THE BELMONT REPORT AND INFORMED CONSENT:

THE IMPACT ON UNSPECIFIED FUTURE RESEARCH

A thesis submitted to the Caspersen School of Graduate Studies

Drew University in partial fulfillment of

the requirements for the degree,

Master of Medical Humanities

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Madison, New Jersey

May 2015

CONTENTS

Chapter One: Introduction……..1

Chapter Two: Background of Informed Consent and the Need to Protect Human Subjects Involved in Research……6

Chapter Three: Research Involving Biospecimens and Biorepositories……...23

Chapter Four: Informed Consent and Its Relationship to Information, Comprehension, and Voluntariness……...28

Chapter Five: Recommendations and Conclusion……61

Works Cited……...67

Chapter One

Introduction

This thesis will examine informed consent and its relationship to unspecified future research with specimens stored in biorepositories. These biorepositories link an individual's specimens, such as tissue or blood, with his/her medical or personal data, and researchers can analyze these samples from a large number of people in order to better understand diseases and conditions.[1] Biorepositories have become prominent, with over three hundred million stored specimens,[2] and the United States has spent over one billion dollars to create and maintain these banks.[3] In recent years, the general public has become more aware of research conducted on banked specimens due to the popularity of Rebecca Skloot's non-fiction book *The Immortal Life of Henrietta Lacks*, which tells the story of how one woman's cells greatly impacted science, all without her knowledge or consent.[4] Although the story of Henrietta Lacks and her HeLa cells is unfortunate, this controversy may ultimately have a benefit, as it prompts a public conversation about what type of research using biospecimens is legally and ethically acceptable.[5] While the issue of biospecimen research is scientific in nature, Skloot's book has made the general

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1. George Gaskell and Herbert Gottweis, "Biobanks Need Publicity," *Nature* 471, no. 7337 (March 10, 2011): 159.

2. Matthew C. Nisbet and Declan Fahy, "Bioethics in Popular Science: Evaluating the Media Impact of *The Immortal Life of Henrietta Lacks* on the Biobank Debate," *BMC Medical Ethics* 14, no. 10 (February 28, 2013): 2, http://www.biomedcentral.com/1472-6939/14/10 (accessed April 15, 2015).

3. Gaskell and Gottweis, 160.

4. Nisbet and Fahy, 3; Rebecca Skloot, *The Immortal Life of Henrietta Lacks* (New York: Broadway Paperbacks, 2011), 1-2.

5. Gaskell and Gottweis, 160; Nisbet and Fahy, 2.

population more aware of the topic through the personal nature of the story.[6] Due to increased public interest, we must now question how we should go about protecting those who choose to donate their biospecimens to future research. Although there are several guidelines and regulations, I will turn to *The Belmont Report* for guidance since this document is a foundation for the protection of human subjects who are involved in research. While the original intention of *The Belmont Report* was to protect human research subjects from physical harms, such as those that occurred at Nuremberg and Tuskegee, it is evident that the ideas found within this powerful document can be applied to present research issues, such as biorepository research and control over one's biospecimens and data.

With this purpose in mind, it is critical to review the difference between accepted medical treatment and what is considered to be research. Although many sources attempt to distinguish between the two concepts, I will be using the criteria found within *The Belmont Report*:

> [T]he term 'practice' refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success . . . . By contrast, the term 'research' designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge.[7]

Using these definitions, we can see that the two main distinctions between accepted practice and research are a proven outcome and the intended recipient of the benefits.

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6. Nisbet and Fahy, 3.

7. U.S. Department of Health, Education, and Welfare, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979), under "Part A: Boundaries Between Practice and Research," http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html (accessed April 15, 2015).

When individuals agree to take part in research, both the investigators and the participants are unsure of how successful the research intervention will be. Additionally, while research usually provides a benefit for future generations, it may not provide any gain for the participant. Therefore, it is essential that everyone is knowledgeable about the expectations of the study at hand before they agree to participate, hence the need for informed consent in research. Information is key to participants, and the level of information that is given will vary, depending on the type of informed consent that is used. In fact, George Gaskell and Herbert Gottweis have found that individuals are more willing to donate their biospecimens when they are aware of what type of research is being conducted using their specimens.[8] In order to prevent their inclusion in research that they disagree with or find unsettling, potential participants need to clearly understand what they are agreeing to before they voluntarily consent to biospecimen research.

The principle of respect for persons is applied through the process of informed consent.[9] *The Belmont Report* makes the distinction between individuals who are capable of acting autonomously and persons with limited autonomy, who are afforded additional protections.[10] Although this is a significant component of *The Belmont Report*, this thesis will not focus on vulnerable groups with diminished autonomy, such as children or decisionally-impaired individuals. The scope of this paper is limited to adults with the capacity to make autonomous decisions. Additionally, respect for persons necessitates

8. Gaskell and Gottweis, 159.

9. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, under "Part C: Applications."

10. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, under "Part B: Basic Ethical Principles."

that individuals "enter into the research voluntarily and with adequate information."[11] These elements, in addition to the comprehension of autonomous individuals, comprise informed consent.[12]

The structure of this paper is as follows: Chapter Two will give the background of informed consent and will briefly examine the applicable regulations, guidelines, and historical events, such as the Nuremberg Code, the Declaration of Helsinki, the Tuskegee Syphilis Study, Henrietta Lacks, and the Code of Federal Regulations. However, I will highlight the components of informed consent found within *The Belmont Report*, particularly whether the consent contains enough information about the proposed research, is easily understood, and is a voluntary decision. Next, Chapter Three will be a discussion regarding biorepositories, with a focus on the tension between biorepositories, unspecified future research, and informed consent.

Chapter Four will transition to the main focus of my thesis, which will be a review of the different types of informed consent (e.g., blanket consent, broad consent, exclusion clauses, opt-out, specific consent, and tiered consent) in relation to the necessary components of consent (i.e., information, comprehension, and voluntariness) as defined in *The Belmont Report*. I will examine the benefits and disadvantages of each type of consent in order to determine which level of consent is most appropriate and ethical for using stored biological specimens for unspecified future research. In Chapter Five, I will determine which type of informed consent best aligns with *The Belmont Report*. I propose that although it places some limitations on scientific progress, specific

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11. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, under "Part B: Basic Ethical Principles."

12. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, under "Part C: Applications."

consent is most appropriate for the protection of human subjects. Specific consent allows individuals to make a fully informed decision based on their own opinions and beliefs. I will also discuss ways to make this type of consent more amenable to those individuals who do not wish to have as much detailed information when making their decisions. This discussion will be followed by my concluding remarks.

Chapter Two

Background of Informed Consent and the Need to

Protect Human Subjects Involved in Research

The Introduction of Informed Consent

To trace the history of informed consent, we must revisit events that occurred throughout the twentieth-century. The Presidential Commission for the Study of Bioethical Issues notes that the first recorded informed consent for research occurred in 1900 when Walter Reed conducted experiments looking into the spread of yellow fever.[13] After his colleagues first relied on self-experimentation, Reed made the decision to ask volunteers if they wanted to take part in his experiments.[14] Although the first volunteer was merely asked for his verbal permission, a document, with the purpose and risks of the yellow fever experiments, was given to later volunteers.[15] Through an "'exercise of his own free will,'" a "healthy volunteer" would agree to participate.[16] Several years later, in 1907, William Osler, a notable physician, commented on his new views of experimentation based on Reed's method of obtaining a volunteer's permission:

> COMMISSIONER: We were told by a witness yesterday that, in his opinion, to experiment upon man with possible ill-result was immoral. Would that be your view?

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13. Presidential Commission for the Study of Bioethical Issues, "Informed Consent Background" (September 6, 2013): 7, http://bioethics.gov/sites/default/files/Informed%20Consent%20Background%20FORMATTED%209.4.14.pdf (accessed April 15, 2015).

14. Albert R. Jonsen, *The Birth of Bioethics* (New York: Oxford University Press, Inc., 1998), 130.

15. Jonsen, 130.

16. Jonsen, 130-1.

OSLER: It is always immoral, without a definite, specific statement from the individual himself, with a full knowledge of the circumstances. Under these circumstances any man, I think, is at liberty to submit himself to experiments.
COMMISSIONER: Given a voluntary consent, you think that entirely changes the question of morality or otherwise?
OSLER: Entirely.[17]

Nuremberg Code

Although Osler endorsed the use of voluntary consent in human experiments, not everyone shared in his views. During World War II, Nazi physicians conducted experiments on unwilling subjects that included oxygen deprivation, purposeful infection of diseases (e.g., malaria, jaundice, typhus), and genetics studies using twins.[18] When the war ended, the behavior of these physicians was closely examined, and they were "charged with subjecting unwilling victims to medical procedures that were loosely called 'scientific experiments.'"[19] When the trial concluded in 1947, sixteen of the defendants were deemed guilty, and the Nuremberg Code was established.[20] The ten points listed in the Nuremberg Code contain the necessary features for research on human subjects, such as voluntary and informed consent, sufficient background knowledge of the research issue that makes it worth studying, and the importance of a qualified investigator who understands the study and any reasons for which it should be discontinued.[21]

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17. Harvey Cushing, *The Life of Sir William Osler* (Oxford: Clarendon Press, 1925), 2:109.

18. Jonsen, 135.

19. Jonsen, 134.

20. Presidential Commission for the Study of Bioethical Issues, 6.

21. U.S. Department of Health and Human Services, "The Nuremberg Code," http://www.hhs.gov/ohrp/archive/nurcode.html (accessed April 16, 2015).

The Nuremberg Code begins by focusing on the importance of obtaining informed consent:

> The voluntary consent of the human subject is absolutely essential. This means that the person involved . . . should be so situated as to be able to exercise free power of choice . . . and should have sufficient knowledge and comprehension of the elements of the subject matter involved, as to enable him to make an understanding and enlightened decision. This latter element requires that, before the acceptance of an affirmative decision by the experimental subject, there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person, which may possibly come from his participation in the experiment.[22]

This point clearly examines how it is essential for the subject to be given enough information so that he/she understands the study and can make a voluntary decision to be included. This is a common theme of informed consent, which is also included in *The Belmont Report*.

Furthermore, the Nuremberg Code also states that "[t]he experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury."[23] This statement has a current significance because mental suffering is a potential risk when participants' specimens are included in research projects that go against their moral standards, hence the need for specific information to be given.

Declaration of Helsinki

The World Medical Association's (WMA) first version of the Declaration of Helsinki was established in June 1964, and since then, it has been revised numerous

22. "The Nuremberg Code."

23. "The Nuremberg Code."

times.[24] As an international document, it sought to provide guidelines for appropriate research with human subjects.[25] The first version of the Declaration of Helsinki expanded on the Nuremberg Code in three important ways: differentiating between clinical therapeutic research and nontherapeutic biomedical research, recommending a research oversight board, and establishing proxy consent.[26]

The most recent update to the Declaration of Helsinki occurred in October 2013,[27] and it addresses the issue of biospecimen research. In the preamble of the latest version, the WMA states that the Declaration of Helsinki is "a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data."[28] Additionally, the Declaration of Helsinki contains several elements that are relevant to the topic of informed consent. First, the Declaration of Helsinki notes that the rights of the research participants supersede the need for scientific progress.[29] This conflict is the underlying tension between general consent and specific consent. Furthermore, the document notes that potential research participants must voluntarily give their consent only after they are presented with information that is understandable to them.[30] This clearly aligns with the elements of informed consent that are discussed

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24. World Medical Association (WMA), 64th General Assembly, "Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects" (Brazil, 2013), http://www.wma.net/en/30publications/10policies/b3/ (accessed April 16, 2015).

