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BIOLOGY & GENETICS

Advancing Research on Stored Biological Materials: Reconciling Law, Ethics, and Practice

Leslie E. Wolf*

I. INTRODUCTION

How would you feel if your biological materials (blood, skin cells, or the like) were used to develop sperm in a lab?¹ What if

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1. Researchers already have developed mice sperm cells that have led to health offspring. Ker Than, *Healthy Offspring Born from Lab-Grown Sperm*, LIVESCIENCE, July 11, 2006, available at www.livescience.com/animals/060711_stemcell_sperm.html. A British team of researchers recently announced that they had developed human sperm from embryonic stem cells. Cell Medicine, *Human Sperm Created from Embryonic Stem Cells*, available at <http://www.cellmedicine.com/british-ivd-sperm.asp> (last visited Oct. 23, 2009). The British research report has since been retracted. *Retraction*, 9 STEM CELLS & DEV. 1111 (2009). But we can anticipate that sperm ultimately will be derived from stem cells, which requires *some* human biological materials. Although many human embryonic stem cells are derived from excess human embryos from *in vitro* fertilization efforts, other human biological specimens may be used to create them, either by using the nucleus in somatic cell nuclear transfer (or cloning) or, more recently, by inducing somatic cells (e.g.,) into an embryonic state (induced pluripotent stem cells). Gina Kolata, *Scientists Bypass Need for Embryo to Get Stem Cells*, N.Y.

the research were conducted without your knowledge or consent? Most Americans are likely unaware that their biological materials have been stored and been made available for research.² Stored biological materials come from a variety of sources, such as newborn blood spots taken for screening purposes; blood, tissues, and other materials taken for clinical diagnostic purposes; blood or DNA taken for forensic purposes; and materials collected specifically for research purposes.³ As described more fully below, federal regulations permit existing specimens to be used in research without the consent of the individuals who provided the materials. Such materials are an important resource for biomedical research and have been responsible for many scientific advances.⁴

TIMES, Nov. 21, 2007, at A1; *see also*, National Institutes of Health, Stem Cell Basics, <http://stemcells.nih.gov/info/basics/> (last visited Feb. 15, 2010) (describing the basics of stem cells).

2. In 1998, an estimated 282 million biological specimens were stored in the United States, to which an estimated 20 million have been added each year. U.S. NAT'L BIOETHICS ADVISORY COMM'N, RESEARCH INVOLVING HUMAN BIOLOGICAL MATERIALS: ETHICAL ISSUES AND POLICY GUIDANCE 1 (1999), available at <http://govinfo.library.unt.edu/nbac/hbm.pdf> [hereinafter NBAC]. These specimen estimates refer to individual biological material; multiple specimens may come from a single source (*e.g.* from a single blood draw). *Id.* at 13. The stored specimens came from more than 176.5 million individuals. *Id.* at 14. This number represents 65% of the U.S. population in 1999. U.S. Bureau of the Census, Historical National Population Estimates: July 1, 1900 to July 1, 1999, <http://www.census.gov/population/estimates/nation/popclockest.txt> (last visited Aug. 20, 2009). Most of the stored specimens were obtained without consent for research. Eric M. Meslin & Kimberly A. Quaid, *Ethical Issues in the Collection, Storage, and Research Use of Human Biological Materials*, 144 J. LABORATORY & CLINICAL MED. 229, 230 (2004).

3. NBAC, *supra* note 2, at 1–2.

4. For example, stored human biological materials have been critical in identifying genes and gene changes associated with disease or disease susceptibility. *See, e.g.*, Henry T. Greely, *Iceland's Plan for Genomics Research: Facts and Implications*, 40 JURIMETRICS 153 (2000); Jeff M. Hall et al., *Linkage of Early Onset Breast Cancer to Chromosome 17q21*, 250 SCI. 1684 (1990); Ragnheidur Haraldsdóttir, Letter to the Editor, *Iceland's Central Database of Health Records*, 283 SCI. 487 (1999); Christoph Lengauer et al., *Genetic Instability in Colorectal Cancers*, 386 NATURE 623 (1997) (looking at colorectal cancer cell lines). For examples of using stored biological materials in determining causes of mortality and morbidity, see Arthur L. Herbst et al., *Adenocarcinoma of the Vagina*, 284 NEW ENG. J. MED. 878 (1971); Arthur L. Herbst & Robert E. Scully, *Adenocarcinoma of the Vagina in Adolescence*, 25 CANCER 745 (1970); Arthur L. Herbst et al., *Clear-Cell Adenocarcinoma of the Vagina and Cervix in Girls: Analysis of 170 Registry Cases*, 119 AM. J. OBSTETRICS & GYNECOLOGY 713 (1974); Sylvia Wrobel, *Serendipity*, *Science*

However, some individuals may object to at least some uses of their biological materials.⁵ Most recently, the case of *Washington University v. Catalona* drew attention to legal and ethical issues that can arise in research involving stored biological materials.⁶ *Catalona* arose from a dispute, between Dr. Catalona, an internationally known prostate cancer researcher, and his former academic institution, regarding who should have control of biological materials collected over decades and stored for research use. Washington University sought a declaratory judgment establishing its ownership of the materials, and Dr. Catalona counterclaimed that the participants should have the right to direct the transfer of their materials to him.⁷ Eight research participants who donated their biological materials sought to intervene in the case to support Dr. Catalona's claim to their materials. Ultimately, these men were joined as necessary parties to the case.⁸ As has been true in other cases, the *Catalona* court showed little

and a New Hantavirus, 9 FASEB J. 1247 (1995); CTRS. FOR DISEASE CONTROL & PREVENTION, NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY 2007–2008: OVERVIEW (2007), available at http://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/overviewbrochure_0708.pdf. For examples of deriving cell lines for further research, see U.S. NAT'L BIOETHICS ADVISORY COMM'N, ETHICAL ISSUES IN HUMAN STEM CELL RESEARCH (1999); Rebecca Skloot, *Henrietta's Dance*, JOHNS HOPKINS MAG., April 2000 [hereinafter Skloot, *Henrietta's Dance*]; Rebecca Skloot, *Cells that Save Lives are a Mother's Legacy*, N.Y. TIMES, Nov. 17, 2001, at A15 [hereinafter Skloot, *A Mother's Legacy*]. Stored biological materials have also been used to develop new approaches to therapy such as pharmacogenetics, see Urs A. Meyer, *Pharmacogenetics and Adverse Drug Reactions*, 356 LANCET 1667 (2000); C. Roland Wolf et al., *Science, Medicine, and the Future: Pharmacogenetics*, 320 BRIT. MED. J. 987 (2000).

5. There have been several instances in which people have brought lawsuits to assert their objections to use of their biological materials for research purposes. These include *Moore v. Regents of the Univ. of Cal.*, 793 P.2d 479 (Cal. 1990); *Greenberg v. Miami Children's Hosp. Research Inst., Inc.*, 264 F. Supp. 2d 1064 (S.D. Fla. 2003); *Wash. Univ. v. Catalona (Catalona I)*, 490 F.3d 667 (8th Cir. 2007), *cert denied*, 128 S.Ct. 1122 (2008); and *Havasupai Tribe v. Ariz. Bd. of Regents*, 204 P.3d 1063 (Ariz. Ct. App. 2008), discussed *infra* Section III. Other instances people objecting to unauthorized use of their biological materials have been reported in the literature. For example, family members have objected to use of a well-known and widely used cell-line that was developed from materials originally taken from their mother without her knowledge or consent. Skloot, *Henrietta's Dance*, *supra* note 4; Skloot, *A Mother's Legacy*, *supra* note 4.

6. *Wash. Univ. v. Catalona (Catalona I)*, 437 F. Supp. 2d 985 (E.D. Mo. 2006).

7. *Catalona II*, 490 F.3d at 672.

8. *Id.* at 673.

sympathy for the research participants' claims which could impede medical research that may benefit society.⁹

Consistent with the federal regulations regarding such research, the *Catalona* courts saw little harm in using the research participants' stored biological materials in research, even though, in this instance, the research participants were objecting to the continued use of their biological materials, at least at Washington University.¹⁰ The underlying assumptions of the federal regulations are that there are few risks involved in research on stored materials and that most people would agree to such participation. However, those assumptions, may no longer be valid in an era of whole-genome sequencing and large DNA databases, especially as genomic research is increasingly performed on sensitive issues such as IQ, ancestry, and personality traits.¹¹ Moreover, those assumptions are not reasonable in the face of objections.

In this article, I argue that it is time to reconsider our regulatory approach to research involving stored biological materials to better reflect the risks presented by such research and the concerns that some people have about use of their materials. In Section II, I analyze the court cases that address research with stored biological materials to identify how courts have characterized research participants' interests in their materials. In Section III, I analyze how the federal regulations governing human-subject research protect those interests, and the limitations of those protections. In Section IV, I present and evaluate empirical data from a national survey of Institutional Review Board ("IRB") Chairs that demonstrates that IRB Chairs often are reluctant to use the federal regulations to allow research on stored materials without consent when the proposed use is different from the purpose for which the materials were originally collected. I also present empirical data regarding investigator practices in research on stored materials, as well as empirical data from the literature

9. *Catalona I*, 437 F. Supp. 2d at 1002 (stating that "[i]f left unregulated and to the whims of a [research participant], these highly-prized biological materials would become nothing more than chattel going to the highest bidder.").

10. *Id.*; *Catalona II*, 490 F.3d at 676.

11. Deborah A Bolnick et al., *The Science and Business of Genetic Ancestry Testing*, 318 SCI. 399, 399 (2007); Kenneth Offitt, *Genomic Profiles for Disease Risk: Predictive or Premature?*, 299 JAMA 1353, 1353 (2008).

concerning participant preferences regarding consent and control over their donated biological materials. Taken together, these data recommend recognizing donor control over the research use of materials, even though this right of control is not fully recognized in the court opinions and in the federal regulations. Finally, in Section V, I make recommendations for changing the federal regulations and guidance to take into account the changing scientific landscape, risks to participants, and preferences evidenced by the empirical data. This can be done without unnecessarily impeding research involving stored biological materials.

II. HOW COURTS HAVE RESPONDED TO PEOPLE WHO HAVE OBJECTED TO THE USE OF THEIR BIOLOGICAL MATERIAL IN RESEARCH

A. *MOORE V. REGENTS OF THE UNIVERSITY OF CALIFORNIA*

Our discussion begins with the case of *Moore v. Regents of the University of California*,¹² the first, and for a long time, the only case on research use of biological materials. *Moore* is unique in that Mr. Moore was a patient and the biological materials at issue were collected in the clinical setting but applied to research and later commercial use. This clinical context may have colored the court's view of Mr. Moore's claims.

1. The Facts

John Moore went to the University of California Los Angeles (UCLA) Medical Center in October 1976 for treatment for hairy-cell leukemia.¹³ His doctor, David Golde, drew blood, bone marrow, and other bodily substances from Mr. Moore to confirm his diagnosis, and ultimately recommended that Mr. Moore have his spleen removed to slow down the progression of

12. *Moore v. Regents of the Univ. of Cal.*, 793 P.2d 479 (Cal. 1990).

13. *Id.* at 481. Hairy cell leukemia is a blood and bone marrow cancer in which the bone marrow makes abnormal lymphocytes (a white blood cell), which look hairy when viewed under a microscope. As these abnormal lymphocytes proliferate, they build up in the blood and bone marrow and crowd out other blood cells, such as healthy white blood cells, red blood cells, and platelets. If the cells collect in the spleen, it may swell. National Cancer Institute, General Information About Hairy Cell Leukemia, <http://www.cancer.gov/cancerinfo/pdq/treatment/hairy-cell-leukemia/patient/> (last visited Nov. 4, 2009).

disease. Mr. Moore consented in writing.¹⁴

Over the next 7 years (from November 1976 to September 1983), Mr. Moore returned to UCLA from his home in Seattle several times. He understood from Dr. Golde that such visits were required for his care.¹⁵ At each visit, Dr. Golde took samples of Mr. Moore's blood, blood serum, skin, bone marrow, and sperm.¹⁶ Dr. Golde told Mr. Moore, when asked, that the specimen collections could only be performed at UCLA under Dr. Golde's supervision.¹⁷

In 1979, Dr. Golde established a cell line from Moore's T-lymphocytes. As explained by the court,

A T-lymphocyte is a type of white blood cell. T-lymphocytes produce lymphokines, or proteins that regulate the immune system. Some lymphokines have potential therapeutic value. If the genetic material responsible for producing a particular lymphokine can be identified, it can sometimes be used to manufacture large quantities of the lymphokine through the techniques of recombinant DNA.¹⁸

Mr. Moore's T-lymphocytes were valuable because they overproduced certain lymphokines, making it easier to identify the gene responsible for the lymphokine.¹⁹ The University Regents filed for a patent on the cell line, called "Mo," and the method for producing lymphokines from the cell line in January 1981; the patent was issued in March 1984.²⁰ Dr. Golde was listed as an inventor on the patent and, pursuant to UCLA policy, was eligible to share in any royalties or profits from the patent.²¹ UCLA and Dr. Golde negotiated development agreements with respect to the cell line that provided Dr. Golde with salary support and stock.²² Reportedly, Dr. Golde received 75,000 shares of stock in Genetics Institute Inc., and both Dr. Golde and UCLA received \$440,000 in research grants from Genetics Institute Inc. and Sandoz Pharmaceutical Corp. to develop products using the patent.²³

14. *Moore*, 793 P.2d at 481.

15. *Id.*

16. *Id.*

17. *Id.*; see also Dennis McLellan, *John Moore, 56; Sued to Share Profits from His Cells*, L.A. TIMES, Oct. 13, 2001, at B16.

18. *Moore*, 793 P.2d at 481 n.2.

19. *Id.* at 481-82.

20. *Id.*; see also McLellan, *supra* note 17.

21. *Moore*, 793 P.2d at 482.

22. *Id.*

23. Philip Hager, *Justices Deny Patients' Rights to Tissue Profits*, L.A.

At some point during the seven years, Moore became suspicious about Dr. Golde's actions. When he asked specifically about the potential financial value of his cells, Dr. Golde denied such value.²⁴ In 1983, Mr. Moore signed a consent form to participate in a research study, but refused to sign over any rights he had in any cell line or any potential product that might be developed from any tissue samples obtained from him.²⁵ In his lawsuit, Moore alleged that the reason Golde required him to come to UCLA was because Golde wanted to obtain more of Moore's cells to use in research from which Golde might benefit financially.²⁶

2. The Legal Proceedings

John Moore sued Dr. Golde, among others, upon learning of the use of his bodily materials to create a cell line.²⁷ In support of his claims, Mr. Moore alleged that Dr. Golde knew that some of his blood products and components had both commercial and scientific value before his surgery and that Dr. Golde decided to use his spleen for research before the surgery, but did not inform him of this intention.²⁸ The defendants successfully demurred to all of Mr. Moore's causes of action at the trial court.²⁹ The Court of Appeal reversed the trial court's decision.³⁰ The California Supreme Court granted review of the Court of Appeal decision.³¹ Following its decision, only the cause of action for breach of the physician's disclosure obligations survived.³²

The California Supreme Court described the surviving

TIMES, July 10, 1990, at A1.

