. http://www.cnn.com/2012/07/03/health/allowed-sell-organs-time/
127.Perriello T. May 28, 2010. Honoring Henrietta Pleasant-Lacks. Congressional Record. 156(83):E1008-1009. Link

128.Pielke, R. Aug 2010. In Retrospect: *Science-The Endless Frontier. Nature.* 466:922-923. http://sciencepolicy.colorado.edu/admin/publication_files/2010.24.pdf
129.Pirnay, J-P. et al. 2015. Access to Human Tissue Banks for Research and Product Development. *EMBO Reports*. 16 (5): 557-562. https://www.ncbi.nlm.nih.gov/pubmed/25851645
130.Powell, K. 2005. Stem cell niches: It's the ecology stupid! *Nature.* 435: 268-270. http://www.nature.com/nature/journal/v435/n7040/full/435268a.html
131.Presidential Commission for the Study of Bioethical Issues. September 2011a. Letter Exchange between the Commission and President Barack Obama. *In* Ethically Impossible: STD Research in Guatemala from 1946-1948: v-vi. Link
132.Presidential Commission for the Study of Bioethical Issues. December 2011b. Letter Exchange between the Commission and President Barack Obama. *In* Moral Science: Protecting Participants in Human Subjects Research. v-vi.Link
133.Presidential Commission for the Study of Bioethical Issues. December 2012. President's Bioethics Commission Posts Study Guide Related to its Historical Investigation of the 1940s U.S. Public Health Service STD Experiments in Guatemala https://bioethicsarchive.georgetown.edu/pcsbi/node/787.html
134.Pridan, D. 1964. Rudolf Virchow and social medicine in historical perspective. *Medical History.* 8(3): 274-278. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1033391/
135.Radley, J. et al. 2011. Stress risk factors and stress-related pathology: Neuroplasticity, epigenetics, and endophenotypes. *Stress*. 14 (5): 481-497. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3641164/
136.Reardon, S. July 21, 2015. US tailored-medicine project aims for ethnic balance. Nature.com http://www.nature.com/news/us-tailored-medicine-project-aims-for-ethnic-balance-1.18023
137.Rogers, M. 2011. *Finding Henrietta Lacks: How a Young Write Broke the Story in 1976*. Ebook. Amazon Kindle. http://www.amazon.com/Finding-Henrietta-Lacks-Michael-Rogers-ebook/dp/B005ED9D06
138.Roxland, B. 2010. 2010 report: egg donation for stem cell research: how New York State developed its foversight and compensation policies. World Stem Cell Summit. http://cfile206.uf.daum.net/attach/122079394D37CA4702719F
139.Roxland, B. 2012. New York State's landmark policies on oversight and compensation for egg donation to stem cell research. *Regenerative Medicine.* 7(3):397. http://www.futuremedicine.com/doi/abs/10.2217/rme.12.20
140.Rucker, P. & Eliperin, J. July 19, 2013. Obama Asks Americans to 'Do Some Soul Searching' Following the Trayvon Martin Case. *The WashingtonPost.com.* https://www.washingtonpost.com/politics/obama-asks-americans-to-do-some-soul-searching-following-trayvon-martin-shooting/2013/07/19/2ba9276c-f09a-11e2-9008-61e94a7ea20d_story.html
141.Ruwende, C. et al. 2002. Natural selection of hemi and heteroszygotes for G6PD deficient in Africa by resistance to severe malaria. Nature. 376:246-249. http://www.nature.com/nature/journal/v376/n6537/abs/376246a0.html
142.Scudellari, M. Nov 20, 2013. HPV: Sex, cancer, and a virus. *Nature.* 503:330-332. http://www.nature.com/news/hpv-sex-cancer-and-a-virus-1.14194
143.Seppa, N. March 7, 2015. The mess that is stress. *The Scientist.* 187(5):18-23. https://www.sciencenews.org/article/chronic-stress-can-wreak-havoc-body
144.Senior, A. 2011. Haunted by Henrietta: The archive, immortality and the biological arts. Contemporary Theatre Review, 21(4): 511-529. http://www.tandfonline.com/doi/full/10.1080/10486801.2011.610306?scroll=top&needAccess=true&
145.Servick, K. Sept 25, 2015. Can 23andMe have it all? *Science.* 349(6255):1472-1477. Link
146.Shakespeare, T. & Watson, N. 2002.The social model of disability: An outdated ideology. *Research in Social Science and Disability*. 2:9-28.https://www.um.es/discatif/PROYECTO_DISCATIF/Textos_discapacidad/00_Shakespeare2.pdf
147.Shanks, Peter.April 28, 2010a. When Cultures Collide. *Biopolitical Times Blog.* The Center for Genetics and Society http://www.biopoliticaltimes.org/article.php?id=5175
148.Shanks, P. Aug 4, 2010b. Stem Cell Education and Hype. *Biopolitical Times.* Center for Genetics and Society. http://www.biopoliticaltimes.org/article.php?id=5309
149.Shay, C. June 3, 2010. Bone Marrow Transplants: When Race is an Issue. *Time Magazine.* http://content.time.com/time/health/article/0,8599,1993074,00.html
150.Shire, E. Aug 29, 2014. The Silent Shame of HPV. *The Daily Beast.* http://www.thedailybeast.com/articles/2014/08/29/the-silent-shame-of-hpv.html
151.Skloot, R. 2010. *The Immortal Life of Henrietta Lacks.* Random House: NY. http://rebeccaskloot.com/the-immortal-life/
152.Skloot, R. March 23, 2013. The Immortal Life of Henrietta Lacks, the Sequel. *New York Times*:SR4. http://www.nytimes.com/2013/03/24/opinion/sunday/the-immortal-life-of-henrietta-lacks-the-sequel.html?