25. Baruch A. Brody, *The Ethics of Biomedical Research: An International Perspective* (New York: Oxford University Press, Inc., 1998), 34.

26. Brody, 34.

27. "Declaration of Helsinki."

28. "Declaration of Helsinki," under "Preamble."

29. "Declaration of Helsinki," under "General Principles."

30. "Declaration of Helsinki," under "Informed Consent."

within *The Belmont Report*. Lastly, consent is required before any research is conducted on identifiable biospecimens.[31] Because the Declaration of Helsinki is frequently amended, it has clearly been able to take into account the present concerns of the scientific and research community.

Tuskegee Syphilis Study

A historical event that strongly demonstrates the importance of informed consent is the Tuskegee Syphilis Study, which was conducted by the U.S. Public Heath Service.[32] Beginning in 1932 and lasting four decades,[33] the events that transpired were concurrent with the inception of the Nuremberg Code and the Declaration of Helsinki. There were several facets of this study that make its occurrence disturbing. Participants were never asked for their consent to take part in a study that intentionally denied treatment for syphilis and that did not adequately explain what would occur if their syphilis remained untreated.[34] However, they were given other incentives that may have influenced their decision to participate, such as free meals and treatment for any other health issues besides syphilis.[35] These benefits were enticing to the participants, who were poor black men.[36] Their educational status was used against them, which allowed the researchers to circumvent informed consent. Additionally, because this unethical study was only

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31. "Declaration of Helsinki," under "Informed Consent."

32. Presidential Commission for the Study of Bioethical Issues, 7.

33. Jonsen, 147.

34. Presidential Commission for the Study of Bioethical Issues, 6.

35. Jean Heller, "Syphilis Victims in U.S. Study Went Untreated for 40 Years," *New York Times*, July 26, 1972.

36. Heller.

conducted on black men, it has left many African Americans wary of medical research.[37] As previously noted, the Tuskegee Syphilis Study was being conducted by the U.S. Public Health Service at the same time that the United States was condemning the Nazis' similar unethical treatment of their prisoners in World War II. In response to the Tuskegee Syphilis Study, Allan M. Brandt noted, "[t]he study also raises significant questions about . . . scientific bureaucracy."[38] His comments showed the need for stricter guidance regarding informed consent for research that would adequately protect the human subjects.

Henrietta Lacks

Another significant event that highlights the importance of both informed consent and biospecimen research is the story of Henrietta Lacks. In 1951, Lacks, a poor black woman, arrived in the gynecology clinic at Johns Hopkins after discovering a lump on her cervix.[39] Following a biopsy, it was discovered that Lacks had cervical cancer;[40] her cells would soon become part of research conducted by Dr. George Gey, who sought to be a pioneer in growing a human immortal cell line.[41] When Lacks arrived for her treatment, she signed a form to permit her operation, but before the surgery began, she had her cervical tissue collected for Gey's research, without her knowledge or permission.[42] The cells, later referred to as HeLa cells, were invaluable as they

37. Amy Harmon, "Where'd You Go With My DNA?" *New York Times*, April 25, 2010.

38. Allan M. Brandt, "Racism and Research: The Case of the Tuskegee Syphilis Study," *The Hastings Center Report* 8, no. 6 (December 1978): 27.

39. Skloot, 13-6.

40. Skloot, 27.

41. Skloot, 30.

continuously multiplied, proving to be immortal human cells.[43] Without telling Lacks, Gey had the HeLa cells shipped to scientists and researchers around the world.[44] Lacks died less than a year after her diagnosis,[45] but her cells were of such scientific importance, that researchers began to collect biospecimens from her family as well.[46] When working with the Lacks family, informed consent was never obtained, and there were several communication barriers between the researchers and the Lacks family, such as language and education, which led to misinterpretation.[47] Over twenty years after Lacks died, the family finally learned that cells that had been obtained from Lacks were alive and being studied in laboratories.[48] Not only was all of this done without permission, but the HeLa cells were, and continue to be, extremely profitable for researchers, yet the Lacks family was given no compensation.[49]

In the afterword to her book, Skloot notes that "[t]here are, essentially, two issues to deal with: consent and money. For most people, knowing if and how their tissues are being used in research is a far bigger issue than profiting from them."[50] This continues to be an issue in the present. In an article from the *New York Times*, Skloot notes that banked biospecimens are used for a variety of beneficial purposes, such as creating

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42. Skloot, 31, 33.
43. Skloot, 40-1.
44. Skloot, 57.
45. Skloot, 86.
46. Skloot, 184-5.
47. Skloot, 182-3.
48. Skloot, 179-81.
49. Skloot, 194-5.
50. Skloot, 317.

vaccines or developing new drugs, but it is difficult for individuals to know how to feel when their cells and tissues are used without their knowledge for research that goes against their beliefs or produces potentially harmful information.[51]

The Belmont Report

The stricter guidance that Brandt called for following the Tuskegee Syphilis Study came in the form of the National Research Act, passed by Congress and signed into law by President Richard Nixon on July 12, 1974.[52] It created the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (hereafter referred to as the Commission).[53] Although the Commission had several duties, one important task was to determine "[t]he nature and definition of informed consent in various research settings."[54] The Commission was also responsible for identifying additional safeguards that would be necessary when consenting certain vulnerable populations;[55] however, as previously noted, informed consent in relation to those with limited autonomy will not be explored within this thesis.

Albert R. Jonsen was appointed to the Commission, and he details his experiences in his book *The Birth of Bioethics*. The discussion regarding the role of informed consent in research took place at the Belmont House from February 13-16, 1976.[56] The

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51. Rebecca Skloot, "Taking the Least of You," *New York Times*, April 16, 2006.

52. Jonsen, 99; Presidential Commission for the Study of Bioethical Issues, 8; The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, under "Summary."

53. *National Research Act of 1974*, Public Law 93-348, § 201, *U.S. Statutes at Large* 88 (1974): 348, http://history.nih.gov/research/downloads/PL93-348.pdf (accessed April 16, 2015).

54. *National Research Act*, § 202.

55. *National Research Act*, § 202.

56. Jonsen, 102.

Commission recognized that several seminal guidelines for research and informed consent of human subjects already existed, namely the Nuremberg Code and the Declaration of Helsinki, but they determined that these issues needed to be explored more thoroughly.[57] After reviewing the writings of several bioethicists, it was decided that "'the central question is how to reconcile protection of individual rights with fruitful pursuit of the collective enterprise.'"[58] Although several principles were deemed important, Joseph V. Brady believed that the principles of "beneficence, freedom, and justice" were most necessary.[59] After much deliberation and revisions,[60] *The Belmont Report* was published on April 18, 1979.[61]

Applying the Research Principles in *The Belmont Report* to Informed Consent

The Belmont Report is divided into three sections. It begins with the differences between accepted medical practice and research before it transitions to the ethical principles necessary for research (i.e., respect for persons, beneficence, and justice), and how investigators can apply these principles to essential components of research (i.e., informed consent, the assessment of risks and benefits, and the selection of subjects).[62] Since this paper will focus on informed consent, it is imperative that I explore its

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57. Jonsen, 102.

58. Transcript of the 15th meeting of The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, February 13-15, 1976, Meeting files, Archive box 26, National Reference Center for Bioethics Literature, Georgetown University, Washington, D.C., quoted in Albert R. Jonsen, *The Birth of Bioethics* (New York: Oxford University Press, Inc., 1998), 102.

59. Jonsen, 103.

60. Jonsen, 103-4.

61. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

62. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

connection to the principle of respect for persons. In order to practice and uphold respect for persons, *The Belmont Report* states that it is necessary "that individuals should be treated as autonomous agents."[63] Tom L. Beauchamp and James F. Childress explain,

> To respect autonomous agents is to acknowledge their right to hold views, to make choices, and to take actions based on their values and beliefs . . . . Respect for autonomy obligates professionals in health care and research involving human subjects to disclose information, to probe for and ensure understanding and voluntariness, and to foster adequate decision making.[64]

In fact, *The Belmont Report* lists information, comprehension (or understanding), and voluntariness as the three necessary elements of informed consent.[65] These concepts will be explored in the next paragraphs.

Information

Whenever an individual is asked to participate in an activity, he/she expects to know what will take place during his/her involvement, along with his/her rights and responsibilities during that activity. This same idea of knowing what to expect holds true for a work commitment, an extracurricular event, and especially research. *The Belmont Report* states that information that is pertinent to research participants encompasses "the research procedure, their purposes, risks and anticipated benefits, alternative procedures (where therapy is involved), and a statement offering the subject the opportunity to ask questions and to withdraw at any time from the research."[66] In the case of

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63. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, under "Part B: Basic Ethical Principles."

64. Tom L. Beauchamp and James F. Childress, *Principles of Biomedical Ethics*, 7th ed. (New York: Oxford University Press, 2013), 106-7.

65. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, under "Part C: Applications."

biorepositories, all of the above elements would be applicable with the exception of alternative procedures.

Although it is agreed that the above elements must be discussed in order for the consent to be informed, what level of information is enough, too little, or too much? Among other theories, both *The Belmont Report* and Beauchamp and Childress discuss the "reasonable person standard."[67] That is, "the information to be disclosed should be determined by reference to a hypothetical reasonable person. Whether information is pertinent or material is to be measured by the significance a reasonable person would attach to it in deciding whether to undergo a procedure."[68] Although a worthwhile starting point, there are several drawbacks. *The Belmont Report* notes that the research participant is a volunteer, which is different than a patient.[69] Since the research is optional, volunteers may have different standards of information disclosure than patients who may have exhausted all other choices. Additionally, Beauchamp and Childress note that there is no standard definition of the "reasonable person."[70] Even if there were one definition that was accepted by the research community, personal experiences and attitude play a role in determining what is acceptable to each individual. This subjectivity, in terms of the level and amount of information, would make it impossible to have a one-size-fits-all definition of a "reasonable person" that pleases every research

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66. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, under "Part C: Applications."

67. Beauchamp and Childress, 126; The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, under "Part C: Applications."

68. Beauchamp and Childress, 126.

69. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, under "Part C: Applications."

70. Beauchamp and Childress, 126.

participant and his/her needs. Although Beauchamp and Childress believe that each participant should receive the information that he/she finds relevant, they recognize that it is more practical to first supply the information that a reasonable person needs and then complement that information with specific details that fit each individual's needs.[71] This belief will be important in my final discussion of this paper.