24. *Moore*, 793 P.2d at 485–86.

25. ROBERT F. WEIR & ROBERT S. OLICK, THE STORED TISSUE ISSUE: BIOMEDICAL RESEARCH, ETHICS, AND LAW IN THE ERA OF GENOMIC MEDICINE 5–6 (2004).

26. *Moore*, 793 P.2d at 481.

27. His claims included causes of action for: (1) "Conversion," (2) "lack of informed consent," (3) "breach of fiduciary duty," (4) "fraud and deceit," (5) "unjust enrichment," (6) "quasi-contract," (7) "bad faith breach of the implied covenant of good faith and fair dealing," (8) "intentional infliction of emotional distress," (9) "negligent misrepresentation," (10) "intentional interference with prospective advantageous economic relationships," (11) "slander of title," (12) "accounting," and (13) "declaratory relief." *Id.* at 482 n.4.

28. *Id.* at 481.

29. *Id.* at 482.

30. *Id.* at 483.

31. *Moore*, 793 P.2d at *passim*.

32. *Id.* at 480.

cause of action as being “properly . . . characterized either as the breach of a fiduciary duty to disclose facts material to the patient’s consent or, alternatively, as the performance of medical procedures without first having obtained the patient’s informed consent”.³³ Basic principles of informed consent led the court to conclude that:

(1) a physician must disclose personal interests unrelated to the patient’s health, whether research or economic, that may affect the physician’s professional judgment; and (2) a physician’s failure to disclose such interests may give rise to a cause of action for performing medical procedures without informed consent or breach of fiduciary duty.³⁴

The court took pains to mention that it is not unlawful for a physician to conduct research in his practice area; indeed, such research may benefit patients like Mr. Moore. Nevertheless, a patient is entitled to know about the conflicting loyalties that may exist when a physician is also a researcher.³⁵

It is important to note where the court’s concern lies. It is not in the use of Mr. Moore’s biological materials without his consent. Rather, it is the failure of Dr. Golde to inform Mr. Moore of Golde’s research interest in these materials that was different from, and could affect, Moore’s medical interests. Indeed, the court notes:

If a physician has no plans to conduct research on a patient’s cells at the time he recommends the medical procedure by which they are taken, then the patient’s medical interests have not been impaired. . . . On the other hand, a physician who does have a preexisting research interest might, consciously or unconsciously, take that into consideration in recommending the procedure. In that instance . . . the physician’s extraneous motivation may affect his judgment and is, thus, material to the patient’s consent.³⁶

The court specifically rejected Mr. Moore’s claim of conversion of his biological materials, “a tort that protects against interference with possessory and ownership interests in personal property.”³⁷ According to the court, Mr. Moore was arguing that “he continued to own his cells following their removal from his body, at least for the purpose of directing their use, and that he never consented to their use in

33. *Id.* at 483.

34. *Id.*

35. *Id.* at 483–84.

36. *Id.* at 484.

37. *Id.* at 487.

potentially lucrative medical research.”³⁸ The court declined to accept this argument, concluding that it would place too much of a burden on science.

In effect, what Moore is asking us to do is to impose a tort duty on scientists to investigate the consensual pedigree of each human cell sample used in research. To impose such a duty, which would affect medical research of importance to all of society, implicates policy concerns far removed from the traditional, two-party ownership disputes in which the law of conversion arose. Invoking a tort theory originally used to determine whether the loser or the finder of a horse had the better title, Moore claims ownership of the results of socially important medical research, including the genetic code for chemicals that regulate the functions of every human being’s immune system.³⁹

The court reasoned that:

[T]here are several reasons to doubt that he did retain any such [ownership] interest. First, no reported judicial decision supports Moore’s claim, either directly or by close analogy. Second, California statutory law drastically limits any continuing interest of a patient in excised cells. Third, the subject matters of the Regents’ patent—the patented cell line and the products derived from it—cannot be Moore’s property.⁴⁰

Moore turned to cases regarding unauthorized use of likeness to try to support his conversion claim. The court rejected this analogy to privacy laws by pointing, not to the uniqueness of Mr. Moore’s cells (or their uniqueness to him), but rather to the purpose for which they were used. The goal was to create lymphokines, which are not unique to individuals.⁴¹ Following the California Supreme Court’s decision, Mr. Moore and UCLA reached what Mr. Moore referred to as a “token” settlement.⁴² He was quoted as saying: “Without my knowledge or consent, the doctors and the research institutions used a part of me for their own gain. They stole something from me.”⁴³ He also reportedly stated:

To learn that their position was that they owned a part of me. . . . I think demeaned is a good word. . . . There was a sense of betrayal. . . . I means why didn’t he just tell me?. . . To me, it was a total invasion of a person’s right to control the use of their own genetic code, their own flesh and blood. . . . I certainly have no objection to scientific research . . . but it was like rape. In a sense you have been violated...

38. *Id.*

39. *Id.* at 487–88 (footnotes omitted).

40. *Id.* at 489 (although the court does recognize in n.20 that Moore does not seek actual possession of his cells).

41. *Id.* at 490.

42. McLennan, *supra* note 17.

43. *Id.*

for dollars.⁴⁴

3. Implications

Although only binding in California, *Moore's* influence has been felt well beyond California's borders and, for a decade, was the sole case addressing an individual's interests in the use of the biological materials derived from his body for research. The case is useful to those engaging in biobanking, because it indicates that individuals do not retain interests in their biological materials when they are outside the body.⁴⁵ But it is important to remember the context in which the case arose. Mr. Moore was a patient first and his biological materials were collected during his medical treatment and used in research. That clinical context may help to explain the court's decision.

First, the biological materials that Dr. Golde used and later patented were generally thought to be clinical waste.⁴⁶ Had Dr. Golde discarded the spleen, Mr. Moore would have had no complaint; few people want or expect to receive the materials that are removed during surgery. Indeed, hospitals are expected to get rid of medical waste properly. Second, no one questioned the quality or appropriateness of the surgical care that Dr. Golde provided Mr. Moore. On the other hand, the doctors' concealment of their financial interests in Mr. Moore's cells, while asking Mr. Moore to make multiple trips from his Seattle home to Los Angeles, seemed to be a violation of the doctor's duty to act in the best interests of his patient. Thus, the court talked about *physicians'* obligations to disclose financial interests to *patients*; the court did not explicitly discuss *researchers'* obligations to disclose financial interests when collecting biological materials from research participants (although California research institutions have interpreted it as doing so).⁴⁷ Nor does the court consider what rights research

44. WEIR & OLICK, *supra* note 25, at 9.

45. "Biobanks," also referred to as "biorepositories," are places that collect and store samples of biological material, such as urine, blood, tissue, cells, DNA, and RNA for research. They may also include medical information about individuals whose biological material are stored. See National Cancer Institute, U.S. National Institutes of Health: Dictionary of Cancer Terms, www.cancer.gov/dictionary/?CdrID=561323 (last visited Feb. 11, 2010); see also Eve-Marie Engels, *Biobanks as Basis for Personalised Nutrition? Mapping the Ethical Issues*, 2 GENES & NUTRITION 59, 59 (2007).

46. See *Moore*, 793 P.2d at 491–92.

47. See, e.g., sample consent form language from the University of

participants might have under the federal regulations.⁴⁸

B. *GREENBERG V. MIAMI CHILDREN'S HOSPITAL RESEARCH INSTITUTE, INC.*⁴⁹

1. The Facts

The *Greenberg* case arose out of parents' efforts to find a genetic test for Canavan disease, a fatal, inherited, degenerative brain disease that was affecting their children.⁵⁰ Children born with Canavan disease suffer from imperfect development of the myelin sheath, the fatty covering around nerve fibers in the brain.⁵¹ Over time, build up of chemicals causes the brain to become spongy. Symptoms appear early in infancy (3–6 months) and progress rapidly. They include mental retardation, loss of previously acquired motor skills, feeding difficulties, floppiness or stiffness in muscles, and an increasing head circumference.⁵² Children with Canavan disease do not crawl, walk, sit, or talk. Over time, they may have seizures, paralysis, blindness, or hearing loss.⁵³ Children with this disease typically die before they are 4 years old.⁵⁴

Canavan disease is a recessive genetic condition. That is, a person who carries one copy of the gene is not affected. However, if both parents carry a copy of the gene, there is a 1 in 4 chance (25%) with each pregnancy that the disease will affect their child.⁵⁵ Although it can occur in any ethnic group, Canavan disease is more frequent among people of Ashkenazi

California, San Francisco, UCSF Guidance on Research Topics and Issues, <http://www.research.ucsf.edu/chr/Guide/chrHumanBioSpec.asp> (last visited Nov. 4, 2009). University of California guidance incorporates this language in response to the lawsuit. OFFICE OF THE PRESIDENT, UNIV. OF CAL., SYSTEMWIDE IRB DIRECTORS MEETING SUMMARY 1 (2008).

48. 45 C.F.R. § 46.101–.124 (2009).

49. *Greenberg v. Miami Children's Hosp. Research Inst., Inc.*, 264 F. Supp. 2d 1064 (S.D. Fla. 2003).

50. See Canavan Foundation, What Is Canavan Disease?, <http://www.canavanfoundation.org/canavan.php> (last visited Nov. 4, 2009); National Institute of Neurological Disorders and Stroke, National Institute of Health, NINDS Canavan Disease Information Page, <http://www.ninds.nih.gov/disorders/canavan/canavan.htm> (last visited Nov. 4, 2009) [hereinafter NINDS Canavan].

51. Canavan Foundation, *supra* note 50.

52. *Id.*

53. *Id.*

54. NINDS Canavan, *supra* note 50.

55. *Id.*

Jewish descent from eastern Poland, Lithuania, and western Russia, as well as among people of Saudi Arabian descent.⁵⁶

In 1987, there was no test for Canavan disease. Thus, potential parents could not ascertain whether they were at risk for having a baby with Canavan disease. Parents of children with Canavan disease could not test their fetus to know if it was affected.⁵⁷ At that point, Daniel and Debbie Greenberg, who had lost two children to Canavan disease, approached Dr. Matalon, a research physician then at the University of Illinois at Chicago, and proposed a research collaboration with the goal of developing a genetic test for Canavan disease.⁵⁸ The Greenbergs and the Chicago Chapter of the National Tay-Sachs⁵⁹ and Allied Disease Association, Inc. (NTSAD) located other Canavan families to participate in the research by providing tissue (blood, urine, and autopsy samples), financial support, and help in finding other Canavan families.⁶⁰ Dr. Matalon continued his relationship with the Greenbergs and the organization, including receipt of tissue and blood samples, medical information, and financial support, when he moved to Miami Children's Hospital Research Institute, Inc. in 1990.⁶¹

56. *Id.*

57. *Greenberg v. Miami Children's Hosp. Research Inst., Inc.*, 264 F. Supp. 2d 1064, 1066 (S.D. Fla. 2003).

58. *Id.* at 1067; *see also*, Chicago-Kent College of Law, Honors Scholar Class Project: *Greenberg v. Miami Children's Hospital et al.*, <http://www.kentlaw.edu/honorsscholars/projects/greenberg.html> (last visited Nov. 4, 2009) (discussing the facts of the case and the legal assistance provided by the Law School in regards to the lawsuit).

59. Tay-Sachs is a fatal genetic disorder affecting lipid (fat) storage. Children affected by Tay-Sachs develop build-up of a fatty substance (*ganglioside GM2*) in their tissues and nerve cells in their brain. Infants with Tay-Sachs appear to develop normally for their first few months, but as the fatty material builds up, their mental and physical abilities begin to deteriorate. Eventually, the child becomes blind, deaf, unable to swallow, and paralyzed. The child may also experience dementia, seizures, and an increased startle reflex. Most children die before age 4. As with Canavan, Tay-Sachs is a recessive genetic disorder that has particularly high incidence among people of Eastern European and Ashkenai Jewish descent. There is a 1 in 4 chance of having an affected child if both parents are carriers. A genetic test has been available for several decades. National Institute of Neurological Disorders and Stroke, National Institute of Health, NINDS Tay-Sachs Disease Information Page, <http://www.ninds.nih.gov/disorders/taysachs/taysachs.htm> (last visited Nov. 4, 2009)

60. *Greenberg*, 264 F. Supp. 2d at 1067.

61. *Id.*

In 1993, using the biological samples, family pedigree information, contacts, and financial support provided by the Greenbergs and other families affected by Canavan disease, Dr. Matalon successfully isolated the gene responsible for the disease.⁶² The families continued to provide materials to learn more about the disease. In 1994, Matalon applied to patent the genetic sequence that he had identified.⁶³ The patent was granted in 1997.⁶⁴ As a result of the patent, Matalon and Miami Children's Hospital could "restrict any activity related to the Canavan disease gene, including: carrier and prenatal testing, gene therapy and other treatments for Canavan disease, and research involving the gene and its mutations."⁶⁵ In 1998, the Greenbergs and other families who had participated in the collaboration learned of the patent and Miami Children's Hospital's plan to enforce the patent and seek exclusive licensing agreements and royalty fees from centers offering Canavan disease testing, an action that could limit access to testing.⁶⁶

2. The Legal Proceedings

In 2000, the Greenbergs, other parents of affected children, and the non-profit organizations involved in the research collaboration filed a complaint against Matalon and Miami Children's Hospital, among others. Their causes of action included (1) lack of informed consent, (2) breach of fiduciary duty, (3) unjust enrichment, (4) fraudulent concealment, (5) conversion, and (6) misappropriation of trade secrets.⁶⁷ The plaintiffs asserted that they had understood that:

[A]ny carrier and prenatal testing developed in connection with the research for which they were providing essential support would be provided on an affordable and accessible basis, and that Matalon's research would remain in the public domain to provide the discovery of more effective prevention techniques and treatments and, eventually, to effectuate a cure for Canavan disease.⁶⁸

The plaintiffs sought a permanent injunction against the

62. *Id.*

63. *Id.*

64. *Id.*

65. *Id.* As is typical, Dr. Matalon was listed as inventor on the patent, but, because it was developed while he was employed by the Miami Children's Hospital, the hospital held the license.

66. *Id.*

67. *Id.* at 1068.

68. *Id.* at 1067.

defendants from enforcing the patent rights, as well as damages in the form of reimbursement of royalties from the patent, estimated at over \$75,000, as well as reimbursement of the financial contributions the plaintiffs had made to support the research.⁶⁹

3. Implications

The plaintiffs faced a motion to dismiss their complaint for failing to state a claim upon which relief could be granted.⁷⁰ The court granted this motion, except for the claim of unjust enrichment.⁷¹ But it is important to look at how the court approached some of these claims. The plaintiffs alleged in their complaint that defendants had breached their duty to obtain informed consent by failing to disclose information that might influence the families' decision to participate or decline to participate in research. Specifically, plaintiffs claimed that the intent to file a patent application and enforce that patent was material and ought to have been disclosed. That is, had they been informed of the intent to "commercialize" the results of their contributions," they would not have contributed.⁷² On the other hand, the defendants contended that "there was no actual human experimentation as part of an ongoing relationship alleged in the complaint"; thus, there was no obligation to obtain informed consent.⁷³ The court held that, although a duty of informed consent in medical research did attach at some point, the duty did not extend to disclosures of economic interests of researchers who are not also in a therapeutic relationship with the donor.⁷⁴ As in *Moore*, the court expressed concern about the chilling effect on medical research that might result if it imposed such a duty of economic disclosure.⁷⁵ With

69. *Id.* at 1068.