pagewanted=all&_r=2&mtrref=undefined&gwh=78D66C08844D3B4AA8CB8A6FF49ECE71&gwt=pay&assetType=opinion
153.Snyderman, N. March 15, 2013. A Mother's Fight. Rock Center with Brian Williams. *NBCnews.* (Producers, Amy Schmitz and Amy Schmitz and Stacey Naggier).(7:56min) http://www.nbcnews.com/video/rock-center/47824570#47824570
154.Stark, L. Spring 2010. Epigenetics online: Multimedia resources. *CBE-Life Science Education Journal*. 9(1):6-9. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2830163/
155.Sugarman, J., Zoloth, L. & Hempel, C. October 4 2010. FullviewMedia. The Immortal Life of Henrietta Lacks - lessons for stem cell researchers and patients. World Stem Cell Summit, Pasadena, CA. http://www.stemcellcurriculum.org/video_world-stem-cell-conference.html (1:05 min).
156.Thayer, Z. & Kuzawa, C. 2011. Biological memories of past environments: Epigenetic pathways to health disparities. *Epigenetics*. 6(7): 798-803. http://www.tandfonline.com/doi/abs/10.4161/epi.6.7.16222
157.Trotter, J. 2006. Book Review: Black Markets: The Supply and Demand of Body Parts. *NEJM.* 355:1183-84. Link
158.Truog, R. et al. 2012. Paying patients for their tissues: The legacy of Henrietta Lacks. *Science*. 337 (6090): 37-38. Link
159.Ullman, A. 2007. Pasteur-Koch. Distinctive Ways of Thinking about Infectious Diseases. *Microbe.* 2(3): 383-387. http://www.asm.org/index.php/component/content/article/114-unknown/unknown/4469-pasteur-koch-distinctive-ways-of-thinking-about-infectious-diseases
160.VanderWalde, A., & Kurzban, S. 2011. Paying human subjects in research: Where are we, how did we get here, and now what? *Journal of Law, Medicine & Ethics.* 39(3):543-558. Link
161.Verspaget, C. 2004. The Anarchy Cell Line. Biodifference- The Political Ecology as part of BEAP'04. The Lawrence Wilson Art Gallery. Stem Cells Across the Curriculum. Link
162.Wadman, M. 2005. Licensing fees slow advance of stem cells. *Nature.* 435(7040):272-273. http://www.nature.com/nature/journal/v435/n7040/full/435272a.html
163.Wadman, M. June 26, 2013. Medical research: Cell division. *Nature.* 498: 422- 426. http://www.nature.com/news/medical-research-cell-division-1.13273 (Podcast and Video).
164.Washington, H. 2006. *The Dark History of Medical Experimentation on Black Americans From Colonial Times To the Present*. DoubleDay Publishers. New York. 501.https://books.google.com/books/about/Medical_Apartheid.html?id=4ZmJvC3f-m0C
165.Weasel, L. 2004. Feminist intersections in science: Race, gender and sexuality through the microscope. *Hypatia*. 19(1) Winter:183-193. Link
166.WHO.1946. Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946; signed on 22 July 1946 by the representatives of 61 States (Official Records of the World Health Organization, no. 2, p. 100) and entered into force on 7 April 1948. http://www.who.int/governance/eb/who_constitution_en.pdf
167.Widdows, H. & Cordell, S. 2011. Why communities and their goods matter: Illustrated with the example of biobanks. *Public Health Ethics.* 4 (1):14-25. http://phe.oxfordjournals.org/content/4/1/14.abstract
168.Wilson-Roe, H. & Roe J. 2013. A Brush With Immortality. London Science Museum. Link
169.Williams, C. 2012. Court Rejects Obama Plea to Reconsider Bone Marrow Ruling. *LA Times.* http://articles.latimes.com/2012/mar/28/local/la-me-bone-marrow-20120328
170.Winikoff, D. & Winikoff R. 2003. The charitable trust model for genomic biobanks. *NEJM*. 349:2280-84. http://www.nejm.org/doi/full/10.1056/NEJMsb030036
171.Zhao, C & Yang, H. Jan 2012. Approved assays for detecting HPV DNA-Design, indications and validation. *Cytopathology and More.* http://www.captodayonline.com/Archives/0112/0112k_cytop_approved.html
172.Zimmer, C. 2013. A family consents to medical gift, 62 years later. *The New York Times Science Blog.* http://www.nytimes.com/2013/08/08/science/after-decades-of-research-henrietta-lacks-family-is-asked-for-consent.html
173.Zimmer, C. Sept 10, 2015. A Pregnancy Souvenir: Cells That Are Not Your Own. *The New York Times* http://www.nytimes.com/2015/09/15/science/a-pregnancy-souvenir-cells-that-are-not-your-own.html?_r=0&mtrref=undefined&gwh=476ED4D798BE23996DAE9AA0D4F66062&gwt=pay