Comprehension

The importance of a potential participant's understanding of the proposed research was not recognized until the 1970s; before that, the disclosure of information was given highest priority.[72] If one does not adequately understand the information being presented, he/she may not realize what he/she is authorizing. In respect to research, it is necessary for the participant to fully grasp the purpose, risks, and benefits of the study in order to be properly informed. *The Belmont Report* notes, "[b]ecause the subject's ability to understand is a function of intelligence, rationality, maturity and language, it is necessary to adapt the presentation of the information to the subject's capacities. Investigators are responsible for ascertaining that the subject has comprehended the information."[73] How can investigators determine adequate understanding? First, we must recognize that sufficient information is the foundation for comprehension. Beauchamp and Childress believe that "persons understand if they have acquired pertinent information and have relevant beliefs about the nature and consequences of

71. Beauchamp and Childress, 127.

72. Tom L. Beauchamp, "Informed Consent: Its History, Meaning, and Present Challenges," *Cambridge Quarterly of Healthcare Ethics* 20, no. 4 (October 2011): 515.

73. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, under "Part C: Applications."

their actions."[74] Additionally, they note that when information is unclear, it can severely impair an individual's understanding.[75] Therefore, the information presented should be detailed, yet straightforward and explicit. Also, in relation to biorepositories, it is imperative to have a common language between the researchers and the potential participants, and uncommon terminology will need to be clearly defined before consent is obtained.

Voluntariness

Since participating in research is not mandatory, it is important that all individuals agree to partake in any research on their own terms. *The Belmont Report* states that consent is voluntary only when it is "free of coercion and undue influence."[76] For biorepository research, consent may be involuntarily given for several reasons. First, researchers may promise participants a direct benefit from any research results, which may not be true since the benefits of biorepository research will usually be felt by future generations after numerous samples are collected and analyzed. Additionally, a participant may be influenced to consent if the biorepository is specifically focusing on a disease or condition that is prominent in his/her family.[77] Again, the benefits will probably not be seen until many years later. Although the participant may be happy to help future generations, he/she should clearly understand that most likely, there would

74. Beauchamp and Childress, 131.

75. Beauchamp and Childress, 132.

76. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, under "Part C: Applications."

77. John S. Luque et al., "Formative Research on Perceptions of Biobanking: What Community Members Think," *Journal of Cancer Education* 27, no. 1 (March 2012): 97.

not be a direct benefit to any family members who are currently suffering from the disease or condition being researched.

Code of Federal Regulations

As per the U.S. Department of Health and Human Services (HHS), *The Belmont Report* played a strong role in the formulation of the current regulations set forth by the federal government.[78] Using *The Belmont Report* as a guiding document, both HHS and the U.S. Food and Drug Administration (FDA), an agency of HHS, updated their policies in 1981 to make them more consistent with one another.[79] Ten years later, HHS, along with fourteen other areas of the federal government, agreed to the "Common Rule," which "outlines the basic provisions for IRBs [Institutional Review Boards], informed consent, and Assurances of Compliance."[80]

Regulations for the protection of human subjects can be found in Title 45 Code of Federal Regulations (CFR) Part 46 (HHS) and Title 21 Code of Federal Regulations (CFR) Part 50 (FDA). When outlining the requirements for informed consent, both documents state that in order for a human subject to be involved in research, "an investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate."[81] This statement is clearly influenced by *The Belmont Report*'s

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78. U.S. Department of Health and Human Services, "Federal Policy for the Protection of Human Subjects ('Common Rule')," http://www.hhs.gov/ohrp/humansubjects/commonrule/ (accessed April 17, 2015).

79. "'Common Rule.'"

80. "'Common Rule.'"

81. U.S. Department of Health and Human Services, "Title 45 Code of Federal Regulations Part 46: Protection of Human Subjects, 2009," § 46.116, http://www.hhs.gov/ohrp/policy/ohrpregulations.pdf (accessed April 17, 2015); U.S. Food and Drug Administration, "Title 21 Code of Federal Regulations Part

requirements of information, comprehension, and voluntariness as the necessary components of informed consent. Additionally, both regulations continue by stating the necessary elements of informed consent, such as the purpose of the research, an outline of the procedures, benefits, risks, alternative treatments, and the opportunity to withdraw;[82] a similar statement is found within *The Belmont Report*.

Although *The Belmont Report* highlights the importance of informed consent and 45 CFR 46 and 21 CFR 50 look to this document as a guide, the federal regulations do find some exceptions for informed consent. These current exceptions are thoroughly explored in the "Guidance on Research Involving Coded Private Information or Biological Specimens," disseminated by the Office for Human Research Protections (OHRP) in October 2008. For example, if "private information" is obtained from a living person but it is not "individually identifiable," the research is not considered to involve human subjects,[83] and therefore, consent does not need to be obtained. Furthermore, HHS delineates research that is exempt from federal regulations. For biospecimens, the applicable exemption would be 45 CFR 46.101(b)(4), which highlights two caveats that allow for exemptions: the prior existence of the specimens and how the information is recorded.[84] If the exemption applies, then consent is not needed for the research activity to commence.

50: Protection of Human Subjects, 2014," § 50.20, http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=50&showFR=1 (accessed April 17, 2015).

82. "45 CFR 46," § 46.116; "21 CFR 50," § 50.25.

83. U.S. Department of Health and Human Services, "Guidance on Research Involving Coded Private Information or Biological Specimens," Office for Human Research Protections (October 16, 2008), under "Background," http://www.hhs.gov/ohrp/policy/cdebiol.html (accessed April 17, 2015).

Francis S. Collins, director of the National Institutes of Health (NIH), has recently noted, "[O]ur policy is lagging years and maybe decades behind the science. It's time to catch up."[85] Therefore, in July 2011, an advance notice of proposed rulemaking (ANPRM) was announced, requesting the public's thoughts for how federal regulations could be updated to reflect the many changes in research, including the growth and popularity of biorepositories.[86] In this notice, it has been proposed that a broad version of consent could be used for research conducted on residual tissue from clinical procedures, and research using these specimens would be exempt from IRB review.[87] Later in this paper, both the benefits and drawbacks of broad consent will be examined. Without IRB review, the flaws of a broad consent document may go unnoticed.

Another proposed change is the revision of the category of exempt research, which was previously described. Specifically, "research that only involves the use of data or biospecimens collected for other purposes, even if the researcher intends to retain identifiers, would now come within the new Excused category," meaning that it will not be subject to IRB review.[88] However, broad consent would be implemented for biospecimens that fell within this new category, which is a departure from the current

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84. "45 CFR 46," § 46.101; Office for Human Research Protections, under "Research Not Involving Human Subjects Versus Exempt Human Subjects Research."

85. Rebecca Skloot, "The Immortal Life of Henrietta Lacks, the Sequel," Sunday Review, *New York Times*, March 23, 2013.

86. U.S. Department of Health and Human Services, "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators," Office of the Secretary, Federal Register 76, no. 143, July 26, 2011, 44512, http://www.gpo.gov/fdsys/pkg/FR-2011-07-26/pdf/2011-18792.pdf (accessed April 17, 2015).

87. Office of the Secretary, 44515.

88. Office of the Secretary, 44518-9.

policy that does not require consent for this type of research.[89] Additionally, it is possible that the consent form would also contain several levels of tiered consent,[90] which offers a compromise to critics of broad consent. Again, tiered consent will be discussed in more detail later in this paper.

89. Office of the Secretary, 44519.

90. Office of the Secretary, 44519-20.

Chapter Three

Research Involving Biospecimens and Biorepositories

According to the National Cancer Institute's (NCI) Biorepositories and Biospecimen Research Branch, "[b]iospecimens are materials taken from the human body, such as tissue, blood, plasma, and urine that can be used for cancer diagnosis and analysis."[91] Because of their particular focus, the NCI limits its definition of biospecimens to oncology research, but the same types of human materials that the NCI describes are also used for research on many other conditions, such as heart disease or obesity. On a larger scale, a biorepository is "where biospecimens are stored and made available for scientists to study for clinical or research purposes."[92] Biorepositories may also be referred to as biobanks. Once stored in the biorepository, the biospecimens can be classified as a "coded sample" (i.e., a code links the specimen to a donor who can then be identified) or as "de-identified" (i.e., no linkage exists that can easily identify the donor).[93] Oftentimes, the biospecimens are used for future research,[94] and biorepositories combine the biospecimens with medical records in order for investigators to learn more about human genotypes and phenotypes.[95] Biorepositories can be found throughout the

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91. Biorepositories and Biospecimen Research Branch, "Patient Corner," under "What are Biospecimens and Biorepositories," National Cancer Institute, http://biospecimens.cancer.gov/patientcorner/default.asp (accessed April 17, 2015).

92. Biorepositories and Biospecimen Research Branch, under "What are Biospecimens and Biorepositories."

93. Biorepositories and Biospecimen Research Branch, under "Glossary."

94. Biorepositories and Biospecimen Research Branch, under "What are Biospecimens and Biorepositories."

95. Henry T. Greely, "The Uneasy Ethical and Legal Underpinnings of Large-Scale Genomic Biobanks," *Annual Review of Genomics and Human Genetics* 8 (September 2007): 344.

United States, and their size, purposes (general versus specific medical conditions), location (local versus national), and owners (private versus government) can vary.[96] Additionally, the specimens may be collected solely for research, but biorepositories may also include residual specimens, such as extraneous tissue from a clinical procedure (e.g., a biopsy or surgery).[97]

Biorepositories initially began on a smaller scale. Researchers focused on specific conditions (e.g., breast cancer), and they would collect samples and medical information only as it related to this particular disease.[98] Henry T. Greely notes that if breast cancer was prevalent in a certain family, researchers would study the entire family (both affected and unaffected individuals) in order to establish disease trends.[99] Because the researcher and the family worked closely together for long periods of time, they would establish a relationship.[100] Like an individual who sees a particular doctor over many years, the relationship between the researcher and the family was often built on trust and respect. Additionally, not only did the researcher gain scientific knowledge, but families hoped that this newfound information could help limit the prevalence of the disease in their family.[101] It was a mutual partnership that benefitted both parties. Because only specific diseases were being studied and samples were not easily or widely

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96. Biorepositories and Biospecimen Research Branch, under "What are Biospecimens and Biorepositories"; Greely, 344.

97. Noor A. A. Giesbertz, Annelien L. Bredenoord, and Johannes J. M. van Delden, "Inclusion of Residual Tissue in Biobanks: Opt-In or Opt-Out?" *PLoS Biology* 10, no. 8 (August 2012): 1, http://www.plosbiology.org/article/fetchObject.action?uri=info:doi/10.1371/journal.pbio.1001373&representation=PDF (accessed April 17, 2015).