70. *Id.* at 1066.

71. This claim likely survived because, in addition to providing biological materials and medical histories, the plaintiffs provided substantial financial support to the defendants for the research. *Id.* at 1072. This is a substantially different circumstance than, for example, in the *Moore* case, where John Moore supplied his cells but provided neither financial nor intellectual support for derivation of the resulting cell line.

72. *Id.* at 1068.

73. *Id.* at 1069.

74. *Id.* at 1070 (distinguishing *Moore v. Regents of the Univ. of Cal.*, 793 P.2d 479 (Cal. 1990)).

75. *Id.* at 1070.

respect to the claim of conversion, the court, as the *Moore* court did, refused to find any “contemporaneous expectations of return of the body tissue and genetic samples” when they were donated, and thus, found no cause of action.⁷⁶ This theory depended on a property interest, which the court did not find. However, the decision failed to recognize other interests plaintiffs might have in controlling the uses to which their bodily materials were put.

C. *WASHINGTON UNIVERSITY V. CATALONA*⁷⁷

1. The Facts

Dr. Catalona was an internationally renowned urologist, urologic surgeon, and medical researcher, who also developed the prostate-specific antigen (PSA) test used for prostate cancer screening. From 1976-2003, Dr. Catalona was employed at Washington University (WU).⁷⁸ Dr. Catalona conducted research concerning the genetic basis of prostate cancer.⁷⁹ To further this goal, Dr. Catalona played a substantial role in establishing the Genitourinary (GU) Biorepository at Washington University, which stored, maintained, and distributed the biological specimens collected by Dr. Catalona and other WU physicians.⁸⁰

76. *Id.* at 1074.

77. *Wash. Univ. v. Catalona (Catalona II)*, 490 F. 3d. 667 (8th Cir. 2007) *cert. denied*, 128 S.Ct. 1122 (2008).

78. *Id.* at 670; Urological Research Foundation, The Site for Prostate Cancer Information from Dr. William Catalona, <http://www.drcatalona.com/default.asp> (last visited Nov. 4, 2009). Washington University is renowned in its own right. It is a private research university in St. Louis, Missouri, that includes a prestigious medical school. *Catalona II*, 490 F.3d at 670. The medical school was ranked 4th among medical schools in National Institutes of Health research awards in fiscal year 2005. National Institutes of Health, NIH Awards to Medical Schools by Rank Fiscal Year 2005, <http://report.nih.gov/award/rank/medttl05.htm> (last visited Nov. 19, 2009) (2005 is the last year for which NIH provided ranked data). The medical school was ranked 3rd for research by the U.S. News and World Report in 2009. U.S. News & World Report, Research Rankings: Best Medical Schools, <http://grad-schools.usnews.rankingsandreviews.com/best-graduate-schools/top-medical-schools/research-rankings> (last visited Nov. 4, 2009).

79. *Catalona II*, 490 F.3d at 670.

80. *Id.* at 671–72. To give a sense of the size of the GU Repository, when the permanent injunction hearing was held, there were 3,500 prostate tissue samples from WU patients, 100,000 blood or serum samples from over 28,000 men (75% of whom were not WU patients), and DNA samples from 4,400 men (including WU patients and patients’ family members). *Id.*

In 2003, Dr. Catalona accepted a faculty position at Northwestern University.⁸¹ To facilitate his continued research on the genetics of prostate cancer, he sent a letter to his patients and research participants asking that they agree to transfer their stored biological materials to Northwestern.⁸² In all, between 50,000 and 60,000 research participants received his letter, and about 6,000 returned the transfer agreement which stated:

I have donated a tissue and/or blood sample for Dr. William J. Catalona's research studies. Please release all of my samples to Dr. Catalona at Northwestern University upon his request. I have entrusted these samples to Dr. Catalona to be used only at his direction and with his express consent for research projects.⁸³

The materials collected in the GU Biorepository had been obtained from individuals who consented to participate in genetic research. Their consent was documented in written consent forms.⁸⁴ The court of appeals noted several relevant clauses from the consent forms. First, they "often used the term 'donation' to describe the biological sample's transfer from the [research participant] to a WU physician or medical technician."⁸⁵ They also typically included a provision in which the research participant "agree[s] to waive any claim [he] might have to the body tissues that [he] donate[s]" and "waive[s] the right to any new material or process developed through research involving [his] tissues."⁸⁶ Finally, participants had been informed that "[y]our participation is voluntary and you may choose not to participate in this research study or withdraw your consent at any time," with some of the forms (but not all) noting that research participants could ask that their materials be destroyed if they decided to withdraw, but they could not ask that results already obtained be destroyed.⁸⁷ The right to request destruction of materials was also contained in a genetic research information brochure given to research participants to review and sign.⁸⁸

81. *Id.* at 672.

82. *Id.*

83. *Id.*

84. *Id.* at 671.

85. *Id.*

86. *Id.* Because Dr. Catalona conducted prostate cancer research, all research participants were male.

87. *Id.*

88. *Id.*

2. The Legal Proceedings

Washington University filed a declaratory judgment action against Dr. Catalona to establish its ownership of the samples in the GU biorepository. Dr. Catalona counterclaimed, seeking a declaration of the research participants' rights to transfer the materials to him.⁸⁹ After Washington University moved for summary judgment, Dr. Catalona moved for a preliminary injunction, and after numerous delays, the trial court held a hearing on whether to grant a permanent injunction.⁹⁰ Before the hearing, eight of Dr. Catalona's patients who were also research participants sought to intervene in the litigation.⁹¹ The court found the research participants were necessary parties to the litigation and they were joined as defendants.⁹² The district court found in favor of WU, concluding that 1) WU was the owner of the biological materials, 2) neither Dr. Catalona nor the research participants had any ownership interest in the specimens, and 3) the transfer agreements signed by the research participants had no legal effect.⁹³ Dr. Catalona appealed the ruling.⁹⁴ The court of appeals stated the question on appeal: "We are asked to determine the ownership of biological materials contributed by individuals for the purpose of genetic cancer research and currently housed on the campus of Washington University."⁹⁵

The court of appeals ultimately affirmed "the well-reasoned opinion and judgment of the district court."⁹⁶ The court of appeals agreed with the district court that the research participants had made an *inter vivos* gift of their materials.⁹⁷ In support of its conclusion, the court pointed out that the research participants were informed that they would not have control over the materials; for example, the brochure made clear that materials could be shared with non-WU researchers

89. *Id.* at 672.

90. *Id.* at 673.

91. *Id.*

92. *Id.*

93. *Id.*; Wash. Univ. v. Catalona (*Catalona I*), 437 F. Supp. 2d. 985, 1002 (E.D. Mo. 2006).

94. Wash. Univ. v. Catalona (*Catalona II*), 490 F. 3d. 667, 673 (8th Cir. 2007) *cert. denied*, 128 S.Ct. 1122 (2008).

95. *Id.* at 670.

96. *Id.* at 677.

97. *Id.* at 674.

without further permission.⁹⁸ That the research participants retained some rights, specifically the right to request destruction of the materials, did not alter the court of appeals' view that WU had control over the materials.⁹⁹

3. Implications

Neither the district court nor the court of appeals was particularly sympathetic to the participants' interests. Unlike the court of appeals, which noted that the donation was conditioned on the right to withdraw, the district court rejected the claim that research participants who agreed to give researchers their biological materials for research had a right to withdraw their specimens.¹⁰⁰ The court stated that: "There is nothing stated in the governing federal regulations which equates a right to discontinue participation with a right to control the disposition and use of the excised biological materials."¹⁰¹ Supporting this position, the court pointed to testimony that, when a participant discontinued participation, three things could happen: "1) WU may destroy the sample; 2) WU may store the sample indefinitely without any further use; or 3) WU may remove all identifying markers and use the sample in exempt "anonymized" research."¹⁰² Indeed, the court went on to note that "[n]o one questioned WU's ability to simply store the samples indefinitely after a [research participant] discontinue[d] participation in a research project."¹⁰³ Finally, Dr. Ludbrook and Prentice both testified that anonymization [was] a response available to WU when a [research participant] [chose] to discontinue participation in research."¹⁰⁴ As a result,

The Court [found] that the right to discontinue participation in a

98. *Id.*

99. *Id.*

100. *Wash. Univ. v. Catalona (Catalona D)*, 437 F. Supp. 2d 985, 999–1000 (E.D. Mo. 2006).

101. *Id.* at 999.

102. *Id.*

103. *Id.*

104. *Id.* Dr. Ludbrook was the WU IRB Chair, *see*, Washington University in St. Louis School of Medicine, Cardiovascular Division, Philip A. Ludbrook, <http://cardiology.wustl.edu/details.aspx?NavID=571> (last visited Feb. 11, 2010); Dr. Prentice is an expert in human subjects research, *see* Public Responsibility in Medicine and Research, www.primr.org/Aboutus.aspx?id=1250 (regarding Dr. Prentice's receipt of the PRIM&R Distinguished Service Award) (last visited Feb. 11, 2010).

research project [meant] nothing more than the [research participant had] chosen not to provide any more biological materials pursuant to one or more research protocols; i.e., not to make any more *inter vivos* gifts of donated biological materials to WU. Nothing more can or should be read into this right possessed by the [research participant] at all times.¹⁰⁵

As discussed in section V below, the court's conclusion (and the expert testimony on which it was based) fundamentally misread what the right to withdraw from participation in research, mandated by the federal regulations governing human subjects research, means when biological materials are collected and stored for research purposes. Underlying the court's conclusion was the assumption that the only risks such research presents to donors are threats to confidentiality.¹⁰⁶ The cases discussed in this section, and the empirical data discussed in section III below, however, suggest otherwise. The court of appeals did not reject this conclusion (indeed, its endorsement of the lower court's decision suggests it accepted it). Thus, the *Catalona* courts appeared to eliminate one of the few protections available to those who donate their biological materials to research who subsequently change their minds about the materials' continued use.

As in the *Moore* decision, the district court expressed concern about the public policy implications of allowing Dr. Catalona and the research participants to prevail in their claim. The court noted the value of biological materials to medical research: "Medical research can only advance if access to these materials to the scientific community is not thwarted by private agendas." It went on to consider the consequences of honoring research participants' wishes: "If left unregulated and to the whims of a [research participant (RP)], these highly-prized biological materials would become nothing more than chattel going to the highest bidder."¹⁰⁷ The court went on to state:

Allowing an RP to choose who can have the sample, where the sample will be stored, and/or how the sample can be used is tantamount to a blood donor being able to dictate that his/her blood can only be transfused into a person of a certain ethnic background, or a donated

105. *Id.* at 1000.

106. It is also not clear whether the court would acknowledge such rights, given that it finds that Washington University's agreement to apply the Belmont Principles does not form a basis for asserting research participants' rights, because research participants are not parties or third-party beneficiaries to the agreement. *Id.* at 1000.

107. *Id.* at 1002.

kidney being transplanted only into a woman or man.¹⁰⁸

Even if the research participants did not have the right to transfer their materials to Dr. Catalona (at least under the terms of the consent forms that they signed), research participants could still have legitimate reasons for wishing to remove their biological materials and DNA from medical research. Indeed, the court of appeals noted that: “Noticeably absent from the record is any mention the [research participants] ever were informed they could physically withdraw or request the return of their biological samples.”¹⁰⁹

It is ironic that among those who have sought to remove their materials from research have done so not to prevent others from sharing the benefits of research, but rather to broaden access or to avoid exploitation and research viewed to denigrate a person’s racial or ethnic background.¹¹⁰

D. *HAVASUPAI V. ARIZONA STATE UNIVERSITY*¹¹¹

1. The Facts

In 2004, the Havasupai tribe brought suit against Arizona State University (ASU) and some of its researchers for using their biological materials in research without their consent.¹¹² The name of the tribe, Havasuw ‘Baaja (Havasupai), translates to “the people of the blue green waters,” a reference to the

108. *Id.*

109. Wash. Univ. v. Catalona (*Catalona II*), 490 F.3d 667, 676 (8th Cir. 2007) *cert. denied*, 128 S.Ct. 1122 (2008).

110. See, e.g., Greenberg v. Miami Children’s Hosp. Research Inst., Inc., 264 F. Supp. 2d 1064 (2003) (seeking to ensure broader access to genetic testing for Canavan disease); Havasupai Tribe v. Ariz. Bd. of Regents, 204 P.3d 1063 (Ariz. Ct. App. 2008) (seeking return of materials to prevent use of tribal biological materials in research that is contrary to tribal beliefs or interests).

111. *Havasupai Tribe*, 204 P.3d at 1063. Although the appellate court notes that it takes the facts primarily from the Hart Report—the independent investigation that ASU arranged—because of the procedural posture of the case, the appellate court viewed “the facts and the inferences . . . in the light most favorable to the [Havasupai] as the parties against whom summary judgments were entered.” *Id.* at 1067 n.2 (citing Prince v. City of Apache Junction, 912 P.2d 47, 49 (Ariz Ct. App. 1996)).

112. *Id.* at 1070. The Havasupai are not alone in their complaints. Other Natives Peoples have objected to research uses of their biological materials. See Rex Dalton, *Tribe Blasts ‘Exploitation’ of Blood Samples*, 420 NATURE 111, 111 (2002). ETC Group, About ETC Group, <http://etcgroup.org/en/about> (last visited Nov. 4, 2009).

spectacular waterfalls that are located on their lands.¹¹³ The Havasupai are the “traditional guardians of the Grand Canyon.” According to Havasupai history, they have inhabited the canyon from the beginning.¹¹⁴ They believe that the retreat of waters from a global flood carved the Grand Canyon, which they consider the birthplace of the human race.¹¹⁵ The Havasupai are a federally recognized Native American tribe, with about 650 enrolled members.¹¹⁶ Approximately 450 members live on the tribe’s reservation located near the Grand Canyon.¹¹⁷

Because many in the tribe suffered from diabetes, in 1990 the Havasupai requested assistance in understanding the cause of diabetes within the tribe.¹¹⁸ With the approval of the Tribal Council, who encouraged tribe members to participate, the ASU researchers ultimately collected over 200 blood samples from tribal members for diabetes research.¹¹⁹

John Martin, an anthropology professor at ASU, had a long-standing relationship with the Havasupai. He had spent a year with the tribe in 1963 for his doctoral dissertation.¹²⁰ Over decades, Dr. Martin had worked on a number of issues, including education, community action and development studies, and social and environmental studies.¹²¹ Based on their relationship with— and trust in— him, in 1989 the Havasupai asked Dr. Martin for assistance concerning the perceived epidemic of diabetes within the tribe.¹²² He brought in two other ASU researchers, Linda Vaughan, a professor in

113. Betsy Bruner, People of the Blue-Green Water, ARIZ. DAILY SUN, Feb. 8, 2009, available at http://azdailysun.com/articles/2009/02/08/news/arts_and_entertainment/sunday_arts/20090208_sunda_190449.txt.