98. Greely, 345.

99. Greely, 345.

100. Greely, 345.

101. Greely, 345.

available, these biorepositories were extremely limited in their uses.[102] The researcher only thought to collect the information relevant to the disease at hand, which controlled how the data could be manipulated.[103] Furthermore, the quantity of samples was limited, so it was uncommon for the primary researcher to share with other investigators.[104]

By the end of the twentieth-century, it became clear that it was rarely a single gene that caused a disease to manifest in an individual.[105] Therefore, the original biorepositories that focused on the effect specific genes had on a certain disease in a particular family became outdated in favor of much larger biorepositories.[106] The newer biorepositories with countless biospecimens are extremely important to researchers. With the myriad of samples, researchers can examine different characteristics and traits of these biospecimens, and because this is being done easily and inexpensively on a large scale, it allows generalizable patterns to be established.[107] These patterns can enable researchers to learn more about disease progression and response to treatment,[108] which is beneficial to individuals who are diagnosed with these diseases. Biospecimen and biorepository research are also more convenient for participants than typical clinical trials because other than their one time donation of their specimens, they are not "active"

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102. Greely, 345.

103. Greely, 345.

104. Greely, 345-6.

105. Greely, 346.

106. Greely, 346.

107. Biorepositories and Biospecimen Research Branch, under "Why are Biospecimens Important in Cancer Research"; Mats G. Hansson et al., "Should Donors Be Allowed to Give Broad Consent to Future Biobank Research?" *The Lancet Oncology* 7, no. 3 (March 2006): 266; Greely, 347.

108. Biorepositories and Biospecimen Research Branch, under "Why are Biospecimens Important in Cancer Research."

participants.[109] Therefore, participation does not require numerous visits to monitor and assess how they are reacting to the research treatment. These types of visits can impede on their daily lives and activities. On the other hand, because the biorepositories are so large, study a wide variety of diseases and conditions, and include numerous investigators from around the country, participants do not establish a relationship with the researchers, nor are they necessarily participating in studies that directly affect their families.[110] When you combine these issues with cutting edge technology that produces infinite possibilities for research opportunities, they "create or exacerbate the ethical tensions around genomic biobank efforts."[111]

Tension Between Informed Consent and Biorepository Research

As stated in *The Belmont Report*, information, comprehension, and voluntariness are the necessary components that make up informed consent in research.[112] Although the necessity of these elements is agreed upon, they are difficult to implement when biospecimens are stored and later used for future unspecified research. Adequate information might not always be available, it may be challenging for participants to comprehend what they are entitled to and what rights they are giving up, and it is difficult to gauge voluntariness when participants do not know what they are agreeing to. Oftentimes, it is unclear how much information needs to be given to prospective participants. Some critics believe that participants should know exactly what they are

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109. Gert Helgesson, "In Defense of Broad Consent," *Cambridge Quarterly of Healthcare Ethics* 21, no. 1 (January 2012): 41.

110. Greely, 347.

111. Greely, 345.

112. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, under "Part C: Applications."

agreeing to. In response to a more general version of informed consent, Greely states that the "goodwill" of participants is

> being put at risk by the ways some of these biobanks plan to operate, ways that threaten to abuse the trust with which these donations were given . . . ways that jeopardize, for the sake of administrative convenience and short-term research gains, the interests, the wishes, and, I believe, the rights of those who contributed to these resources.[113]

On the opposite end of the spectrum, those who support a more general version of informed consent say that it promotes scientific progress. They claim that by restricting consent to one instance, it is less invasive to potential participants and limits administrative inconveniences.[114]

113. Greely, 344.

114. Greely, 357-8.

Chapter Four

Informed Consent and Its Relationship to Information,

Comprehension, and Voluntariness

Types of Informed Consent

Table 1 lists some of the different levels of informed consent that can be utilized when speaking with potential participants.

Table 1. Types of informed consent

Type	Description
Blanket	Also known as open, generic, or general consent. Provides participants a choice on whether they intend to participate for any and all future research.
Broad	Provides participants a choice on whether to participate for future research based on a broad category, e.g., cancer, heart disease, or behavioral research.
Specific	Also known as repeated consent or reconsent. Participants have to consent to each and every future study.
Tiered	Also known as line-item or multilayered consent. Provides participants with multiple options for them to select. The range of options varies and can include whether participants desire to be recontacted, whether they will allow their samples and information to be used for commercial research, and different choices for areas of research in which they would allow their samples and information to be used.
Opt-out	Inaction is treated as a signal of consent.

Sources: Adapted from Zubin Master and David B. Resnik, "Incorporating Exclusion Clauses into Informed Consent for Biobanking," *Cambridge Quarterly of Healthcare Ethics* 22, no. 2 (April 2013): 204; Noor A. A. Giesbertz, Annelien L. Bredenoord, and Johannes J. M. van Delden, "Inclusion of Residual Tissue in Biobanks: Opt-In or Opt-Out?" *PLoS Biology* 10, no. 8 (August 2012): 4, http://www.plosbiology.org/article/fetchObject.action?uri=info:doi/10.1371/journal.pbio.1001373&representation=PDF (accessed April 18, 2015).

Although all of the above-mentioned consents are utilized in research, which one is most appropriate for unspecified future research involving biospecimens? Are there any that would not result in an adequate informed consent for biospecimen research? Are the

demands for informed consent in biospecimen research too high or too low? Where do we set the threshold? As Beauchamp notes,

> If one uses overly demanding criteria of informed consent—such as full disclosure and complete understanding—then an informed consent can hardly ever be obtained. Conversely, if underdemanding criteria such as a signed consent form are used, an informed consent becomes too easy to obtain, and the term loses its moral significance.[115]

The following sections will explore the different types of informed consent in more detail and how they incorporate the elements of information, comprehension, and voluntariness. Additionally, for each type of informed consent, I will address the concerns of critics.

Blanket Consent and Broad Consent

Although they are separate and distinct types of consent, I will discuss blanket consent and broad consent together because they do have many similarities.

Information

As described in Table 1, blanket consent is a very open-ended consent in which potential participants are asked if they want to donate biospecimens to be banked for a wide range of future research that is yet to be defined. Broad consent is similar to blanket consent, but it focuses on research in a general category, such as cancer or neurological disorders. Since the future research is unspecified, we know that the information that is being given to the participants in both types of consent is vague. However, when a participant gives broad consent, it may be easier for him/her to have an idea of the types of projects that may be pursued (e.g., cancer), whereas blanket consent can incorporate any type of approved biomedical research project.

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115. Beauchamp, 517.

When the information being given to participants is ambiguous, it can have both benefits and drawbacks. For the participants, they do not need to worry about being recontacted whenever their samples are being used. In a study undertaken by Laura M. Beskow and Elizabeth Dean, they interviewed participants in order to assess their opinions and understanding of informed consent and biospecimen research.[116] One question they asked subjects was, "How would you feel about being contacted at a later time to participate in additional research?"[117] Only one-quarter of the surveyed individuals would feel uncomfortable being recontacted, giving reasons like, "'I would look at being contacted as an inconvenience.'"[118] Since only one-quarter of the participants gave a response of feeling distressed by recontact, it would follow that the majority of people in this study would not mind being recontacted. The people who found repeated contact to be bothersome might believe that they gave their overarching consent for research once, which was enough for them, and what the researchers do with their specimens now is no longer their concern. Furthermore, Sara Chandros Hull and her colleagues conducted a study with nearly twelve hundred participants at five medical centers around the United States.[119] When they asked participants if research could be conducted on their leftover specimens, many responded that they would want to be notified about the research that would be taking place, and it did not matter whether the leftover specimens were anonymized (72% would want to be informed) or identifiable

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116. Laura M. Beskow and Elizabeth Dean, "Informed Consent for Biorepositories: Assessing Prospective Participants' Understanding and Opinions," *Cancer Epidemiology, Biomarkers and Prevention* 17, no. 6 (June 2008): 1441.

117. Beskow and Dean, 1444.

118. Beskow and Dean, 1443-4.

119. Sara Chandros Hull et al., "Patients' Views on Identifiability of Samples and Informed Consent for Genetic Research," *The American Journal of Bioethics* 8, no. 10 (October 2008): 63-4.

(81% would want to be informed).[120] Based on the results of both of the above studies, it would seem that the issue of recontact is not an entirely negative factor for potential participants.

Additionally, not having to recontact participants is also a benefit to the researchers. In order for the results to be meaningful, the researchers would need to study many samples, which entails numerous variables over a lengthy period of time. During the course of any study, it is guaranteed that participants might change addresses or phone numbers or even die.[121] If it were mandatory for investigators to recontact all participants in order to obtain permission for each project, they would inevitably lose participants with each subsequent study due to these difficulties. Therefore, the sample size of the biorepository would be affected due to administrative problems and not based on the participants' decisions to reconsent to further projects.[122] Also, maintaining a database that continually checks in on participants and updates their personal information would be time consuming,[123] but blanket consent and broad consent eliminate this cost and inconvenience for researchers.[124]

On the other hand, when the informed consent is general and does not provide enough information to the participants, the research expectations may be misinterpreted. If the investigators are free to pursue any approved research with the biospecimens and the participants are not given any information about the direction the research might be

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120. Hull et al., 64-5.

121. Helgesson, 41.

122. Helgesson, 41; Andrea Boggio, "Biobanks and the 'Well-Being' of Humanity: Integrating Consent to Research with the Capability Approach," *Critical Public Health* 20, no. 1 (March 2010): 88.

123. Hansson et al., 266.

124. Greely, 344; Helgesson, 44; Boggio, 88.

taken, then participants may become upset, angry, or frustrated if their specimens are used in controversial research that could lead to stigmatization or discrimination.[125] An excellent example of this is the Havasupai Indians and research conducted by Arizona State University.

Diabetes runs rampant in the Havasupai population, and the tribe reached out to John Martin, an anthropologist they trusted, to see what could be done to help minimize the disease and its effects.[126] The tribe gave broad consent for the use of their blood to Therese Markow, a geneticist, who provided a simplified consent form due to the Havasupai tribe's lack of higher education and language barrier.[127] Several years later, in 2003, a Havasupai tribe member sat in on a presentation at Arizona State University and what she heard made her question whether her tribe had given permission for this research project, which was not about diabetes.[128] During this presentation, the Havasupai learned that their blood was used to study inbreeding, schizophrenia, and tribal origins.[129] A settlement occurred between the Havasupai and Arizona State University, and this resolution is noteworthy "because it implied that the rights of research subjects can be violated when they are not fully informed about how their DNA might be used."[130]

In this particular instance, the Havasupai were a vulnerable population, but this situation could happen with any group of individuals. As Beauchamp notes, it was the

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125. Greely, 356; Zubin Master and David B. Resnik, "Incorporating Exclusion Clauses into Informed Consent for Biobanking," *Cambridge Quarterly of Healthcare Ethics* 22, no. 2 (April 2013): 206.