114. Grand Canyon Hotels & Tours, The Havasupai Tribe and Havasupai Waterfalls, <http://www.grandcanyon.com/havasupai.html> (last visited Nov. 18, 2009).

115. *Id.*

116. Havasupai, About Havasupai, <http://www.havasupaitribe.com/about.html> (last visited Nov. 4, 2009).

117. *Id.*

118. Havasupai Tribe v. Ariz. Bd. of Regents, 204 P.3d 1063, 1067 (Ariz. Ct. App. 2008).

119. *Id.*

120. *Id.* at 1066; Paul Rubin, *Indian Givers*, PHOENIX NEW TIMES, May 27, 2004, available at <http://www.phoenixnewtimes.com/2004-05-27/news/indian-givers>.

121. *Havasupai Tribe*, 204 P.3d at 1066.

122. Rubin, *supra* note 120.

nutrition, and Therese Markow, a zoology professor with expertise in genetics.¹²³ Dr. Markow expressed interest in expanding the diabetes study to other topics, including schizophrenia, although Martin told her that the tribe likely would not agree to such a study.¹²⁴ The original diabetes study, including collection of blood, genetic research, and disease education, was funded by ASU.¹²⁵ However, before blood was collected, Dr. Markow began seeking funding for schizophrenia research on the tribe.¹²⁶

In 2003, Dr. Martin reportedly made a phone call to a Havasupai tribal member, Carletta Tilousi, that ultimately led to the lawsuit against Dr. Martin and other ASU researchers.¹²⁷ He told Ms. Tilousi that an ASU student was about to defend a dissertation that involved use of tribal blood in his research.¹²⁸ Ms. Tilousi attended the presentation at ASU in which the doctoral candidate, Daniel Garrigan, reported that DNA from 100 Havasupai blood samples used in his research demonstrated that the people had migrated to Arizona from Asia.¹²⁹ This conclusion contradicted the Havasupai's traditional spiritual beliefs that the tribe originated in the Grand Canyon.¹³⁰ Ms. Tilousi stated that "I knew we wouldn't have given this guy or anyone permission to do that study. I started to think, 'How dare this guy challenge our identity with our own blood, DNA.' Then I remembered when many of us gave blood years ago for a diabetes project. I wondered if this was the same blood."¹³¹ During the question-and-answer period, Ms. Tilousi challenged the doctoral candidate about whether he had obtained permission to use the blood for the study. According to Ms. Tilousi, the candidate

123. *Id.*

124. *Havasupai Tribe*, 204 P.3d at 1066–67; Rubin, *supra* note 120.

125. Rubin, *supra* note 120.

126. *Id.*

127. *Id.* Dr. Martin apparently learned in 2002 that ASU researchers had continued to use the Havasupai samples after the early diabetes studies had failed to find a genetic basis for the prevalence of the disease among the Havasupai. He complained to several ASU officials about the research uses without the tribe's consent. *Havasupai Tribe*, 204 P.3d at 1067.

128. Rubin, *supra* note 120.

129. *Havasupai Tribe*, 204 P.3d at 1067; *see also*, Rubin, *supra* note 120.

130. *Havasupai Tribe*, 204 P.3d at 1067; Rubin, *supra* note 120.

131. Rubin, *supra* note 120.

“was really nervous. He said no, not to his knowledge.”¹³² After the presentation, Dr. Martin informed “the Havasupai Tribal Council that ASU may have ‘mishandled’ blood samples taken as part of the diabetes research project.”¹³³

Responding to the Havasupai complaints, and with their agreement, ASU hired an independent investigator to look into the use of the samples.¹³⁴ The independent investigator found conflicting information about the original consent for use of the samples.¹³⁵ A script for an oral discussion of the study included references to schizophrenia and depression research, and a written consent form described the purpose of the research as “to study causes of behavioral/medical disorders.”¹³⁶ However, researchers informed the investigator that they did not think the tribe understood their consent to cover research on other behaviors, such as schizophrenia and depression.¹³⁷ However, there was agreement that the blood samples were used in numerous studies at ASU and other institutions, resulting in at least 23 scholarly papers, articles, and dissertations, including papers on schizophrenia and “inbreeding” in the Havasupai population.¹³⁸ Apparently, a genetic component to the tribe’s diabetes study was proposed and rejected shortly after the project began.¹³⁹ According to reports, Dr. Markow instructed a psychiatrist to review tribal medical records for diagnoses of schizophrenia, a review which was conducted “alone at night, without tribal permission, after the clinic closed.”¹⁴⁰ Dr. Markow’s research on schizophrenia within the tribe continued

132. *Id.*

133. *Havasupai Tribe*, 204 P.3d at 1067.

134. Rubin, *supra* note 120. ASU initially agreed to investigate in April, 2003. When no information was forthcoming one month later, the Tribe issued a “banishment order” for all ASU faculty and employees from the reservation. The tribe also informed ASU that it would hold a press conference to discuss concerns. At that point, the university offered to hire an external investigator, to be selected with the tribal council. The tribe agreed, executing a Joint Confidentiality and Cooperative Investigation Agreement. The formal investigation was conducted by Stephen Hart, a Phoenix attorney. *Havasupai Tribe*, 204 P.3d at 1067–68.

135. Rubin, *supra* note 120.

136. *Id.*

137. *Id.*

138. *Id.*; see also *Havasupai Tribe*, 204 P.3d at 1067–68; Rubin, *supra* note 120.

139. *Havasupai Tribe* 204 P.3d at 1066–67.

140. Rubin, *supra* note 120.

for an additional five years.¹⁴¹

According to news reports, the title of the consent form used with the Havasupai was “Medical Genetics at Havasupai,” but the first research protocol submitted to the IRB was entitled “Schizophrenia in the Havasupai.”¹⁴² It was ultimately approved as “Schizophrenia: A Genetic Model,” as were other studies entitled “Diabetes in Havasupai” and “Stress Following the Havasu Flood.”¹⁴³ The oral script used during the consent process did mention schizophrenia, although not as a specific focus of the study.¹⁴⁴ It read: “We are conducting research to try to identify factors that causes some of the health problems experienced by the Havasupai and other Native American peoples. Many of these diseases, such as diabetes, schizophrenia, depression, are complicated and so we try to look at as many factors as possible.”¹⁴⁵ The written consent stated only that the purpose of the project was to “study the causes of behavioral/medical disorders.”¹⁴⁶ The Havasupai were also promised that “no one’s name will appear on the tubes containing the stored blood,” although there were reports that at least two labs received blood vials with names on them.¹⁴⁷ Dr. Markow reportedly told the independent investigator that written consent meant she and her colleagues could use the Havasupai blood for research purposes as they saw fit.¹⁴⁸

2. The Lawsuit

In 2004, following the report, the Havaupai sued ASU and the researchers, including John Martin and Therese Markow, who supervised the doctoral candidate whose presentation triggered the dispute, in two separate lawsuits for misuse of the biological materials.¹⁴⁹ One of the lawsuits involved up to

141. *Id.*

142. *Id.*

143. *Id.*

144. *Id.*

145. *Id.*

146. *Id.*

147. *Id.*

148. *Id.*

149. *Havasupai Tribe v. Ariz. Bd. of Regents*, 204 P.3d 1063, 1070 (Ariz. Ct. App. 2008). At the time the suit was brought, Dr. Markow had already left Arizona State and became director of the University of Arizona Center for Insect Science. *Lawsuits Against UA Researcher Move to State Court*, AP

72 Havasupai tribal members (at times) whose blood was used in the research; the other was brought by the entire tribe.¹⁵⁰ Both cases were originally filed in state court, were removed to federal court by the defendants, where the federal law and *parens patriae* claims were dismissed, and then remanded back to state court where they were consolidated.¹⁵¹ The tribe's allegations extended not only to the use of their materials in studies they found objectionable, but also to the handling of the materials.¹⁵² They alleged that ASU researchers erroneously destroyed some of the tribal blood and lost other samples through transfers within and outside the university.¹⁵³ Indeed, they claimed that some cell lines were lost when freezers failed and there were no backups.¹⁵⁴ In keeping with their beliefs, the tribe wanted all samples returned so that they could bury them.¹⁵⁵ As Tribal vice chair Dianna Uqualla said when asked what the tribe was seeking, other than compensation:

First, I would like all of the blood returned to us. There are people, loved ones, who gave blood and who have passed away. But their blood is still out there somewhere, I think. Blood is very important to us. We need a ceremony with ASU officials present to bury that blood.¹⁵⁶

The tribe also claimed that tribal members had endured "severe mental and emotional harm, suffering, fright, anguish, shock, nervousness, and anxiety."¹⁵⁷ The Havasupai alleged that "ASU's actions have invaded the personal privacy of Havasupai tribal members and the cultural and religious privacy of the Havasupai Tribe."¹⁵⁸ Plaintiffs' counsel claimed that:

ASU has simply left our Clients to worry about the possible uses and

NEWSWIRE, May 5, 2005, [hereinafter *Lawsuits*]. She took the Havaupai samples with her, although tribal members say they were promised that the samples would be kept securely at ASU. Rubin, *supra* note 120.

150. *Lawsuits*, *supra* note 149; Kerry Fehr-Snyder, *ASU Law Prof Denounces Collecting Havasupai DNA*, ARIZ. REPUBLIC (Phoenix), Mar. 20, 2004, at 3B.

151. *Havasupai Tribe*, 204 P.3d at 1066 n.1, 1070 n.4.

152. *Id.* at 1069.

153. *Havasupai Tribe Sues ASU, Board of Regents*, AP STATE & LOCAL WIRE, March 16, 2004.

154. Rubin, *supra* note 120.

155. *Id.*

156. *Id.*

157. *Id.*

158. *Havasupai Tribe v. Ariz. Bd. of Regents*, 204 P.3d 1063, 1068 (Ariz. Ct. App. 2008).

locations of their blood samples, the violation of their religious values and beliefs, whether these samples have been lost, and whether they will continue to be used for additional unauthorized purposes. Many of our Clients now fear going to the health clinic, seeking medical attention, or providing blood samples for medical diagnosis or treatment.¹⁵⁹

ASU and the researchers involved denied any wrongdoing.¹⁶⁰ Instead, they pointed to the value of the research in trying to understand the biological underpinnings of the health issues of the Havasupai.¹⁶¹ Dr. Markow's attorney was quoted as saying, "The defendants feel very strongly that they didn't do anything wrong. Whatever kind of misunderstanding occurred should never have ended up in a lawsuit, and it will have a chilling effect on medical research across the country."¹⁶²

The trial court entered summary judgment against the plaintiffs on the grounds that they did not comply with Arizona's notice of claim statute, which requires claimants to include the amount claimed and the facts supporting the claimed amount.¹⁶³ This statutory requirement applies to claims against a public entity or employee, with the goal of permitting the government entity to "investigate the claim, assess its potential liability, reach a settlement prior to litigation, budget and plan."¹⁶⁴ The appellate court reversed the lower court decision.¹⁶⁵ It noted that, "[a]lthough the Tribe's notices do not describe the nature of the injury incurred, invasions of privacy relating to tissue samples such as the Tribe described in its claim notices naturally give rise to subjective personal injury, even when, as here, the samples are given voluntarily."¹⁶⁶ The court also noted that other cases had recognized claims of violation of privacy when blood samples were tested without consent, but that quantifying the resulting injury from them is challenging, given the personal nature of

159. *Id.* at 1069 (emphasis removed).

160. *Lawsuits*, *supra* note 149.

161. *Id.*

162. *Id.*

163. *Havasupai Tribe*, 204 P.3d at 1071.

164. *Id.* at 1072 (citing ARIZ. REV. STAT. ANN. § 12-821.01(A) (2003); *Deer Valley Unified Sch. Dist. No. 97 v. Houser*, 152 P.3d 490, 492 (Ariz. 2007)).

165. *Id.* at 1066.

166. *Id.* at 1076.

such tests.¹⁶⁷ Thus, the tribe's claims were revived. There may be other procedural hurdles, including consideration of the timeliness of their notice of claim that may limit their ability to pursue these claims.¹⁶⁸

3. Implications

The Havasupai cases give another example of objections that some individuals or groups may have to research use of their biological materials, as well as the detrimental effect that such research uses might have on other research. One tribal member, Roland Manakaja, summed up the Havasupai complaint by saying, "It was wrong of them to use my blood for whatever they used it for without my permission. We were just trying to get help for our diabetes, nothing else. How can we trust anyone anymore?"¹⁶⁹ The Havasupai are not alone; they have received support from other Native American organizations. For example, the National Congress of American Indians ("NCAI") issued a resolution "Supporting the Havasupai Indian Tribe in their Claim Against the Arizona Board of Regents Regarding the Unauthorized Use of Blood Samples and Research."¹⁷⁰ In it, the NCAI expresses its support for "the efforts of the Havasupai Indian Tribe to protect against unauthorized genetic research on its Members and other indigenous populations" and its opposition to "all unauthorized genetic research on Native American populations by . . . any individuals or institutions."¹⁷¹ Other groups have provided financial support for the litigation.¹⁷²

Considering the Havasupai claims, ASU law professor Gary Marchant has commented that "[a]ll genetic research is

167. *Id.* at 1076 (citing *Norman-Bloodsaw v. Lawrence Berkley Lab.*, 135 F.3d 1260, 1269 (9th Cir. 1998); *Doe v. High-Tech Inst., Inc.*, 972 P.2d 1060, 1064 (Colo. App. 1998)), n.12 (*United States v. Comprehensive Drug Testing, Inc.*, 513 F.3d 1085, 1104 (9th Cir. 2008)).

168. *Id.* at 1079.

169. Rubin, *supra* note 120.

170. Nat'l Cong. of Am. Indians, *Supporting the Havasupai Indian Tribe in Their Claim Against the Arizona Board of Regents Regarding the Unauthorized Use of Blood Samples and Research*, Res. SAC-06-019, 2006 Cong., 63rd Sess., available at <http://www.ncai.org/ncai/resolutions/doc/SAC-06-019.pdf>.

171. *Id.*

172. See Press Release, Nat'l Indian Gaming Ass'n, National Indian Gaming Association Chairman to Deliver Check to Havasupai Indian Tribe (July 15, 2006), available at <http://www.indiangaming.org/info/pr/press-releases-2006/index.shtml>.

based on an assumption that I'm pretty sure is now crumbling, the assumption of no property rights for DNA donors."¹⁷³ Whether or not the law comes to recognize *property* rights of DNA donors, the Havasupai cases and others suggest a need to rethink and strengthen the rights of DNA donors over the research use of their biological materials.

E. COMMON FEATURES OF CASES

Although the cases discussed here differ factually, they demonstrate that people may object to research uses of their biological materials, whether or not the specimens are identifiable.¹⁷⁴ The potential objections are multiple. For Moore, it was the use of his materials for commercial purposes without his permission. He felt used and betrayed by his physician and the other researchers working with him.¹⁷⁵ For the Greenbergs and the other families affected by Canavan disease, the commercial use was also objectionable. Unlike Mr. Moore, the *Greenberg* families were fully aware that their materials were being used – indeed, they actively participated in collecting the materials for research use. However, they never would have agreed to the use if they had understood that other families potentially affected by Canavan disease would have to pay to access the medical test they helped make possible.¹⁷⁶ For the Havasupai, the objections were more fundamental. Their materials had been used in research that threatened the core of their identity and stigmatized to them individually and as a group. Even without these objectionable uses, they may still have sued ASU for the additional uses because the loss of control of the samples had spiritual implications. They may have been willing to give their materials for research purposes they recognized as relevant to

173. Fehr-Snyder, *supra* note 150.

174. Specimens are considered “identifiable” if they can be linked to a specific individual either directly (e.g., through information like a name, medical record number, or birth date) or indirectly through a coding system. Office for Human Research Protections, Department of Health and Human Services, Guidance on Research Involving Coded Private Information of Biological Specimens, <http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm> (last visited Oct. 30, 2008) [hereinafter Guidance].

175. *See supra* Section II.a.

176. *See supra* Section II.b.

the health and well-being of their community, despite the spiritual implications. Perhaps they did not realize that their biological materials would not be fully consumed in that research. However, once it became clear that those materials remained, they expressed their wish to control the use and disposal of their biological materials. Although the reasons may be different, the plaintiffs who supported Dr. Catalona appeared to share some of the Havasupai's desire for control—they wanted to be sure that their materials were being used for the work they supported, and by a researcher in whom they had confidence.

How important did the plaintiffs consider their interests in their biological materials? So important that they were willing to bring suit, with all the financial, emotional, and time burdens involved in litigation, and despite the long odds of winning.¹⁷⁷ In each case, the plaintiffs faced substantial hurdles in even bringing their claims. All of the cases have been decided on the pleadings—on motions to dismiss or summary judgment.¹⁷⁸ In each case, the court substantially narrowed the potential causes of action. As will be discussed *infra*, their cases may have been hampered, in part, because of how research involving biological materials is treated within the human subjects research regulatory framework.

III. HUMAN BIOLOGICAL MATERIALS WITHIN THE HUMAN SUBJECTS RESEARCH REGULATORY FRAMEWORK

To understand how research involving biological materials

177. Others have expressed concern or dissatisfaction with how biological materials have been used in research. *See, e.g.*, Jill Jensen, *Lawsuit Filed Over Collection of Infant DNA*, NBC ACTION NEWS, March 12, 2009, available at http://www.nbcactionnews.com/content/aroundtheweb/story/Lawsuit-Filed-Over-Collection-of-Infant-DNA/61nyl0_9nEi-Eetup_WS1w.csp (describing lawsuit filed against Minnesota state health department for collecting and storing blood and DNA from infants without consent). Requests for DNA from historical figures, such as Presidents Jefferson and Lincoln, have been subject to debate. Edward Colimore, *Lincoln's 'Shroud of Turin'*, PHILA. INQUIRER, April 13, 2009, available at <http://garmuslib.org/pdf/Lincoln.pdf>; James Dao, *A Family Get-Together of Historic Proportions*, N.Y. TIMES, July 14, 2003, at A9. In addition, patients have brought suit against Myriad Genetics, challenging the product of research on DNA samples—the patent on the BRCA1 and BRCA2 gene. John Schwartz, *Cancer Patients Sue Testing Company and Government Over Gene Patents*, N.Y. TIMES, May 13, 2009, at A16.

178. The Havasupai case is the only case still pending, after the tribe's claims were revived by the appellate court.

is treated within the human subjects research regulatory framework, it is first necessary to understand that framework. This section begins with a description of the Common Rule and the exceptions under that rule. It next examines how scientific developments are challenging the underlying assumptions that have permitted biological materials to be used under the exceptions to the Common Rule requirements.

A. THE COMMON RULE

Beginning in 1974, the federal government instituted regulations to govern the conduct of research involving human subjects.¹⁷⁹ The regulations apply to research conducted by the federal government or supported by the federal government (e.g., through contract or grants). Universities and other institutions holding a federalwide assurance may agree to apply the regulations to non-federally funded research, as well.¹⁸⁰ Sixteen government agencies have adopted the Common Rule governing human-subjects research, which differs in only relatively minor ways from the separate Food and Drug Administration regulations.¹⁸¹

179. ROBIN LEVIN PENSLAR, PROTECTING HUMAN RESEARCH SUBJECTS: INSTITUTIONAL REVIEW BOARD GUIDEBOOK xviii–xxiv (1993).

180. The regulations specify to what they apply at 45 C.F.R. § 46.101 (2008). In addition, institutions that engage in research that is covered by the regulations (i.e., universities and other institutions receiving federal money to conduct research) must provide assurance to the Department of Health and Human Services that they will comply with the provisions of those regulations. 45 C.F.R. 46.103 (2008). The current form of that assurance is called the “federalwide assurance.” Its name indicates that it is approved for federalwide use, i.e., other federal departments or agencies that subscribe to the Common Rule may rely on it. The federalwide assurance applies to all non-exempt human subjects research that is conducted or funded by a federal department or agency that has adopted the Common Rule, and institutions may voluntarily extend its coverage to all human subjects research conducted at the institution. Office for Human Research Protections, Department of Health and Human Services, Federalwide Assurance Frequently Asked Questions, <http://www.hhs.gov/ohrp/FWAfaq.html> [hereinafter Federalwide] (last visited Oct. 21, 2009). Even if institutions extend the coverage of the federal regulations, there are important gaps in coverage (especially research by private companies that is not otherwise covered by the FDA regulations). Meslin & Quaid, *supra* note 2, at 230.

181. The Common Rule refers to 45 C.F.R. pt. 46, subpart A, issued by the Department of Health and Human Services. Additional signatories include the Department of Agriculture, Department of Commerce, Department of Defense, Department of Education, Department of Energy, Department of Housing and Urban Development, Department of Justice, Department of Veterans Affairs,

The federal regulations apply to all research that involves human subjects.¹⁸² “Research” is defined as a “systematic investigation . . . designed to develop or contribute to generalizable knowledge.”¹⁸³ A “human subject” is defined as a “living individual about whom an investigator (whether professional or student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information.”¹⁸⁴ Human-subject research within the scope of the regulations must be reviewed and approved by an Institutional Review Board (IRB) before it can begin.¹⁸⁵ Consent to participate is also required, and the regulations specify information that must be disclosed to the

Department of Transportation, Consumer Product Safety Commission, Environmental Protection Agency, Agency for International Development, National Aeronautics and Space Administration, National Science Foundation. Federalwide, *supra* note 180. The Central Intelligence Agency must comply with the Common Rule, as well as the special protections for pregnant women and fetuses, prisoners, and children under Executive Order 12333. *Id.* The Food and Drug Administration regulations are substantially similar to the Common Rule. The FDA regulations apply to all research involving products regulated by the FDA. Both the Common Rule and the FDA regulations have exceptions to informed consent, but the circumstances are different; the FDA authorizes emergency research under specified circumstances and does not recognize the waiver of consent available under 45 C.F.R. 46.116 (c) and (d). *See* 21 C.F.R. § 50.1–3 (2009); *see also* Guidance for Institutional Review Boards and Clinical Investigators, 19988 Update, <http://www1.va.gov/oro/apps/compendium/Files/appendix.htm> (last visited Feb. 15, 2010).

182. 45 C.F.R. § 46.101 (2008).

183. 45 C.F.R. § 46.102(d) (2008).

184. According to the regulations, “[i]ntervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject’s environment that are performed for research purposes. “Interaction” includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.” 45 C.F.R. § 46.102(f) (2008).

185. 45 C.F.R. § 46.101 (requiring IRB approval); 45 C.F.R. § 46.107 (2008) (establishing requirements for IRB composition); 45 C.F.R. § 46.109 (2008) (outlining IRB review of research); 45 C.F.R. § 46.111 (2008) (setting criteria for IRB approval of research).

participant.¹⁸⁶

There is no question that research in which tissue samples are obtained prospectively from living people specifically for research falls within the definition of human subjects research. Whether the material is obtained by blood draw, tissue biopsy, or cheek swab, it involves an “intervention or interaction with” a living individual. Nevertheless, there are several ways in which research involving preexisting specimens may not constitute “human subjects research.” According to guidance from the Office for Human Research Protections (OHRP), research involving only coded specimens¹⁸⁷ does not involve human subjects *if*:

- (1) the private information or specimens were not collected specifically for the currently proposed research project through an interaction or intervention with living individuals; and
- (2) the investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain because, for example: (a) the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, until the individuals are deceased (note that the HHS regulations do not require the IRB to review and approve this agreement); (b) there are IRB-approved written policies and operating procedures for a repository or data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased; or (c) there are other legal requirements prohibiting the release of the key to the investigators, until the individuals are deceased.¹⁸⁸

186. 45 C.F.R. § 46.111 (2008) (requiring informed consent from research participants); 45 C.F.R. § 46.116 (2008) (providing requirements for informed consent).

187. When specimens are coded, the specimens are given a unique identifier (code). Ideally, the code is unrelated to identifying information (e.g., name, medical record number, birth date), making it difficult, if not impossible, to reconnect the specimen the individual donor without access to the list linking the code to the identifying information. See NBAC, *supra* note 2, at 17.

188. Office for Human Research Protections, Department of Health and Human Services, Guidance on Research Involving Coded Private Information of Biological Specimens, <http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm> [hereinafter Guidance] (last visited Oct. 30, 2008). It is important to note, however, that if the investigator somehow obtains individually identifiable information during the course of the study, the research would then involve human subjects and be subject to IRB review, unless determined to be exempt. *Id.* The guidance considers specimens “coded” when “(1) identifying information (such as name or social security number) that would enable the investigator to readily

Example (a) is often called the “honest broker” agreement.¹⁸⁹ Using this type of arrangement, one investigator might share specimens she has already collected with another investigator. Because the second investigator did not obtain the specimens through interaction or intervention with the specimen donors and does not—and because of the agreement, cannot—receive personally identifiable information about the donors, her research does not qualify as “human subjects research.” A more efficient approach to specimen sharing is to create a central repository that houses the materials and takes responsibility for ensuring they are used in conformance with the regulatory requirements.¹⁹⁰ Example (b) addresses this approach. Like the honest broker approach, there are agreements that prohibit release of identifiable information. However, the agreements protecting the identifiable information apply to any investigator who seeks to use the repository specimens rather than being negotiated on an *ad hoc* basis.

Research that constitutes “human subjects research” may still be exempt from the federal regulations and, thus, from IRB review. Research involving existing specimens may be exempt if they are “publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.”¹⁹¹ The federal government makes some specimens that it collects, such as specimens collected through the National Health and Nutrition Examination Survey (NHANES) study, available to qualified researchers.¹⁹²

ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof (i.e., the code); and (2) a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.” *Id.*

189. For a fuller description of the “honest broker,” see Rajiv Dhir et al., *A Multidisciplinary Approach to Honest Broker Services for Tissue Banks and Clinical Data: A Pragmatic and Practical Model*, 113 *CANCER* 1705 (2008); Institutional Review Board, University of Pittsburgh, Honest Broker, <http://www.irb.pitt.edu/exempt/honestbroker.htm> (last visited Oct. 21, 2009).

190. Efficiency comes from combining materials, resources (such as freezers and computers), and personnel. Many institutions have encouraged investigators to use central resources for biological materials they collect in order to take advantage of these efficiencies and to exert greater control over the use of such materials (and, thus, hopefully to avoid misuse).

191. 45 C.F.R. § 46.101(b)(4) (2008).

192. ENVTL. PROT. AGENCY, HANDBOOK FOR USE OF DATA FROM THE

Although the specimens may be coded, researchers are not provided with identifiers. Finally, some specimens may be available through companies that provide specimens for a fee. All of these sources of specimens would qualify as “publicly available,” and, thus, research using them may be exempt from the federal regulations. In addition, the researcher can fall within the exemption by taking steps to avoid having identifiers. For example, even if specimens have individually identifiable information on them, if the researcher records information without the identifiers (e.g., by code not linked to the identifiers and to which the key is not retained), the research may be exempt. Similarly, the researcher can strip identifiers from the sample so that the research can qualify as exempt. The regulations specifically refer to *pathological* and *diagnostic* specimens in this exemption. Thus, the regulations clearly contemplate that materials collected for clinical purposes may be used for research and may fall outside the regulations governing human subjects research. Importantly, for all of these examples, it is assumed that the specimens were collected for some other purpose (whether for research or clinical purposes) rather than the current research. Otherwise, there would be an interaction or intervention with a living subject that would put the research within the scope of the federal research regulations.

Finally, even non-exempt human subjects research may be conducted without consent if it meets certain criteria. Specifically, research may be conducted without consent if:

- (1) the research involves no more than minimal risk to the subjects;
- (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects;
- (3) the research could not practicably be carried out without the waiver or alteration; and
- (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation.¹⁹³

A researcher may wish to conduct research under a waiver of consent described above, for example, when she wishes to use identifiable specimens for a purpose not addressed when the participant consented to the donation. There is no additional

NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEYS (NHAHES): A GOLDMINE OF DATA FOR ENVIRONMENTAL HEALTH ANALYSES ii (2003) [hereinafter EPA].

193. 45 C.F.R. § 46.116(d)(1)–(4) (2008).

physical risk to subjects because the materials have already been collected. Other risks likely can be minimized by attention to confidentiality protections. To meet the requirements under the regulations for the waiver that the research would not be “practicable” without the waiver, the researcher probably would need to be using a very large number of specimens that were collected some time ago.

As the discussion demonstrates, much research involving human biological materials could be undertaken without the knowledge or consent of the individuals who donated the materials.