126. Amy Harmon, "Indian Tribe Wins Fight to Limit Research of Its DNA," *New York Times*, April 21, 2010.

127. Harmon, "Indian Tribe Wins Fight."

128. Harmon, "Indian Tribe Wins Fight."

129. Harmon, "Indian Tribe Wins Fight."

130. Harmon, "Indian Tribe Wins Fight."

"researchers' responsibility to communicate what might happen with the samples,"[131] and this should hold true no matter who the participants are. The Havasupai requested for help in curtailing the prevalence of diabetes in their tribe, and therefore, they would have no reason to believe that the researchers had other plans in mind for their specimens. As members of the scientific community, investigators realize that blanket consent or broad consent opens up a range of research possibilities, but the general public may not understand just how far reaching this open-ended consent may be. When participants are not given enough information, they do not grasp that the results of the research in which they were included can be damaging to how they or others view themselves.[132]

However, Gert Helgesson disagrees with the viewpoint that general consent is impermissible just because research exists that could potentially stigmatize the participants. He argues that if participants truly understand the concept of broad consent and what it involves, they should recognize that there is a chance that their specimens will be included in studies that they do not approve of.[133] While he specifically states broad consent, it is likely that he would extend this argument to blanket consent as well. Additionally, Helgesson feels that those who agree to a more generalized consent should be at ease because the review boards have a responsibility to make sure that any studies that are conducted with the biospecimens are appropriate. He explains,

> It is the job of the review board to assess risks, along with other aspects of the study, as it is submitted to the board for approval. This means that if people are willing to trust the quality of the assessments made by the review boards, then

131. Beauchamp, 521.

132. Greely, 350.

133. Helgesson, 45.

> they do not need to predict future risks tied to individual projects . . . . This is what people who are willing to give broad consent autonomously choose to do.[134]

It is true that IRBs have the responsibility of ensuring that the studies being conducted are suitable; however, an IRB did approve the Havasupai study and that proved to be very damaging to the participants. Later in this paper, I will discuss in more detail how IRB members, researchers, and participants have different opinions of informed consent and what should and should not be included.

Furthermore, past injustices play a role in the amount of information participants want to know. For example, in a recent study that explored attitudes towards donating to a biorepository, it was found that the African American participants believed "that research was conducted for the benefit of white populations, while minority groups have been unjustly used as 'lab rats' or 'guinea pigs.'"[135] It is clear that events such as the Tuskegee Syphilis Study still have an influence on how certain groups are wary of research. Additionally, other historical events that were mentioned in this recent study by African American and Hispanic participants were the Guatemala syphilis experiments and Henrietta Lacks.[136] If the minority participants in this study were asked whether they would want to know more about biorepository research before giving their consent, they would most likely say yes. They would want to ensure that they were not being taken advantage of and used for research that would benefit other groups and not them. A blanket consent or broad consent would probably not sit well with them because it would not detail the type of research that would be conducted.

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134. Helgesson, 47.

135. Luque et al., 96.

136. Luque et al., 97.

Comprehension

The Havasupai case also demonstrates how comprehension is difficult to ascertain in blanket consent or broad consent. Stephen J. O'Brien, a geneticist with the NIH, understands the situation Markow, the researcher in the Havasupai case, has been put in, but he firmly believes that it was her duty to assess the tribe's level of understanding when she obtained their consent.[137] Again, the Havasupai are a vulnerable population, but O'Brien's claim is universal to all research participants. In a study conducted at Vanderbilt University Medical Center, Jill M. Pulley and her colleagues wanted to gain insight on patient attitudes regarding a proposed biorepository.[138] After assessing the approximately one thousand completed questionnaires, they categorized study participants into five groups based on their survey responses: supportive of research, altruistic, passively supportive, skeptical, and decisively opposed.[139] In response to the question "'Do you assume that research might be conducted on blood and tissues taken from your body that are no longer needed for your care?'" the researchers observed that almost all of the decisively opposed participants falsely believed that their permission would need to be obtained.[140] Pulley and her colleagues believe that this is "an education challenge" and that individuals need to realize that this type of research in which individuals cannot be identified is permitted without consent under 45 CFR 46.101(b)(4).[141] Although in this specific situation, participants in the study were

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137. Harmon, "Where'd You Go?"

138. Jill M. Pulley et al., "Attitudes and Perceptions of Patients Towards Methods of Establishing a DNA Biobank," *Cell and Tissue Banking* 9, no. 1 (March 2008): 56.

139. Pulley et al., 58.

140. Pulley et al., 61.

confused about the need for informed consent and not the actual information within the informed consent, it still showcases that researchers need to ensure that participants understand what they are agreeing to when they give their blanket consent or broad consent.

Voluntariness

As I stated earlier when discussing the history of biorepositories, it used to be the case that individuals who donated biospecimens usually worked with a researcher that they trusted in order to learn more about a disease or condition that afflicted many of their family members. Having confidence in a researcher and donating to a cause that is personal says a lot about voluntariness.

Let us first discuss having trust in one's physician or researcher. In Beskow and Dean's research, they posed a general question to participants: "How would you feel if this consent form were asking you to have your blood drawn just to give to the Biorepository?"[142] Approximately half of the respondents had concerns, and a common apprehension was that participants would not know who was using their specimens for research.[143] Specifically, one participant stated, "'when it comes to giving blood, taking medication, unless my doctor prescribes it, I wouldn't do it.'"[144] Additionally, John S. Luque and his colleagues found that an individual's affiliation with his/her physician played a role in donating specimens to a biorepository.[145] People put a great deal of faith

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141. Pulley et al., 62; "45 CFR 46," § 46.101.

142. Beskow and Dean, 1443.

143. Beskow and Dean, 1442.

144. Beskow and Dean, 1443.

145. Luque et al., 94.

and trust in a doctor that they have know for a lengthy period of time and who may have even treated many other family members. When a close family doctor makes a statement (whether it be about a diagnosis, treatment, or research) to an individual, he/she believes the physician because they have built a relationship, and it would be difficult for the patient to consider that his/her physician is taking advantage of him/her. Let us assume that this specific physician knows of an investigator who is researching heart disease. If the physician broached this subject with his/her patient, the patient would probably believe that his/her doctor was recommending him/her for the study because the physician truly believed he/she was an ideal candidate. The patient would then use his/her own beliefs and knowledge in combination with the words of a trusted physician to make a voluntary decision to take part in the research. This is supported by the findings of Alanna Kulchak Rahm and her colleagues. When they asked how much trust the participants had in their large healthcare system, many answered positively (on a five-point scale, 94% gave a score of three or higher), citing trust as motivation to donate.[146] Based on these results, the confidence and trust one has in his/her own personal physician seems to extend to the physician's network of colleagues. However, it should be noted that the majority (67%) of these study participants had no knowledge of a biorepository, but they were still willing to make a donation out of trust.[147] Blind trust should not be the only motivating factor in deciding to donate specimens to a biorepository. Trust in a physician or researcher might open the door to a conversation, but substantial information is also necessary for a decision to be voluntary.

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146. Alanna Kulchak Rahm et al., "Biobanking for Research: A Survey of Patient Population Attitudes and Understanding," *Journal of Community Genetics* 4, no. 4 (October 2013): 446-7.

147. Rahm et al., 446-7.

On the other hand, assume that this same patient was going for a routine check-up in a hospital, and an unknown investigator approached him/her to ask for permission to use his/her biospecimens for research. Having no knowledge about this researcher, the patient is unsure of the truthfulness and honesty of this unfamiliar person's words. In that very moment, this patient might agree to participate, but on later reflection, he/she may feel that he/she was persuaded to partake in a study in which he/she might not ordinarily take part. When reviewing both situations, it is more likely that the patient would voluntarily agree to take part in research conducted by an investigator who is familiar to his/her personal physician, while that same patient might feel some sense of regret and unease about agreeing to participate in research with the unfamiliar investigator. In most cases of biospecimen research, the participant will not know the researcher who is using his/her samples. Would he/she have voluntarily agreed to participate had he/she known that the researcher was someone with whom he/she did not have any connection?

Additionally, if an individual knows that a biorepository concentrates on a specific area of research, he/she may be more likely to donate if he/she has a personal or family history of the disease. Tom Tomlinson found that individuals who suffered from cancer were more likely to donate to a biorepository because they felt it was a way of "giving back something in return for the medical advances that may save their lives."[148] Tomlinson's views are demonstrated in the study conducted by Luque and colleagues, in which they recruited ninety-five participants into different focus groups in an effort to learn more about their perceptions of biorepositories.[149] They made sure to recruit

148. Tom Tomlinson, "Respecting Donors to Biobank Research," *The Hastings Center Report* 43, no. 1 (January-February 2013): 42.

149. Luque et al., 92-3.

diverse community members, paying particular attention to race (White = 37.9%, Black/African American = 34.7%) and language (Spanish speaking = 38.9%, Non-Spanish speaking = 59%).[150] When the focus group members were asked about the benefits of donating biospecimens, family history was found to be very important. One African American woman (18-29 years) stated, "'I have had members of my family die of cancer, and so anything I can do to be of assistance as far as education and research.'"[151] This sentiment held true across all age ranges (18-29 years, 30-54 years, and 55 years and older).[152] This voluntariness to participate in research might not translate to diseases or conditions with which the individual has no connection.

How Can Blanket Consent and Broad Consent Address the Concerns of Critics?

One of the main issues with blanket consent and broad consent in unspecified future research is that it does not give enough information to participants. Not only are they not given enough facts when signing the informed consent, but also as research using their specimens is proposed and carried out, participants are not provided with any updates. It has been suggested that communication systems, such as a biorepository bulletin or webpage, are put into place so that participants have an opportunity to keep abreast of current research projects.[153] If this plan was implemented, Greely believes that this would allow researchers to give participants the ability to "opt out" of studies that made them feel uncomfortable.[154]

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150. Luque et al., 93.

151. Luque et al., 95.

152. Luque et al., 96.

153. Greely, 358.

154. Greely, 358.

Although these measures satisfy the need for more information, how can we ensure that participants are paying attention? Obviously the participants have responsibility over their own personal affairs, which includes paying their bills or keeping updated on committees or projects they are involved in, which can be parent committees at school or research projects like the biorepository. In fact, Helgesson believes that for an "observant participant," there is no difference between general consent for future studies and specific consent.[155] This seems to place more responsibility on the participant to keep informed with research updates rather than give the biorepository any accountability in the matter. How many participants are truly observant in regards to research? In all other types of medical research, when participants come in for follow-ups, the investigator has the responsibility of reminding the participant to update the participant diary or take the research medication. Additionally, donating specimens to the biorepository is usually a single instance and not a recurring event, so there is no reminder each month like there is when you receive your credit card bill. Therefore, it would probably make more of an impact if updates were sent directly to participants, whether through mail or email, rather than posted on a general webpage. This would put the information directly in the hands of the participants, and then it is their responsibility to open the mail, read it, and contact the biorepository if they have any questions or concerns.

This is best demonstrated in the study conducted by Pulley and her colleagues at Vanderbilt University Medical Center, where they asked the study participants how they

155. Helgesson, 49.

would like to learn more about research using their biospecimens.[156] The possible choices are listed below:

- a letter sent to all patients announcing the research program
- a document that someone at Vanderbilt explains to you in person, with a place to sign and give your written authorization
- a form directly handed to you explaining what will happen
- an article in the newspaper about the project
- a story on the news on TV talking about the project
- a community newsletter sent to all households in the Nashville area
- a statement included in the forms you sign when you check in
- a phone number to call for questions, with a live person answering it
- posters around patient care and waiting areas[157]

More than 80 percent of study participants had positive views of a document explained in person and then signed by the individual, a form directly handed to the individual, or a letter sent to patients; conversely, the participants felt strongly against learning about the projects through mass media.[158] These findings support my view that updates regarding biorepository research are more powerful when they are delivered directly to the participants. Additionally, the methods that were found to be most popular in Pulley and her colleagues' study place responsibility on the investigators of the biorepository, giving them a more active role rather than just relying on the participants to be responsible for seeking out updates.