B. SCIENTIFIC CHALLENGES TO THE COMMON RULE APPROACH

The Common Rule approach to research involving human biological materials rests on the assumption that biological materials can be effectively deidentified.¹⁹⁴ While undoubtedly true when the Common Rule was adopted, recent scientific developments raise questions about the validity of our assumption about our ability to deidentify DNA.¹⁹⁵ As McGuire and Gibbs explain, scientists have been challenging our assumptions about deidentification for at least five years.¹⁹⁶ If a person has access to only seventy-five single-nucleotide polymorphisms (SNPs) from an individual, that person can be identified.¹⁹⁷ Genome-wide association studies generate thousands more SNPs for each individual.¹⁹⁸ As McGuire and Gibbs note, reidentification from a collection of SNPs requires an identified sample or “reference sample”. But as DNA databases proliferate and those data are shared among researchers, reference samples will be more available and reidentification will become more likely.¹⁹⁹ Because they

194. Specimens that have been “deidentified” have had identifiers or codes removed from them.

195. Meslin & Quaid, *supra* note 2, at 230.

196. Amy L. McGuire & Richard A. Gibbs, *No Longer De-Identified*, 312 SCI. 370, 370 (2006).

197. Zhen Lin et al., *Genomic Research and Human Subject Privacy*, 305 SCI. 183, 183 (2004).

198. McGuire & Gibbs, *supra* note 196, at 370.

199. *Id.* Potential reference sources include DNA samples collected by the military, law enforcement, researchers, and health care providers. William W. Lowrance & Francis S. Collins, *Identifiability in Genomics Research*, 317 SCI. 600, 600 (2007). Such databases may be quite comprehensive and are increasing. For example, many states collect, and may retain at least for some period, blood spots from newborn genetic screening. Jensen, *supra* note 177;

perceived greater risk from genome-wide association studies and corresponding public release of data than previously acknowledged, McGuire and Gibbs have recommended that such studies be brought within the human subjects research regulations.²⁰⁰ McGuire and Gibbs and other commentators have not sought to prohibit sharing of genomic data—the science is valuable and advancements depend on such sharing. However, they have brought to light challenges to our underlying assumptions about this type of research that suggest greater oversight may be needed.²⁰¹

Other research strengthens the concerns expressed by McGuire and Gibbs. In a recent article, scientists demonstrated a statistical method for resolving individual genotypes within a mix of DNA samples or datasets containing aggregate single-nucleotide polymorphisms.²⁰² This article

Nora Macaluso, *State Setting Up 'Biobank' for Samples of Newborns' Blood for Disease Research*, 8 MED. RES. L. & POLY REP. 432, 432 (2009). For a number of years, the federal government has collected DNA from those *convicted* of federal crimes in a DNA database used for law enforcement purposes. In 2008, Congress authorized the federal government to collect DNA samples from anyone *arrested* by a federal law enforcement agency and all foreigners who are detained, along with DNA collected from those convicted of federal crimes. States have also been collecting DNA samples from those convicted of, charged with, or arrested for crimes. The federal government also collects DNA from all military personnel in a separate database. Solomon Moore, *F.B.I. and States Vastly Expanding Databases of DNA*, N. Y. TIMES, Apr. 19, 2009, at A1. Commercial sources might also serve as a reference database; numerous companies have been offering genetic testing to individuals for a variety of purposes (e.g., health, genealogy research), and decreasing prices make such testing more accessible. *Risks of Sharing Personal Genetic Information Online Need More Study, Stanford Bioethicists Say*, BUS. WIRE, June 5, 2009, available at http://www.businesswire.com/portal/site/home/permalink/?ndmViewId=news_view&newsId=20090605005014&newsLang=en; Bolnick et al., *supra* note 11, at 399. Indeed, the cost of whole genome sequencing has dropped considerably since the human genome was first completed. W. Gregory Feero, et al., *The Genome Gets Personal—Almost*, 299 JAMA 1351, 1351 (2008); Lisa M. Krieger, *Scientists: Long-Promised '\$1,000 Gene Sequence' Less Than Two Years Off*, SAN JOSE MERCURY NEWS, June 12, 2009, available at <http://www.geneticsandsociety.org/article.php?id=4717>; Brian Dolan, *Illumina Demos Concept iPhone App for Genetic Data Sharing*, MOBIHEALTHNEWS, June 10, 2009, available at <http://mobihealthnews.com/2658/illumina-demos-concept-iphone-app-for-genetic-data-sharing>.

200. McGuire & Gibbs, *supra* note 196, at 371.

201. *Id.* at 370–71; Lowrance & Collins, *supra* note 199, at 600–01.

202. Lowrance & Collins, *supra* note 199, at 601; Nils Homer et al., *Resolving Individuals Contributing Trace Amounts of DNA to Highly Complex*

prompted the NIH (among others) to remove aggregate data obtained from genome-wide association studies from its open access databases.²⁰³ The NIH is now reconsidering its policies on data sharing for such research and is urging others to do the same.²⁰⁴ Such reconsideration of policy should involve OHRP, IRB members and staff, and donors of research materials.

IV. WHAT EMPIRICAL DATA TELL US ABOUT RESEARCH WITH HUMAN BIOLOGICAL MATERIALS

Although the federal regulations provide numerous ways to conduct research with biological samples without the explicit permission of donors, empirical data suggest that this approach is not fully embraced within the research community.

A. IRB CHAIRS STUDY²⁰⁵

Along with colleagues, I conducted an interview study with IRB Chairs to evaluate their perspectives on ethical issues in research involving stored specimens. Our goal was to identify potential barriers to such research, as well as solutions for overcoming these barriers.

1. Methods

We asked Chairs to respond to a hypothetical study that

Mixtures Using High-Density SNP Genotyping Microarrays, 4 PLOS GENETICS 1, 7 (2008), available at <http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1000167>.

203. Jennifer Couzin, *Whole-Genome Data Not Anonymous, Challenging Assumptions*, 321 SCI. 1278, 1278 (2008); Elias A. Zerhouni & Elizabeth G. Nabel, Letter to the Editor, *Protecting Aggregate Genomic Data*, 322 SCI. 44, 44 (2008).

204. Zerhouni & Nabel, *supra* note 203, at 44.

205. The details of the study may be found in Leslie E. Wolf et al., *IRB Chairs' Perspectives on Genomics Research Involving Stored Biological Materials: Ethical Concerns and Proposed Solutions*, 3 J. EMPIRICAL RES. ON HUM. RES. ETHICS 99, (2008). The study was funded by the National Institute of Mental Health (1 RO1 MH064696). The principal investigator was Joseph Catania. Other senior members of the research team were Bernard Lo, M. Margaret Dolcini, and Lance M. Pollack. The study was approved by IRBs for the University of California San Francisco and the Henne Group (which conducted the interviews). The Chairs were recruited from a national sample of IRBs that review mental health-related research protocols. We interviewed a total of 85 Chairs, consisting of 32 Chairs from the 100 institutions receiving the most NIH funding in fiscal year 2002 and 53 Chairs from all other institutions. We had an overall participation rate of 65%. Fifty-five Chairs received the DNA scenario.

proposed to identify a genetic marker for schizophrenia using specimens previously collected for Alzheimer's research.²⁰⁶ The hypothetical study was developed to contain sufficient detail to "ring true" to IRB Chairs, while also raising ethical topics identified in the literature as important. The four ethical topics embedded in the scenario included consent, confidentiality, identifiability of specimens, and recontact of participants. Because we wanted their considered reflections, we sent Chairs the hypothetical study two weeks prior to their interview and asked them to review it in advance of their interview. The interview was conducted using a semi-structured interview guide.²⁰⁷ Chairs were first asked what human subjects concerns they had with the hypothetical study. They then were asked what solutions they could offer to address the concerns they had raised. Finally, they were asked to respond to both ethical concerns and potential solutions identified in the literature and rate their importance and helpfulness, respectively, on a four-point scale.²⁰⁸ Finally, the Chairs were asked some general questions about their approaches to difficult protocols.

The interviews were recorded and transcribed verbatim. We then used the transcriptions to code for predetermined themes and analyze them.

2. Study Results

The study was set up to raise questions about whether the original consent covered the proposed new research use of the

206. Each Chair received two out of three hypothetical studies to review. The topics of the three hypothetical studies included: (1) DNA analysis of stored samples and review of medical records, (2) withdrawal of medication for psychiatric illness in children, and (3) a survey of mental health problems among homeless persons. *Id.* at 100. Only the DNA study is relevant to this discussion.

207. "Semi-structured" means that there were specific questions that were to be asked of all respondents, but that there was also flexibility built into the interview guide, including suggested probes for following up. This approach ensures that the same material is covered with different respondents, but also permits for a full exploration of the Chairs' perspectives in a more natural conversation.

208. When asked to rate the importance of an issue, the 4-point scale was very important, somewhat important, somewhat unimportant, and very unimportant. When asked to rate the helpfulness of a suggestion, the 4-point scale was very helpful, somewhat helpful, somewhat unhelpful, and very unhelpful.

specimens. The purpose of the hypothetical study was “to identify candidate genes for schizophrenia through DNA analysis of stored blood samples” with the goal of ultimately “identifying new targets for innovative drug therapies and to better predict who is at risk for schizophrenia.”²⁰⁹ However, the research will use “blood samples and clinical records (including detailed mental health interviews and family histories) . . . from a community-based sample of 3,000 people over age 60 who volunteered for a study of risk factors for dementia . . . completed 5 years ago.”²¹⁰ The Chairs were told that “[t]he participants authorized researchers in the original study to carry out additional studies ‘related to the research topic,’” but that “[t]he consent form for the original study did not mention subsequent uses of stored materials in other research studies or other future analyses of data in the clinical records.”²¹¹ The IRB had previously approved DNA analyses on apolipoprotein E as a risk factor for Alzheimer’s. To set up the issue of potential waiver of consent, the hypothetical study also included a claim that “it would not be feasible to go back to all participants in the original study to seek their authorization for the use of their samples and clinic records.”²¹²

Eighty-seven percent of the Chairs said that whether the original consent covered the proposed new use of the biological specimens was an ethical concern in the hypothetical study. Moreover, those who raised the issue overwhelmingly (92%) concluded that the consent for the original study did not cover the proposed schizophrenia research.²¹³ In support of their conclusions, Chairs variously noted that schizophrenia is “quite different than dementia,” that such use would “stretch the original agreement . . . too far,” and that allowing the use “could undermine the trust that subjects have in researchers.”²¹⁴ Their concerns about the apparent lack of consent for the proposed new use of the biological materials also was evidenced by the number of Chairs who indicated that either they or their IRB (or both) would not approve the protocol because of the lack of consent. Although they were not specifically asked whether they would approve it, one-third of

209. Wolf et al., *supra* note 205, at 111.

210. *Id.*

211. *Id.*

212. *Id.*

213. *Id.* at 102.

214. *Id.*

chairs who raised questions about scope of consent indicated that those concerns would preclude approval. One Chair summed it up succinctly as being “kind of a show stopper.”²¹⁵

At least some of these Chairs were familiar with the regulatory exceptions that permit some uses of biological materials without consent. Eighty-three percent of Chairs suggested removing identifiers as a solution to conducting research without explicit consent.²¹⁶ Similarly, 31% of Chairs discussed the possibility of waiving consent as a way of resolving the consent issue. Nevertheless, they expressed some reservations about using these approaches. For example, with respect to waiver, all the Chairs expressed concerns about the appropriateness of waiver in the hypothetical study because the researchers could identify the donors of specimens, so that obtaining consent was not “impracticable” as the regulations require, and/or because the research present more than minimal risk.²¹⁷ As one chair commented, “it’s a major concern to use convenience as a way of avoiding doing [the research] properly”—i.e., by obtaining consent for the research use.²¹⁸ This may, in fact, be a misinterpretation of the regulations,²¹⁹ which leaves open the possibility that it is impracticable to obtain consent from a large number of donors even if the researcher knows their identities. Nevertheless, the comment demonstrates the Chairs’ strong preference for consent to possible future uses. Indeed, Chairs most commonly suggested obtaining consent for the proposed new use as a way of avoiding the ethical problems they identified. Chairs suggested that this could be achieved either by “starting over” by obtaining new samples from new participants with consent, contacting the original participants to ask them to consent to the proposed new use, or improving the discussion of future uses of materials in the *initial* consent so that such problems would be avoided.²²⁰ This last suggestion would be impossible to implement in the hypothetical study where materials already have been collected.

215. *Id.*

216. *Id.* at 103.

217. *Id.*

218. *Id.*

219. For regulation text, see *supra* text accompanying notes 178–193.

220. *Id.* at 105.

B. INVESTIGATOR PRACTICES STUDY

In this study, colleagues and I studied investigator protocols and consent forms to determine how they address common ethical issues in research involving stored biological materials.

1. Methods²²¹

We requested study documents from two sources: (1) federally funded general and pediatric clinical research centers (CRCs) and (2) federally funded Specialized Programs of Research Excellence (SPOREs) at the medical schools and research institutions that receive the most NIH funding.²²² NIH funding is an indicator for research volume; thus, we expected these institutions would have sufficient documents for our purposes. In addition, we expected that researchers using these resources would most likely reflect the standards in the field because CRCs and SPOREs are intended to set standards of high quality research and CRCs and SPOREs conduct their

221. Details concerning the study, including the methods and results, were originally reported in Leslie E. Wolf et al., *Genetic Research with Stored Biological Materials: Ethics and Practice*, 40 IRB: ETHICS & HUM. RES. 7, 7–18 (forthcoming March 15, 2010). This study was funded by the National Cancer Institute (R01CA117868). Leslie Wolf was the principal investigator. Other members of the research team included Charles E. McCulloch and Timothy A. Bouley.

222. CRCs are federally-funded centers designed to provide research infrastructure, including space, equipment, laboratory facilities, and access to experts in critical disciplines, to conduct sophisticated patient-oriented research. The general CRCs and pediatrics CRCs differ in terms of the populations they serve. COMM. ON ADDRESSING CAREER PATHS FOR CLINICAL RESEARCH, INST. OF MED., CAREERS IN CLINICAL RESEARCH: OBSTACLES AND OPPORTUNITIES 67–85 (William N. Kelley & Mark A. Randolph eds., 1994). SPOREs are federally-funded programs designed to promote novel, interdisciplinary cancer research, with the specific goal of moving basic research findings from the laboratory to clinical settings. National Cancer Institute, Specialized Programs of Research Excellence, <http://spores.nci.nih.gov/index.html> (last visited Oct. 17, 2009). We recruited CRCs and SPOREs sequentially based on their NIH funding ranking (fiscal year XXXX), starting from the institutions that received the most funding. Some institutions had more than one CRC or SPORE. For CRCs, we selected either the main campus CRC or the one with most NIH funding. If a CRC declined to participate, did not respond, or withdrew from our study after agreeing to participate, we replaced it with the next-largest CRC at the same institution (if one existed). Because we found no readily accessible information about the relative size of SPOREs, we randomly selected one SPORE within eligible institutions with multiple SPORES. If all CRCs or SPOREs at a particular institution declined to participate, we invited the next-highest-funded institution on the NIH list.

own review for scientific merit and regulatory compliance of research protocols that use their resources, in addition to any IRB review.²²³

The request for study documents was made directly to the director of the CRC or the SPORE.²²⁴ To be eligible for study inclusion, they had to have indicated that the study (1) used stored biological material for genetic (DNA) testing; (2) stored biological materials for future genetic (DNA) testing, or (3) stored biological materials for future research where future genetic (DNA) testing was neither explicitly contemplated nor prohibited. With our assistance, CRCs and SPOREs identified potentially eligible studies and requested permission from the investigators to share their study documents with us.²²⁵ All documents were redacted to remove information identifying participants and assigned a code that identified documents from the same institution and from the same investigator so that we could account for clustering in our statistical analyses.²²⁶

We coded the documents according to pre-established topics, focusing on issues of consent, control over specimens, confidentiality, and disclosure of research results to participants, that have been identified as important in the ethics literature, for analysis.²²⁷

2. Results

We ultimately received 139 studies (115 from CRCs and 24 from SPOREs) from 17 general CRCs, 3 pediatric CRCs, and 19

223. Wolf et al., *supra* note 221.

224. We requested eight document sets from CRCs and two from SPOREs. We sought more documents from CRCs because they offered a broader range of research topics; SPOREs' research is limited to cancer. Despite the more limited research topic, SPOREs provided essential data because they include a biorepository as a core function and much cancer research relies on stored biological materials.