Another suggestion for improving blanket consent and broad consent is to involve more laypeople in the review process so that the IRB can understand what is and is not

156. Pulley et al., 59.

157. Pulley et al., 64.

158. Pulley et al., 59.

acceptable in any given community.[159] This is especially true if the community is worried about research that may discriminate against them. For example, the National Institute of General Medical Sciences (NIGMS), a division of the NIH, has a policy for biorepository research with "named populations," who are "a group of people who share a common ethnic or geographic origin."[160] Not only must the biorepository establish a relationship with the population and any community subsets but the participating population should be informed of any updates or deviations to the originally described research and be allowed to discontinue their participation if the research goes against the community's wishes.[161] Therefore, blanket consent or broad consent could be given, but as more specific projects are developed, the community leaders would need to be consulted. If the biorepository and the community leaders have an established relationship as described in the policy, it should not be difficult to contact the community with updates. Then, the community leaders could speak with their own constituents, rather than the biorepository needing to recontact all of the individuals who provided samples. This would prevent a situation similar to the Havasupai tribe from occurring again. Because of the relationship between the researchers and the community, it would be easy to contact the community to provide more information as it became available. Additionally, by forming a relationship, the researchers would learn more about the community and can provide an informed consent that meets their level of understanding.

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159. Greely, 358-9; Master and Resnik, 209; Pulley et al., 56.

160. Coriell Institute for Medical Research, "Policy for the Responsible Collection, Storage, and Research Use of Samples from Named Populations for the NIGMS Human Genetic Cell Repository," under "Introduction" and "Policy," National Institute of General Medical Sciences, https://catalog.coriell.org/0/Sections/Support/NIGMS/CollPolicy.aspx?PgID=220 (accessed April 18, 2015).

161. Coriell Institute for Medical Research, under "Policy," "Elements of Community Consultation," and "Frequently Asked Questions."

In turn, when the community leaders present the information to their constituents, information would be given in a way that was familiar to the community, thereby ensuring their comprehension. Finally, by allowing for the community to withdraw from any research it deems controversial, the consent maintains an element of voluntariness.

Exclusion Clauses

Exclusion clauses could also be useful in providing more transparency in situations involving blanket consent or broad consent, which would aid in offering more information, comprehension, and voluntariness. Zubin Master and David B. Resnik describe exclusion clauses as a way "to capture contentious research that could risk discrimination or stigmatization of individuals or groups and sharing with organizations the public perceives as less trustworthy,"[162] which "helps balance harms to participants and research progress by limiting areas that people might fear the most but still employing models not requiring specific consent."[163] As we have already seen with the Havasupai tribe, certain research topics, such as mental illness or origin, may be sensitive due to cultural attitudes. However, sometimes it is more than just the areas of research that need to be limited. Studies have found that individuals are protective over who can access their data, fearing that the government will turn into "'Big Brother'" and be privy to personal information.[164]

In the simplest scenario, exclusion clauses work best for biorepositories that are geared towards a certain type of disease or condition. Using the example of a cancer biorepository, Master and Resnik believe that by focusing on a certain class of research,

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162. Master and Resnik, 203.

163. Master and Resnik, 208.

164. Beskow and Dean, 1443.

investigators can quell participants' fears by excluding any areas of research that would most likely have no bearing on cancer, such as mental illness.[165] If, in the future, the cancer biorepository expanded to encompass areas that it originally excluded, it would require participants to reconsent.[166] As previously described, this is a serious disadvantage to researchers. However, an informed consent that utilizes exclusion clauses may recruit more initial participants than a blanket consent or broad consent because it provides the participants with choices and restrictions. Therefore, researchers need to weigh the benefits and drawbacks of a blanket consent or broad consent with informed consents that contain exclusion clauses. A general consent would limit the amount of participants and would not require future contact, but an informed consent that contains exclusion clauses may give researchers a larger initial participant population yet would require costly and time consuming recontact if the research was expanded.

Master and Resnik point out that one valuable benefit of exclusion clauses is that they can be adapted to fit many different research scenarios and can be easily inserted into almost any existing consent document.[167] This would allow them to be implemented into biorepositories of different sizes, purposes, locations, and owners. Exclusion clauses also satisfy a participant's need for information.[168] This was best demonstrated in Beskow and Dean's research. When asked to consider donating a biospecimen, a concern among participants was not knowing the type of research that would be done: "'I would want to know more information . . . Narrow it down so that I know my blood

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165. Master and Resnik, 205.

166. Master and Resnik, 206.

167. Master and Resnik, 208.

168. Master and Resnik, 208.

goes to cancer (research).'"[169] The categories of possible research that might be included are important to potential participants. Additionally, another benefit is that "the use of exclusion clauses in informed consent increases transparency and promotes accountability by researchers, biobanks, and research institutions."[170] As previously noted, the Tuskegee Syphilis Study and injustices towards Henrietta Lacks and the Havasupai tribe play a role in how those affected populations feel about research. By defining the type of research that will and will not take place and requiring reconsent to explore areas that were previously excluded, it allows individuals to have some control and rights over how their biospecimens will be used. Finally, Master and Resnik point out that the openness and trust that come with exclusion clauses promote a respectful relationship between the potential participants and investigators.[171] Again, as demonstrated through studies, a close rapport between an individual and a researcher will make it more likely for the individual to donate a biospecimen. This show of good will by the researcher makes the participant feel comfortable with his/her decision, and it will benefit the researcher because he/she will be able to collect more specimens for the biorepository.

Despite the benefits of exclusion clauses in informed consent, they are not without drawbacks. Master and Resnik mention three major difficulties. First, as with anything else, drawing attention to risks will trigger more questions and concerns.[172] If investigators asked individuals for their blanket consent or broad consent for use of their

169. Beskow and Dean, 1443.

170. Master and Resnik, 208.

171. Master and Resnik, 208.

172. Master and Resnik, 208.

biospecimens, there may not be many concerns because not enough information was provided to prompt questions. However, once the exclusion clauses are added to the consent form, participants might be curious why certain categories of research are included or excluded, what exactly the researchers will do with the information, and why they need to know the information. Yes, this will provide more work for researchers, but these participants are making a voluntary choice to contribute to research, and they have a right to be given information that they understand. A second disadvantage is the time and effort that will be used if participants need to be recontacted when the research criteria are expanded.[173] However, as I previously discussed, researchers need to realize that this is a necessary compromise for endorsing transparency in research and gaining the respect of participants. Finally, how will researchers and biorepositories know what options to offer for exclusion clauses?[174] Again, this is where community involvement comes into effect.[175] If a local biorepository becomes involved with community leaders, it would not be difficult to learn what the community values and what they would be concerned about. Therefore, when planning a research project, it would be advantageous to understand the population being studied.

One final consideration that needs to be given to exclusion clauses is their implementation. If the researchers are offering multiple options on their consent forms, they need to determine a reliable method for keeping track of the participants' different choices. Without this type of system in place, exclusion clauses are essentially worthless to participants if their wishes are not being honored.

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173. Master and Resnik, 209.

174. Master and Resnik, 209.

175. Master and Resnik, 209.

Opt-Out

When including residual tissue in biorepositories, an opt-out version of consent may be utilized.[176] Although this type of consent seems to align more closely with the ideals of blanket consent and broad consent, it can be structured in a manner that changes it to a more moderate option. First, it is important to understand why researchers are supportive of an opt-out version of consent. Since consent is obtained in a passive manner (inaction), potential participants who may have neutral feelings toward biospecimen research and are not moved to take the extra steps of withdrawing will be automatically enrolled in the research, thereby increasing the size of the biorepository.[177] Furthermore, the researchers can focus the financial budget on the actual studies they wish to carry out, rather than on recruitment costs.[178] While these reasons are beneficial from an administrative viewpoint, there are concerns that need to be addressed. If the choice to opt-out is not presented or is relegated to the background, many individuals will be unwittingly enrolled in biospecimen research, which may include research that is against their lifestyle or beliefs.[179] This may lead to distrust towards all research,[180] as the general public may feel as if they are being taken advantage of without their permission. To attend to these worries, Noor A. A. Giesbertz and his colleagues suggest

176. Giesbertz, Bredenoord, and van Delden, 1.

177. Giesbertz, Bredenoord, and van Delden, 1.

178. Giesbertz, Bredenoord, and van Delden, 2.

179. Giesbertz, Bredenoord, and van Delden, 3.

180. Giesbertz, Bredenoord, and van Delden, 3.

a "thick" opt-out.[181] Three conditions must be met in order for this method to succeed:

- Awareness is raised among people about inclusion of residual tissue as the default position.
- Adequate information is provided.
- A genuine possibility to object is presented and objections are adequately registered.[182]

These necessary conditions highlight the importance of information and voluntariness. Although an opt-out version of consent is passive, the above requirements allow for potential participants to make an autonomous choice. As Giesbertz and his colleagues note, a thick opt-out has many similarities to an active consent procedure,[183] which will appease those who want to make the choice themselves, rather than having the choice thrust upon them.

Specific Consent

Information

When specific consent is employed, participants know the details of the particular study that they are agreeing to. Additionally, sufficient information is the foundation for the individual's comprehension of the study and willingness to take part. According to Beauchamp, informed consent is obtained "if and only if the person, with substantial understanding and in substantial absence of control by others, intentionally authorizes a health professional to do something."[184] In order for a participant to understand the choice he/she is about to voluntarily make, he/she needs to be provided with enough

181. Giesbertz, Bredenoord, and van Delden, 3.

182. Giesbertz, Bredenoord, and van Delden, 3.

183. Giesbertz, Bredenoord, and van Delden, 3.

184. Beauchamp, 517-8.

information to make that choice. Therefore, it is fundamental to have information about the specific study to which you are donating your biospecimens. During my discussion of blanket consent and broad consent, I noted that participants are agreeing to general research and not known studies; therefore, it reduces the need for recontact, which is convenient for the researchers and promotes scientific progress. However, as Eric M. Meslin and Kimberly A. Quaid note, "the less specific the disclosure…the less informed the subject will be."[185] Now we must decide what holds more weight: participant autonomy or administrative convenience and research progress.[186] I would argue on behalf of individual autonomy because *The Belmont Report* states that "[t]o show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment."[187]

On the contrary, is there a problem with giving too much information to potential participants? What details of the study must be included in order for the consent to be considered "valid informed consent"?[188] Critics claim that specific consent requires "that all information that can be expected to be relevant to at least someone's choice about participation must be given to any potential research participant."[189] Does this comment suggest that every detail of the study needs to be given because it might be pertinent to

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185. Eric M. Meslin and Kimberly A. Quaid, "Ethical Issues in the Collection, Storage, and Research Use of Human Biological Materials," *Journal of Laboratory and Clinical Medicine* 144, no. 5 (November 2004): 231.

186. Master and Resnik, 204.

187. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, under "Part B: Basic Ethical Principles."

188. David Wendler and Christine Grady, "What Should Research Participants Understand to Understand They Are Participants in Research?" *Bioethics* 22, no. 4 (May 2008): 204.

189. Helgesson, 43.

one individual? According to David Wendler and Christine Grady, this approach "seems impractical, if not impossible."[190] It could be assumed that participants may not be interested in learning about certain details of the study, but we should examine some evidence before coming to that conclusion.

In a study conducted by Beskow and her colleagues Joëlle Y. Friedman, N. Chantelle Hardy, Li Lin, and Kevin P. Weinfurt, they sought to determine what information was most crucial for an informed consent for biorepository research by asking participants, investigators, and IRB members for their opinions.[191] Their study included fifty-two adult patients who acted as the prospective biorepository participants, in addition to twelve researchers and twenty IRB members.[192] After reading the consent form twice, all of the study participants were instructed to identify what information was most significant for potential biorepository participants.[193] The consent document contained 207 sentences; the patients found approximately 40 percent of these sentences contained essential information, followed by the researchers (53%) and the IRB members (72.3%).[194] In terms of what type of information was most important, the patients prioritized individual results, privacy, and identifying data.[195] Contrarily, the researchers

190. Wendler and Grady, 204.

191. Laura M. Beskow et al., "Simplifying Informed Consent for Biorepositories: Stakeholder Perspectives," *Genetics in Medicine* 12, no. 9 (September 2010): 567.

192. Beskow et al., "Simplifying Informed Consent," 568.

193. Beskow et al., "Simplifying Informed Consent," 568.

194. Beskow et al., "Simplifying Informed Consent," 568.

195. Beskow et al., "Simplifying Informed Consent," 569.

and IRB members chose sentences focusing on the biorepository and why it was being used for research, personal data, and recontact.[196]

Beskow and her colleagues believe these differences are due to what is at stake among the three groups, such as time (participants); approval of the study and enrollment of subjects (researchers); and protection of human subjects, compliance, and liability (IRB members).[197] While this conclusion is noteworthy, I believe that other factors could also have an effect. The selected patients in this study were not diverse in age (< 55 years = 25%, 55 years and older = 75%), ethnicity (Non-Hispanic = 100%, Hispanic = 0%), and race (White = 82.7%, Non-White = 17.3%).[198] As I previously discussed, both African American and Hispanic participants in other studies feared being mistreated due to previous injustices. Had more African American or Hispanic individuals been recruited to take part in this study, it might have affected the amount and type of information that the patient group found to be essential before giving their informed consent. Information that the white patients found as irrelevant may very well be crucial factors for African Americans or Hispanics, who make up a significant percentage of the population of potential research participants. Therefore, it is difficult to determine if specific informed consent provides too much information, hence negatively affecting the potential participants, when certain demographics find that information necessary to make a decision.

Interestingly, age may also be a factor in how much information a potential participant desires. In the above study, the sample patients skewed heavily towards an

196. Beskow et al., "Simplifying Informed Consent," 569.

197. Beskow et al., "Simplifying Informed Consent," 571.

198. Beskow et al., "Simplifying Informed Consent," 569.

older population. Although Beskow and her colleagues learned that the patients in their study found less than half of the information presented in the informed consent to be necessary, the results might have been different had more patients in the younger demographic been included. Other studies did explore the age variable. When analyzing the participants by age (18-29 years, 30-54 years, and 55 years and older), Luque and his colleagues learned that the youngest group had the most concerns regarding information: "'In order to [donate], I would have to REALLY research that company. I would want to know where…what they are doing, how they are going to do it, everything!' (18-29 years, female)."[199] Rahm and her colleagues found that age was a significant factor in the choice to donate a specimen for unspecified future research, with individuals older than sixty years being most likely to donate.[200] Furthermore, in Beskow and Dean's research, participants believed that consenting to a biorepository included several risks, namely loss of privacy and confidentiality, technological advances, loss of control, and uncertainties about research use.[201] When asked how concerned they were about these risks, one participant replied, "'For me personally, it is not important right now because I am already retired. But for younger person…this might be very critical and very limiting.'"[202] With new technology, data breaches, and the Internet's potential, it is possible that younger generations are more worried about who will have access to their information and how it will affect them. This may become an even bigger problem in the coming years as technology advances and data security becomes more vulnerable. If

199. Luque et al., 96.

200. Rahm et al., 446.

201. Beskow and Dean, 1444.

202. Beskow and Dean, 1444.

young participants are worried about these problems, they may consider specific information about the study to be invaluable when making their decision.

Comprehension

A concern that Beskow and her colleagues had was that lengthy consent forms contain a plethora of information but negatively affect an individual's understanding. As per a case study in *The Hastings Center Report*, consent forms "are growing in length and complexity, becoming ever more intimidating, and perhaps inhibiting rather than enhancing participants' understanding."[203]

In the study conducted by Beskow and Dean that assessed participants' understanding of informed consent and biospecimen research, a more general consent form was used.[204] When they were asked questions to gauge their comprehension, nearly all participants correctly answered that the consent form described research using leftover specimens.[205] Additionally, when asked about the type of research being conducted, more than half of the individuals cited specific conditions such as cancer, heart disease, and obesity.[206] Interestingly, when the interviewees were asked whether they had concerns about donating to the biorepository, a worry was that they did not know what specific studies they would be donating to.[207] Although this study showed that a more general consent form was easily understood, it did not compare the general form with a more specific one, and yet, participants wanted to know more details about the study. To

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203. "Is Longer Always Better?" *The Hastings Center Report* 38, no. 3 (May-June 2008): 10.

204. Beskow and Dean, 1448-50.

205. Beskow and Dean, 1442.

206. Beskow and Dean, 1442.

207. Beskow and Dean, 1442.

mitigate this problem, Wendler and Grady suggest that during the informed consent process, the individual who is obtaining consent should ask whether the potential participant has further questions or concerns.[208] However, the ability to ask meaningful questions depends on the amount of information given to the participant in the first place. Beauchamp calls this "a proper climate of exchange."[209] An open-ended request for a participant's questions and concerns might be stifled if only broad details regarding the study are provided. If more specific details are given, then the questions become more thoughtful and relevant to the topic at hand because the individual has a framework for asking questions, thus improving his/her comprehension.

Voluntariness

In order to make a decision using one's own judgment and free will, it is imperative that he/she has sufficient information and understands the choices. Therefore, voluntariness, the third component of informed consent, builds off the elements of information and comprehension. As I will discuss below, an important facet of voluntariness is transparency, which shows respect for the individual who is making the donation.

Individuals who make a donation of their biospecimens for future research are doing so because they want to help find cures for devastating diseases and conditions, and they personally believe this is the right thing to do. Not everyone feels the need to help this cause, and for those who choose to donate, they may have their preferences about what areas researchers should be focusing on. A person's culture and beliefs are highly influential in making these decisions. Tomlinson believes that "biobank donors

208. Wendler and Grady, 205.

209. Beauchamp, 519.

most certainly have an 'interest' in what is later done with their donation . . . . [I]t's a nonwelfare interest in preserving the moral significance of their donation."[210] For a religious person who believes in the sanctity of life, he/she may feel uneasy about donating to a biorepository that uses specimens to learn more about pre-implantation genetic diagnosis (PGD), a method that screens embryos and selects against harmful traits and conditions.[211] This detailed information would be considered highly relevant to an individual who is trying to determine how the research goals align with his/her own interests and opinions.[212] For example, PGD research might remind Jewish people of Nazi eugenics experiments.[213] Therefore, the goals of the researcher and the potential participant do not correspond. Additionally, some individuals may be concerned about their specimens being used in studies that would earn a large profit by the researchers, and they do not wish to support this aim.[214] Both of the above situations play an important role in the individual's voluntary decision to donate specimens. By knowing more specific details about the studies, a decision to participate becomes a deliberate one.

Is it the responsibility of the researcher or the biorepository to protect against this type of injustice? According to Tomlinson, there is "an obligation to protect donors against becoming complicit in research they would find objectionable."[215] This supports the need for specific consent in biorepository research, which allows an individual the

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210. Tomlinson, 42.

211. D. Gareth Jones, "Is PGD a Form of Eugenics?" in *A Tangled Web: Medicine and Theology in Dialogue*, ed. R. John Elford and D. Gareth Jones (Switzerland: Peter Lang AG, 2009), 143.

212. Hull et al., 66; Wendler and Grady, 205.

213. Jones, 143.

214. Wendler and Grady, 206.

215. Tomlinson, 44.

right to choose what he/she is donating to. In fact, philosophy points to "rights theory as the most important type of theory for expressing the moral point of view."[216] Among many other basic rights, Beauchamp and Childress focus on "the right to not be caused pain or suffering by others," and the corresponding obligation that Tomlinson referred to could be "do not cause pain or suffering to others."[217] In terms of biorepository research, the pain and suffering is not physical but mental or emotional. We can prevent the infliction of this pain by providing the necessary information and choices that allow for a voluntary decision. If specific consent is not utilized, individuals may later find out that their specimens were donated to research they believe is morally wrong. Whatever the research may be, the individual would never voluntarily support this cause. Therefore, specific consent ultimately protects free will and the unnecessary mental or emotional pain of individuals who were denied the chance to make a voluntary decision.

Furthermore, it should be noted that not only do donors want to know about potential research that goes against their interests, but they are also curious about contributing to a study that they feel is important and meaningful.[218] Both research that supports and goes against an individual's beliefs and morals should be considered for a choice to be truly voluntary.

How Can Specific Consent Address the Concerns of Critics?

Tiered Consent

One method that can be utilized in making specific consent more encompassing is tiered consent. Tiered consent allows potential participants to check off areas of research

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216. Beauchamp and Childress, 367.

217. Beauchamp and Childress, 371.

218. Hull et al., 66.

(e.g., cancer, mental illness) or different components of research (e.g., recontact, commercial research) that they will permit.[219] Therefore, it shows respect for the individual by allowing him/her to choose what he/she feels most comfortable with,[220] but the biorepository can conduct research on any area that the participant checks off. Since multiple items can be checked off within a single consent document, the participant is essentially consenting to multiple studies within specific disease areas.

Juli Murphy and her colleagues proposed a study to examine whether potential participants would prefer blanket consent and broad consent, specific consent, or tiered consent (referred to as menu consent or categorical consent in this particular study).[221] They began with sixteen focus groups, and based on the information gathered from these groups, a survey was sent out and completed by nearly forty-seven hundred members of the general public.[222] While meeting with the different focus groups, the researchers learned that the participants had a positive view of an informed consent document that provided a menu of different options.[223] The focus group participants felt that this type of consent would be beneficial to both the donors, who could voluntarily choose the studies that they believed to be significant, and the researchers, who would have access to the specimens for any research areas that the participants checked off.[224] Yet, the focus groups also noted that when given a choice, individuals might prefer to stay away from

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219. Master and Resnik, 206.

220. Donna T. Chen et al., "Research With Stored Biological Samples: What Do Research Participants Want?" *Archives of Internal Medicine* 165, no. 6 (March 28, 2005): 652.