225. Although we used only documents from which all identifying information (e.g., name of investigators, institutions, and experimental drugs) were removed and, thus, consent may not have been required under the federal regulations, we elected to notify investigators of the study and request their permission to include their documents in our study. We did not communicate directly with the investigators and documentation of consent was waived to protect their confidentiality. *Id.*

226. *Id.*

227. *Id.*

SPOREs across the country.²²⁸ We found that investigators overwhelmingly relied on consent when using biological materials for research, even for those twelve studies that used materials that had been collected previously and which may not have fallen within the federal regulations governing human subjects.²²⁹ In addition, when collecting new specimens, 75% of investigators used consent forms that allowed participants to select among different options regarding future use of their specimens, and the majority of investigators limited future research to certain conditions or uses in their consent forms.²³⁰ Because we studied only the documents and did not interview investigators, we cannot determine whether investigators preferred these approaches or whether IRBs, CRCs, or SPOREs required these approaches. Regardless of who determined the approach, our data suggest that actual practices in research involving stored biological materials put more weight on the donors' interests in controlling the use of their own biological materials than the regulations suggest is necessary. This is despite the fact that doing so may limit future research.

Despite this apparent recognition of donors' interests in deciding when and how their biological materials may be used in research, we found nine studies that permitted investigators to continue to use biological materials in research *after* a participant requested to withdraw from the study, provided the researchers removed identifiers. We found this approach ethically and legally problematic. Although the regulations and OHRP guidance permit the use of biological materials without identifiers to be used in research without consent under some circumstances,²³¹ the underlying rationale for those exceptions do not apply in cases where the participant asks to withdraw from study participation. Participants have a right to withdraw from research at any time.²³² The *Catalona* case establishes that the right to withdraw from research does not mean that participants have the right to have their materials returned to

228. *Id.* The overall response rate was 52% (39 of 75 eligible institutions).

229. These twelve studies included seven using only materials that had been previously collected and five that used both existing materials and prospectively collected materials. *Id.* at tbl.2. The federal regulations do not apply to unidentified samples, exempt previously collected materials under certain conditions, and permit waiver of consent. *See supra* Section III.

230. Wolf et al., *supra* note 221.

231. *See* 45 C.F.R. § 46.101(b) (2008); 45 C.F.R. § 46.116 (2008); Guidance, *supra* note 174.

232. 45 C.F.R. § 46.116(a)(8).

them.²³³ However, for research that includes storing biological materials for future use, for the right to be withdraw to be meaningful, research participants must be able to ask to have their materials withdrawn from further research use. The approach to withdrawal that allows research to continue on deidentified specimens misconstrues the regulatory requirements and mistakenly understands the only potential objections to continued use to be ones of confidentiality. To use the materials after a participant requests to withdraw violates the participant's wishes and thus also violates both the ethical principles governing human subjects research and the federal regulations that incorporate those principles.

C. RESEARCH PARTICIPANTS' STUDIES

The other significant, and perhaps most important, stakeholder group in this process is the donors of biological materials. The legal cases reviewed above demonstrate that at least some individuals object to certain uses of their biological materials—enough to bring a lawsuit. Research data provide further evidence that some individuals object to some uses of their biological materials.

A number of research groups have sought to understand public preferences regarding research involving stored biological materials. Their studies have targeted different populations within and outside the United States using a variety of methods.²³⁴ Using meta-analysis to evaluate the data from these diverse studies to reach broader conclusions, Wendler found that most people want to be asked whether their materials can be used in research. At the same time, most (17 out of 20) studies found that a significant majority of people (at least 80%) would donate their materials for research. Wendler's analysis suggests that public opinion and preferences are more consistent with IRB and investigator practices than with the legal approaches discussed previously; that is, the majority of people do not want their biological materials used for research without their consent, even though

233. *E.g.*, *supra* Section II.c.

234. *E.g.*, David Wendler, *One-Time General Consent for Research on Biological Samples*, 332 *BRIT. MED. J.* 544, 544 (2006) (citing to and summarizing thirty studies published in English that report the "views of individuals on consent for research with human biological samples.").

they are generally willing to contribute when asked.

However, Wendler's analysis may not fully take into account the interests of minority groups, a limitation he explicitly acknowledges: "one-time general consent [in which research participants are asked to agree to donate their materials for all future, unspecified research] may not be consistent with the values of some groups. Future research should evaluate its acceptability for groups, such as Native Americans, and areas of the world, such as Latin America, that are not included in the present data."²³⁵ Again, case law provides some evidence that some groups may have concerns about the use of their biological materials in research. The Havasupai, for example, were willing to have their biological materials used for some purposes (i.e., diabetes research), but objected to others,²³⁶ and thus would likely *not* agree with Wendler's proposal for a one-time general consent. The empirical data provide other support for this view. A 2004 study among Native Hawaiians found that Native Hawaiians were more likely than whites (in a national sample) to want researchers to ask their permission to use their biological materials in research.²³⁷ A 2006 study looking at differences between African-American and white cancer patients found no differences in reported willingness to donate materials, reporting that 95% were willing to do so.²³⁸ However, the study did find significant differences between the groups on some issues. In particular, participants from the hospital with the predominantly African-American population were more concerned than those from the hospital with a predominantly white population that researchers might discover genetic

235. *Id.*

236. See discussion *supra* Section II.d.

237. Megan Fong et al., *Native Hawaiian Preferences for Informed Consent and Disclosure of Results from Research Using Stored Biological Specimens*, 11 PAC. HEALTH DIALOG 154, 156 (2004).

238. Rebecca D. Pentz et al., *Research on Stored Biological Samples: Views of African American and White American Cancer Patients*, 140 AM. J. MED. GENETICS PART A 733, 735 (2006). *Contra* Donna T. Chen et al., *Research with Stored Biological Samples: What Do Participants Want?*, 165 ARCHIVES INTERNAL MED. 652, 654 (2005) (finding a difference between African-American and non-Hispanic whites' willingness to donate biological materials, 75% vs. 88% p=0.002). In the Chen et al. study, only about one-quarter of participants were healthy volunteers; the majority were patients or their family members. All were participating at research studies through the Warren G. Magnuson Biomedical Center, National Institutes of Health. These factors may have increased the willingness of people to donate.

information about their racial or ethical group (36% vs. 10%, $p < 0.001$).²³⁹ They also were more likely to express concerns that research interests might take precedence over clinical care, either by taking more tissue than needed (46% v. 26%, $p < 0.001$) or by using tissue in research that was needed for clinical care (37% vs. 21%, $p = 0.0046$).²⁴⁰ The researchers found that people from the predominantly African-American hospital who completed the tissue consent (as part of their surgical paperwork) but refused to participate in their study were more likely to refuse to donate their biological materials than those from the predominantly white hospital.²⁴¹ Importantly, about *one-quarter* of both groups who were actually offered a chance to donate materials for research failed to do so, indicating that even when a majority of people are willing to donate materials for research, a significant minority will not donate. It is also important that participants in that study were all cancer patients, who, for a variety of reasons, may be more willing to donate their biological materials to research.²⁴² In a 2001 study among Jewish Americans, the researchers found that a majority of respondents wanted consent as a requirement for research use.²⁴³ Contrary to the regulatory framework, they felt it was more important to obtain consent for materials collected in the clinical context that may be used for research rather than in research context, presumably because, in the latter case, the donor already knows that the materials will be used in research.²⁴⁴ Participants also felt that consent was more important when research related to genetic traits that may be stigmatizing, compared to research on genetic traits that caused physical illness or non-stigmatizing genetic traits.

239. Pentz et al., *supra* note 238, at 737.

240. *Id.*

241. *Id.* at 739.

242. Cancer patients undergoing treatment may be particularly aware of and interested in medical research that may improve treatments, may appreciate how previous patients' participation in research may benefit them, and may be more likely to agree to participation if their doctors, many of whom may also be researchers, ask them to participate.

243. Marc D. Schwartz et al., *Consent to the Use of Stored DNA for Genetics Research: A Survey of Attitudes in the Jewish Population*, 98 AM. J. MED. GENETICS PART A 336, 338 (2001).

244. *Id.* at 341. It is important to note that this study had a low (20%) participation rate and, as a result, a relatively small (273 participants) sample size.

D. IMPLICATIONS

Taken together, the IRB Chair and investigator studies suggest a reluctance within the research community to take advantage of the portions of the federal regulations governing human subjects research and corresponding OHRP guidance that permit research with human biological materials without consent. Importantly, these practices appear to be more responsive to the preferences of those individuals who provide their materials for use in research than the approaches authorized by the regulations and guidance. The IRB Chair and investigator studies also suggest that research using human biological materials can be conducted despite the reluctance we found to rely on the flexibility in the regulations. This suggests that, contrary to the concerns expressed in case law,²⁴⁵ the legal framework could be changed to better account for participant preferences and IRB Chair and investigator ethical intuitions without impeding important research.

V. RECOMMENDATIONS FOR CHANGE

The foregoing analysis demonstrates that current legal approaches regarding use of biological materials for research are, to some extent, at odds with research practices and research participant preferences. The question is whether that is a difference that needs to be addressed. It is generally understood in the research ethics community that the regulations represent a floor; IRBs can and do impose higher standards if they think doing so is warranted. For example, an IRB may review a research protocol at the full committee level, even though it falls within one of the categories of research that may be reviewed by the IRB Chair or subcommittee of the IRB on an expedited basis.²⁴⁶ In the biological materials research context, IRBs are free to require consent for research involving stored biological materials when such consent is not required by the regulations. Thus, is changing the existing regulatory framework necessary to adequately protect biological materials donors' interests?

There are reasons to believe regulatory changes are

245. See, e.g., *Moore v. Regents of the Univ. of Cal.*, 793 P.2d 479 (Cal. 1990); *Greenberg v. Miami Children's Hosp. Research Inst., Inc.*, 264 F. Supp. 2d 1064 (S.D. Fla. 2003); *Wash. Univ. v. Catalona (Catalona II)*, 490 F.3d 667 (8th Cir. 2007).

246. For an expedited review, see 45 C.F.R. § 46.110 (2008).

warranted to protect the interest of donors in their biological materials. First, not all IRBs will review such research at the higher level.²⁴⁷ Our IRB Chairs Study provides additional support for this concern given that a few Chairs expressed no concerns regarding the hypothetical study that would use biological materials collected for Alzheimer's research in schizophrenia research. Second, to ignore public preferences and interests may undermine trust in research. The current regulatory structure is inconsistent with public preferences, given that it permits research with biological materials to go forward without consent. A widely publicized complaint about research use of biological materials could hinder other research.²⁴⁸ Finally, as the legal cases demonstrate, courts have not recognized donors' continuing interests in their biological materials. The current regulatory framework may contribute to this failure. The current regulatory framework generally fails to recognize donors' interests by excluding much research with biological materials from its protections. Regulatory recognition of donors' interests may advance them in two ways: by making it less likely that donors' interests will be compromised by researchers in the first place because of regulatory protections and by providing a legal foundation for building legal claims should materials be used inappropriately.²⁴⁹

247. There is an extensive literature regarding the variability among IRBs in terms of their interpretation of the regulations. See, e.g., Rita McWilliams, *Problematic Variation in Institutional Review of a Multicenter Genetic Epidemiology Study*, 290 JAMA 360, 360–66 (2003); INSTITUTE OF MEDICINE, PROTECTING DATA PRIVACY IN HEALTH SERVICES RESEARCH 52–56 (2000).

248. Negative publicity has been a problem in other areas of research. For example, gene transfer research was impacted by the death of Jesse Gelsinger in a gene transfer trial at the University of Pennsylvania. See Mark Yarborough & Richard R. Sharp, *Public Trust and Research a Decade Later: What Have We Learned Since Jesse Gelsinger's Death?*, 97 MOLECULAR GENETICS & METABOLISM, 4, 4–5 (2009); Jennifer Couzin & Jocelyn Kaiser, *Gene Therapy: As Gelsinger Case Ends, Gene Therapy Suffers Another Blow*, 307 SCI., 1028 *passim* (2005). Similarly, concerns were raised about stem cell research following allegations of research misconduct against Woo Suk Hwang of South Korea. See David Cyranoski, *South Korean Scandal Rocks Stem Cell Community*, 12 NATURE MED. 4 (2006).

249. Plaintiffs have been forced to articulate, for example, property claims with respect to their biological materials that have been uniformly unsuccessful. Others have commented on the ill fit between the property claims and the plaintiffs' interests. See, e.g., Sonia M. Suter, *Disentangling Privacy from Property: Toward a Deeper Understanding of Genetic Privacy*, 72

While there are important reasons for changing the regulations to better recognize the continuing interests donors may have in their biological materials used for research, there are countervailing interests and a balance must be struck. Our empirical data regarding current research preferences and practices provide some reassurance that requiring more oversight of research involving biological materials than currently is required under the regulations will not prevent such research from going forward. On the other hand, requiring consent to each research use or requiring full committee review of all such protocols may impose significant burdens with respect to review. This may also add to the cost of research, as well as potentially delay it, without significantly increasing protections to the donors of the biological materials. Indeed, it is important to remember that, although people want to be asked whether their biological materials can be used in research, *most* people do not object to most research uses and would be satisfied with a one-time, blanket consent to research use. Requiring them to consent to each individual research protocol, for example, may be unduly burdensome to donors and could even create a disincentive to participation. The following recommendations seek to recognize the interests and concerns some donors may have in the continuing use of their biological materials in research, without unduly burdening the research or other participants.

Amend the regulations to bring research involving biological materials within the definition of "human subjects research" (and thus subject to IRB review). The current exceptions to IRB review for much research involving biological materials are no longer justified, fail to recognize donors' continuing interest in their biological materials and the ways in which they are used, and unnecessarily remove such research from the protections afforded by IRB review. As described above, the regulatory exceptions for research involving biological materials are based on the materials being stripped of their identifiers or provided to researchers without identifiers and the existence of a strict agreement not to share identifying information. However, recent advances in DNA technologies suggest that deidentification may not be feasible. Only a few SNPs are needed to identify an individual, and scientists have demonstrated that it is possible to identify

individual DNA even among samples that include DNA from multiple sources²⁵⁰ The proliferation of DNA databases increases the risk to potential donors whose materials are used in a deidentified manner. For example, the U.S. military currently collects DNA from all personnel. The primary purpose of these samples is to enable identification of remains, but it is possible that at least some data may become available for research purposes. Similarly, federal and state governments have been collecting DNA samples from persons convicted of crimes for law enforcement purposes for years. They are now expanding those collections to those who are arrested – a substantial expansion.²⁵¹ Given these changing circumstances, it is difficult to justify the regulatory exceptions for research with biological materials and deprive those donating materials from the protections offered by IRB review.

Moreover, excluding much research involving biological materials from *human subjects* research, the current regulatory treatment disregards donors' continuing interests in their biological materials. Contrary to the assumptions underlying the regulatory treatment, donors do care about how their biological materials are used. They want to know whether the materials are going to be used in research in the first place. A significant minority also objects to some research uses. Bringing this research more fully within the human subjects research framework would recognize the donors' continuing interests and provide the structure to protect those interests (e.g., IRB review).

There are several steps needed to achieve this goal. The first step is to revoke the OHRP guidance that specifies that genetic research involving stored biological materials is not "human subjects" research when samples or data are deidentified or coded, but identifiers are not shared.²⁵² The second step is to amend 45 C.F.R. § 46.101(b)(4) of the federal

250. See discussion *supra* Section III.b.

251. Moore, *supra* note 199, at A1. Although they may be collected for one purpose, there is little reason to believe that such materials will be used in such a limited fashion. See D.H. Kaye, *Behavioral Genetics Research and Criminal DNA Databases*, 69 LAW & CONTEMP. PROBS. 259, 259–60 (2006) (suggesting that DNA records in law-enforcement databases originally obtained for identification purposes might one day be used in behavioral genetics research).

252. Guidance, *supra* note 174.

regulations to eliminate the exemption for use of pathological specimens or diagnostic specimens. It will require some effort to amend the regulations; the process requires public notice and comment periods. These considerable efforts may explain the limited amendments that have been made over the years that the regulations have been in effect. Given these challenges, it may be possible that OHRP could issue guidance that makes clear that biological materials containing DNA cannot be rendered unidentifiable (thus, rendering this exemption inapplicable), at least as a temporary measure.

That such research should be subject to IRB review does not mean that all research must undergo full committee review.²⁵³ While I am arguing that research involving stored biological materials should always be considered human subjects research within the meaning of the federal regulations and should not be exempt from review, there are many circumstances in which the risks presented by such research will be quite limited. Specifically, when biomaterials are stored in a central repository, under an IRB-approved protocol, we can have some confidence that the interests of the donors of human biological materials will be protected. This is because the IRB has already reviewed and approved the processes for collecting the materials with donors' consent and for distributing materials for research use. IRB review of secondary research uses of the material can be limited, using expedited review. Such review should focus on evaluating whether the proposed

253. There are three potential levels of review under the federal regulations. Although not required under the regulations, federal guidance indicates that research that is eligible for exemption should be reviewed by an IRB to confirm the eligibility. Such review may be conducted by a knowledgeable individual. United States Dept. of Health & Human Services, http://www.hhs.gov/ohrp/policy/exempt_res_det.html (last visited Feb. 15, 2010). The regulations permit research that presents no more than minimal risk and falls within specified categories to be reviewed under *expedited* review procedures. See, 45 C.F.R. § 46.110 (2008). For a detailed list of categories of research eligible for expedited review, see Protection of Human Subjects: Categories of Research that May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure, 63 Fed. Reg. 60364, 60364–66 (Nov. 9, 1998). Such review may be completed by a subcommittee of the IRB and may be reviewed outside a plenary meeting. Finally, all other research must be reviewed by a quorum of the full IRB committee at a plenary meeting. Institutions have been criticized for failing to review research protocols as required under the regulations. See, e.g., Nancy Kass et al., *Controversy and Quality Improvement: Lingering Questions About Ethics, Oversight, and Patient Safety Research*, 34 JOINT COMM'N J. ON QUALITY & PATIENT SAFETY 349, 350–52 (2008).

use is consistent with the uses agreed to in the consent and whether the project poses any new or unique risks that might not have been contemplated when the materials were donated. Requiring this limited level of IRB review, beyond that which the biorepository must conduct as part of its operations provides a check on the biorepository processes, as well as providing an opportunity to identify new or changing risks that may require attention at the individual protocol or at the biorepository level. Should changes be necessary, the IRB would be in a position to identify them and request them of either the specific research protocol or the overarching biorepository protocol.

Requiring consent to research use. A corollary to the first recommendation for treating research involving biological materials as human subjects research is that no biological materials should be used in genetic research without consent from the donor of the materials. This recommendation represents a significant change from the existing regulatory framework, which allows biological materials collected for other purposes (e.g., blood drawn for clinical purposes) to be used in research. However, the lessons from the legal cases and empirical research on public preferences are that people want a say in whether their biological materials are used in research, especially when those materials were initially collected for other purposes. Moreover, some people find some research uses highly objectionable, even when the samples are not directly identifiable. The anecdotal evidence from the legal cases and the data from the empirical research on public preference undermine the assumption supporting the regulatory exceptions.²⁵⁴

Nevertheless, requiring consent does not necessarily mean that donors of biological materials need to consent to each and every research use. Indeed, the majority of people do not want such a role and, to large extent, it seems unlikely that doing so

254. Other commentators have suggested that tissue collection is not research and that other rules are needed. Leonard Glantz et al., *Rules for Donations to Tissue Banks—What Next?*, 358 NEW ENG. J. MED. 298, 302–03 (2008). It is true that some tissue collection is not research. For example, biological materials often are obtained for clinical purposes from biopsies or blood draws. If they are used solely for clinical purposes, their use is non-controversial. The problems that have arisen, including the cases of *Moore*, *Greenberg*, and *Catalona* have arisen in connection with research uses.

will provide additional protections to individuals, though it will certainly add substantially to the burden on research.²⁵⁵ On the other hand, a one-time general consent, proposed by Wendler and others, may not provide adequate protection to donors.²⁵⁶ For example, a general consent would have authorized the uses, such as the migration studies, to which the Havasupai had the strongest objections. Even those research participants who generally support research and were willing to give general consent might have second thoughts based on scientific developments. For example, some may be concerned about the increasing identifiability of their samples. Others may be more concerned about potential use of their materials in new types of research, such as stem cell research, that was not possible when they gave their consent.²⁵⁷

There are some approaches discussed in the literature that address these competing concerns of donor protection and facilitating scientific research.²⁵⁸ The first is to have a robust consent process that gives individuals a good sense of the types of research that their materials may be used for, as well as where the uncertainties lie. Giving donors an opportunity to express their preferences about future research, as recommended in the literature and embraced in practice,²⁵⁹ is a way to respect individuals' interests while facilitating research. Soliciting these preferences provides some basis on which the biorepositories that house these materials and the IRBs that oversee them can make choices about what uses are appropriate and consistent with the donors' consent. The challenge will be defining categories of research sufficiently so that donors of materials and IRBs can determine what uses are

255. Timothy Caulfield et al., *Research Ethics Recommendations for Whole-Genome Research: Consensus Statement*, 6 PLOS BIOLOGY 430, 431–32 (2008).

256. E.g., Wendler, *supra* note 234, at 546–47; Mats G. Hansson et al., *Should Donors Be Allowed to Give Broad Consent to Future Biobank Research?*, 7 LANCET ONCOLOGY 266, 268–69 (2006). *Contra* Timothy Caulfield, *Biobanks and Blanket Consent: The Proper Place of the Public Good and Public Perception Rationales*, 18 KING'S L. J. 209, 215–24 (2007) (laying out an excellent critique of the blanket consent position).

257. See, e.g., Bernard Lo et al., *Informed Consent in Human Oocyte, Embryo, and Embryonic Stem Cell Research*, 82 FERTILITY & STERILITY 559, 560–62 (2004). For example, British researchers recently announced that they had developed sperm from human embryonic stem cells. Cell Medicine, *supra* note 1.

258. See sources cited *supra* note 253.

259. See NBAC, *supra* note 2; Wolf et al., *supra* note 221.

permitted.²⁶⁰ At the edges, IRBs need to act in favor of protection, as the data from our IRB Chair Study suggest that they do.

The second approach is to have a mechanism for accounting for changing circumstances. New types of research may be developed, such as stem cell research and some behavioral genetic research, that were not anticipated and are controversial.²⁶¹ Scientific developments may alter our understanding; for example, recent developments suggest that we may not be able to conduct research with “deidentified” samples. These changes may require that we re-contact those who have provided materials, inform them of the change circumstances, and readdress their preferences and willingness to have their materials used.²⁶² Adopting this approach requires that we ask donors for permission to re-contact them and ask for their contact information. Some participants may object to recontact and, thus, use of their materials may be limited in the future. However, technology makes re-contact more feasible—cheaper and easier than before. Indeed, there may be scientific benefits to maintaining contact with donors of biological materials, and not just when there are developments that might change people’s willingness to allow their materials to be used in research. Some commentators have been arguing for on-going contact.²⁶³ Such contact need not be individual; for example, biobanks may provide aggregate information about research projects for which materials have been used. A significant development that might justify revisiting consent might appropriately be conducted on an opt-out basis; that is, providing relevant information and requesting anyone who objects to continued use to contact the biobank.

Changing the consent processes for research use of biological materials only works for some

260. *E.g.*, Caulfield et al., *supra* note 265, at 431–33; Darren Shickle, *The Consent Problem Within DNA Biobanks*, 37 *STUD. HIST. & PHIL. BIOLOGICAL & BIOMED. SCI.* 503, 505–07 (2006).

261. *See* Amy L. McGuire et al., *Research Ethics and the Challenge of Whole-Genome Sequencing*, 9 *NATURE REVS. GENETICS* 152, 155 (2008) (describing implication of whole genome sequencing for research ethics, particularly the consent issue).

262. Shickle, *supra* note 260, at 507.

263. *E.g.*, Timothy Caulfield et al., *DNA Databanks and Consent: A Suggested Policy Option Involving an Authorization Model*, 4 *BMC MED. ETHICS* 1, 2–3 (2003); Shickle, *supra* note 260, at 507.

circumstances—prospective collections or existing collections for which there is contact information, such that re-contact is feasible. That may eliminate many biological materials from future use, especially older materials, which may be a profound scientific loss.²⁶⁴ Accordingly, we may need to consider other means of taking into account donor interests. Some have suggested community consultation as a way of doing so.²⁶⁵ For example, some Chairs in our study suggested that remaining members of the sample or representatives of the Alzheimer's community could be consulted about the proposed use of the materials for schizophrenia research. The challenge, of course, is in identifying the relevant community and appropriate representatives.²⁶⁶ For example, it should be obvious that community consultation on the use of Havasupai samples would not be valid if it did not contain any Native Americans. However, it may be less clear how closely related the representative must be to the donor group. For example, would it be acceptable to have a consultation that included no Havasupai, but includes other Native American nations? Could a member of a different (perhaps larger) tribe adequately represent the Havasupai's interests? What if there were only one Havasupai (or other Native American) in the group? In the hypothetical in our IRB study, would family members of

264. On the other hand, older materials may be more available for research if the donors are dead; the federal regulations on human subjects research apply only to living individuals. 45 C.F.R. § 46.102(f) (2008). Nevertheless, even those donors may have continuing interests that ought to be considered through the alternative means discussed in this paragraph. Meslin & Quaid, *supra* note 2, at 230.

265. *E.g.*, NBAC, *supra* note 2, at 7–8.

266. This is not a new issue. IRBs are required to have a non-affiliated member, a requirement that is typically interpreted as that for a “community” member who can represent the interests of potential research participants. See Sohini Sengupta & Bernard Lo, *The Roles and Experiences of Nonaffiliated and Non-Scientist Members of Institutional Review Boards*, 78 ACAD. MED. 212, 213–16 (2003). HIV and international researchers, among others, have relied on community advisory boards for feedback on community mores, preferences, and priorities. Stephen F. Morin et al., *Community Consultation in HIV Prevention Research: A Study of Community Advisory Boards at 6 Research Sites*, 33 J. ACQUIRED IMMUNE DEFICIENCY SYNDROME 513, 514–15 (2003). Community-based participatory research engages the community to set research agendas, design community-appropriate research protocols, and return research results to the community. In each of these settings, there have been questions raised about what are the relevant communities and who represents them. See, *e.g.*, Caitlin Kennedy et al., *Faculty Perspectives on Community-Based Research: “I See This Still as a Journey”*, 4 J. EMPIRICAL RES. ON HUM. RES. ETHICS 3, 6 (2009).

Alzheimer's patients be adequate representatives of the donors' interests or do donors need to be represented more directly (e.g., early Alzheimer's patients who were not part of the original sample)? Despite these challenges, we need to identify alternative methods for identifying and protecting donors' interests in existing collections. More research may be needed, but the potential scientific benefits require it.

Robust right to withdraw biological materials. Requiring ongoing communication with donors of biological materials and revisiting consent in some circumstances only makes sense if there is a robust right to withdraw biological materials. The federal regulations governing human subjects research should be understood to include such a right. They explicitly require that participants be told that they "may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled."²⁶⁷ In the case of biobanking, when the subjects' only participation is contribution of their biological materials, this requirement only makes sense if it means that they can ask that their materials be withdrawn from further research use.

As described above, however, the *Catalona* opinions call into question this right. Indeed, the district court concluded that

[T]he right to discontinue participation in a research project *means nothing more* that the [research participant] has chosen not to provide any more biological materials pursuant to one or more research protocols Nothing more can or should be read into this right possessed by the [research participant] at all times.²⁶⁸

The court of appeals focused on whether the participants had a right to physical return of their biological materials and concluded, for a host of good reasons, that they did not.²⁶⁹ Thus, it never turned its attention to what the right to withdraw means when biological materials have been donated. The Havasupai case illustrates the importance of having a robust ability to withdraw. In the on-going communication, the researchers should have notified the Havasupai that the materials were going to be used in new projects on

267. 45 C.F.R. § 46.116(a)(8) (2008).

268. Wash. Univ. v. *Catalona* (*Catalona I*), 437 F. Supp. 2d 985, 1000 (E.D. Mo. 2006).

269. Wash. Univ. v. *Catalona* (*Catalona II*), 490 F.3d 667, 675–77 (8th Cir. 2007), *cert. denied*, 128 S.Ct. 1122 (2008).

schizophrenia and migration. Having learned that their materials might be used in ways they found objectionable, the Havasupai would have the opportunity to withdraw their materials. If the researchers could simply remove identifiers and continue with the research, the Havasupai would still be harmed. Confidentiality was not their sole concern. Only by being able to remove the materials entirely can they protect their interests and avoid harm. That is not to say that removing identifiers and continuing to use biological materials in research is always wrong. Some donors may be concerned only with confidentiality and may feel that removing identifiers (and strong agreements not to try to re-identify materials) is sufficient to address their concerns. However, the default response when someone makes the effort to withdraw their biological materials cannot be to remove identifiers and continue to use them. Rather, donors should be specifically asked whether they want their materials withdrawn entirely from research or whether they would agree to their continued use if their identifiers were removed. Of course, they should also be informed of the limitations of deidentification.

In light of the ambiguity created by the *Catalona* cases, the right to withdraw biological materials needs to be clarified. OHRP should issue guidance that makes clear that people who donate their materials have a right to withdraw them and that, when such requests are made, it is impermissible to continue to use them in de-identified fashion without the donors' explicit permission. Some qualifications are necessary. Biological materials may be finite; if the materials are used up before the request to withdraw is made, withdrawal may not be not feasible. In other instances, identifiers may have been removed from biological materials in such a way that reidentification is not reasonably feasible, although given scientific and technological advances, this limitation may not amount to much in the future. While OHRP guidance is an appropriate first step to help prevent the *Catalona* misinterpretation of the regulations from continuing, ultimately it would be preferable to amend the regulations to specify that the right to withdraw biological materials that are collected and stored pursuant to a research protocol means that those materials can no longer be used in research.

Despite court opinions to the contrary, changing the regulatory framework concerning use of biological materials in research to better respect individuals' preferences and interests

in the biological materials is unlikely to stifle important research. Indeed, such research depends on the willingness of the public to trust researchers with their materials. The evidence suggests that the public trust requires the recognition that research on stored samples is human subjects research and should be afforded all concomitant protection, including the right to withdraw samples for research use.