221. Juli Murphy et al., "Public Perspectives on Informed Consent for Biobanking," *American Journal of Public Health* 99, no. 12 (December 2009): 2129.

222. Murphy et al., 2128-9.

223. Murphy et al., 2131.

224. Murphy et al., 2131.

areas of research that could be stigmatizing, and researchers would be left with an insufficient amount of data, which would prevent meaningful research within these controversial fields.[225] Additionally, tiered consent would be inconvenient to the researchers and the biorepositories since it might be difficult to accurately keep track of the numerous samples and what studies they could be included in.

However, the views of the focus group participants did not translate to the survey respondents. When asked what type of consent was most favorable, survey analysis found that 90 percent of the individuals indicated a preference for either blanket consent (48%) or specific consent (42%), with only 10 percent selecting menu consent.[226] These results are somewhat surprising as menu consent would allow for both autonomy and research progress, thereby benefitting both the biorepository participants and investigators. It is possible that the survey respondents felt strongly about either autonomy or scientific progress, and perhaps only a small amount of individuals viewed them both to be equally important. Or, it is possible that the choices offered to participants in the menu consent did not align with their goals or beliefs.[227] Although menu consent seemed to be the most popular choice among focus group participants, these results did not translate when the more general population was questioned.

Additionally, Donna T. Chen and her colleagues conducted a study at the NIH that examined the different consent options given to previous research participants.[228] After reviewing almost thirteen hundred consent forms that were used in over sixty

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225. Murphy et al., 2131.

226. Murphy et al., 2131.

227. Chen et al., 652.

228. Chen et al., 653.

studies, they determined that the consent options fell into four main categories: do not consent to future research, consent to future research for the same disease under which the specimen was collected, consent to all future research, and recontact the participant before any future research.[229] The results showed that many of the consent forms indicated that a more general consent was preferred.[230] There are several factors that may influence these results. First, the majority of the participants were white (81.9%).[231] It has been noted throughout this paper that their views of research are quite different than the opinions of African Americans or Hispanics. Therefore, Chen and her colleagues recognize that the results of their study may not be generalizable to a larger population.[232] Secondly, nearly 75 percent of the consent forms included participants who donated a specimen because either they or a family member were affected by the condition in question.[233] Again, I have already discussed how a personal or family history of a disease may be influential in someone's choice to make a biospecimen donation. Finally, Chen and her colleagues noted that since the NIH is a known research facility, it could affect how participants viewed the need to participate in research.[234] Individuals who come to the NIH are more likely to be aware that they will be approached for a study, whereas this may be uncommon in a local hospital. All of these factors may have played a role in the participants strongly favoring broad consent. However, Chen and her

229. Chen et al., 653.

230. Chen et al., 654.

231. Chen et al., 653.

232. Chen et al., 655.

233. Chen et al., 653.

234. Chen et al., 655.

colleagues also believe that broad consent is a more straightforward decision, and therefore, it is preferred over a confusing tiered or menu consent with multiple options that may just be too unclear for the potential participants.[235] While a tiered consent seemed to provide a balance between those who support specific consent and those who support blanket consent or broad consent, it has been shown that having too many options may not be preferential for potential participants.

235. Chen et al., 655.

Chapter Five

Recommendations and Conclusion

Making a Decision: Which Type of Informed Consent Aligns Most Closely with *The Belmont Report*?

Throughout this paper, I have reviewed blanket consent, broad consent, and specific consent and how each type of consent upholds the need for information, comprehension, and voluntariness. Although general consent and specific consent have benefits and drawbacks, which consent best exemplifies the necessary elements of informed consent as per *The Belmont Report*? There is a tension between the choice of respect for persons (autonomy) and the need to consent to unspecified future research (scientific progress). An individual's perspective coupled with the context and focus of the research will influence the final decision. The many studies I have reviewed have come to different conclusions, making it difficult to reach a decision. However, there are two factors that are significant in this assessment: *The Belmont Report* and historical events.

Although *The Belmont Report* was written over thirty years ago, the ideas discussed within this document are still relevant and applicable today. Individuals who choose to participate in any type of research need to know what they are agreeing to, understand how it will affect them, and do so out of their own free will. This holds true regardless of how much time has passed since the publication of *The Belmont Report*. Additionally, the foundation of *The Belmont Report* is the protection of research participants. One way to protect them is to give them the choice to involve themselves in

research that they feel aligns with their goals. This cannot be done when the individual does not know what he/she is agreeing to do.

Furthermore, *The Belmont Report* came into existence because of incidents like the Tuskegee Syphilis Study. There is a long history of apologizing after situations of research abuse, such as the Guatemala syphilis experiments[236] and the injustices towards the Havasupai tribe.[237] Adhering to the principles and standards of *The Belmont Report* may help to prevent such reparations. Years from now, researchers do not want to look back and make apologies for taking advantage of individuals who did not have sufficient information to understand the research that they agreed to take part of. These past abuses cause people to become uneasy with contributing to research, and this has been seen among many minority groups. Furthermore, the story of Henrietta Lacks and other more recent cases regarding ownership of biospecimens leads Skloot to believe that "the question isn't whether people have the ability to control their tissues; it is how much science should be obligated (ethically and legally) to put them in the position to do so."[238] By presenting potential participants with a specific consent form, rather than a more general form, it allows them to take control of the situation by choosing what type of research they want their tissues to be used for. Most likely, they will choose research that is meaningful to them and that aligns with their personal beliefs and goals.

What makes this difficult is that scientific progress hinges on individuals donating specimens to unspecified future research. Scientific progress is important and

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236. Mark Parascandola, "Medical Experiments in Guatemala," *Research Practitioner* 11, no. 6 (November-December 2010): 221.

237. Harmon, "Indian Tribe Wins Fight."

238. Skloot, "Taking the Least of You."

worthwhile, but should we take advantage of people who are willing to contribute but do not fully understand the consequences? Again, *The Belmont Report* is about protecting the human subject, not ensuring the advancement of science. While many researchers may believe that it is unnecessary for individuals to fully understand what they are agreeing to when they donate their biospecimens, this thesis is about informed consent and the elements that comprise it, as described in *The Belmont Report*. Therefore, since I am using *The Belmont Report* as the guiding document, I must favor the individual's autonomy and right to make a decision, which ultimately is specific consent. Specific consent allows an individual to make a choice each time he/she is approached for research, which enables the potential participant to amend his/her beliefs about what types of studies are agreeable or objectionable.[239] A study that focuses on mental illness may be upsetting to a person when he/she is first approached for research, but years later, this same person may find mental illness to be an important topic to study. Of course, this change of heart can also work in the opposite direction, but specific consent allows an individual to choose what is best for himself/herself in each instance. Additionally, many participants and researchers feel that specific consent is a sign of consideration of an individual's moral beliefs.[240]

Specific consent takes into account that individuals want detailed information. Yet not every potential participant favors comprehensive and inclusive information, so how should we protect these subjects from knowing too much? There are ways to make specific consent more agreeable to those who oppose it. This can be accomplished through supplemental materials, as demonstrated in a 2010 study conducted by Beskow

239. Murphy et al., 2131.

240. Tomlinson, 45; Murphy et al., 2131.

and her colleagues from Duke University. They presented participants with a digital two-page consent form, and throughout the form, there were opportunities to learn more information than what was presented.[241] If the individual opted to learn more, they would be taken to a list of Frequently Asked Questions (FAQs), which provided the information that could be seen in a lengthy consent form but was redacted from the two-page form.[242] Additionally, the participants were asked whether any of the information found in the FAQs should be reincorporated into the consent form.[243] Even after referencing the FAQs, approximately 60 percent of the individuals surveyed thought the shortened form was sufficient.[244] The remaining participants determined that there was more information that needed to be included in the shorter form, but the number of sentences (range = 0-71 sentences) and information chosen was not agreed on.[245] If a study specific short consent form was used, detailed information about the study would be presented to all participants, and individuals who sought more information could consult the supplemental material. On the other hand, the additional resources would not overwhelm those who were satisfied with the condensed version of the specific consent form. This compromise would satisfy the need of those individuals who prefer to have specific and detailed information, yet at the same time, it would respect the preference of others who feel that too much information would adversely affect their understanding.

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241. Laura M. Beskow et al., "Developing a Simplified Consent Form for Biobanking," *PLoS One* 5, no. 10 (October 2010): 4, http://www.plosone.org/article/fetchObject.action?uri=info:doi/10.1371/journal.pone.0013302&representation=PDF (accessed April 19, 2015).

242. Beskow et al., "Developing a Simplified Consent," 4.

243. Beskow et al., "Developing a Simplified Consent," 4.

244. Beskow et al., "Developing a Simplified Consent," 4.

245. Beskow et al., "Developing a Simplified Consent," 4.

Conclusion

As highlighted in my introductory remarks, the purpose of this thesis was to examine informed consent and its relationship to unspecified future research using *The Belmont Report* as a guiding document. When the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research came together in 1976 to discuss informed consent, they sought to create a new guiding document for investigators. While the Nuremberg Code and the Declaration of Helsinki were highly influential in protecting the rights of human research subjects, both the Tuskegee Syphilis Study and the injustices towards Henrietta Lacks showed that more regulation and guidance was necessary. *The Belmont Report* highlighted the three necessary elements of informed consent: information, comprehension, and voluntariness. Together, these components would help ensure that a participant's autonomy was not ignored.

As science and technology have advanced in recent years, progress is made through biospecimen research. In order to learn more about diseases and conditions, investigators need human subjects to donate their specimens for the sake of science. There is a tension regarding what type of consent should be used to inform these participants of the research of which they will be a part. A more general blanket consent or broad consent allows for investigators to have unrestricted access to specimens in order to pursue different areas of research, some of which are controversial or stigmatizing. In this scenario, when the specimen is donated, participants do not know for what study their blood or tissues will be used, and they are not offered detailed information before making their decision. On the other hand, a specific informed consent

takes into account the individual's choice, as well as his/her beliefs and opinions, but it slows down scientific progress.

While an argument could be made for both points of view, I believe that specific consent protects those who choose to donate their specimens to research. These individuals can have confidence with specific consent, knowing that their rights and beliefs are respected. This method of consent closely aligns with *The Belmont Report*. When adequate information is provided, the participant has the opportunity to ask specific and relevant questions to enhance his/her understanding of the study before voluntarily giving consent. This is what makes *The Belmont Report* an essential document to human subjects research. As science and research continue to progress, *The Belmont Report* can be adapted to fit any research scenario, whether it includes physical harms, such as those endured in the Tuskegee Syphilis Study, or mental harms, like those experienced by the Havasupai tribe.

Biospecimen and biorepository research will continue to grow and expand, so investigators and IRBs need to examine informed consent closely to ensure that research participants are afforded the protections they deserve. While not every participant desires such thorough information, essential study details should be provided to participants. Those who want to be informed will be aware of what is being asked of them and their rights as research participants. The future of biospecimen and biorepository research is directly impacted by the integrity of informed consent. Establishing a consent process that is sensitive to, and protective of, the rights of its participants will positively support the continuation of biospecimen research.

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