

Nos. 06-2286 & 06-2301

IN THE
United States Court of Appeals for the Eighth Circuit

THE WASHINGTON UNIVERSITY,

Plaintiff-Appellee,

v.

WILLIAM J. CATALONA,

Defendant-Appellant,

and

RICHARD WARD, ET AL.,

Defendants-Appellants.

Appeal from the United States District Court
for the Eastern District of Missouri, Eastern Division
The Honorable Stephen N. Limbaugh, Senior District Judge

**BRIEF FOR AMICI CURIAE CORNELL UNIVERSITY, DUKE
UNIVERSITY, EMORY UNIVERSITY, THE GEORGE WASHINGTON
UNIVERSITY, JOHNS HOPKINS UNIVERSITY, MAYO CLINIC,
THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR
UNIVERSITY, THE UNIVERSITY OF MICHIGAN, THE UNIVERSITY
OF MINNESOTA, THE UNIVERSITY OF PITTSBURGH,
THE UNIVERSITY OF ROCHESTER, AMERICAN COUNCIL
ON EDUCATION, ASSOCIATION OF AMERICAN MEDICAL
COLLEGES AND ASSOCIATION OF AMERICAN UNIVERSITIES,
IN SUPPORT OF PLAINTIFF-APPELLEE AND AFFIRMANCE**

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RULE 26.1 CERTIFICATION

Pursuant to Rule 26.1 of the Federal Rules of Appellate Procedure, amicus curiae Cornell University states that it has no parent corporation and no publicly held company owns 10 percent or more of its stock.

Amicus curiae Duke University states that it has no parent corporation and no publicly held company owns 10 percent or more of its stock.

Amicus curiae Emory University states that it has no parent corporation and no publicly held company owns 10 percent or more of its stock.

Amicus curiae the George Washington University states that it has no parent corporation and no publicly held company owns 10 percent or more of its stock.

Amicus curiae Johns Hopkins University states that it has no parent corporation and no publicly held company owns 10 percent or more of its stock.

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Amicus curiae the University of Minnesota states that it has no parent corporation and no publicly held company owns 10 percent or more of its stock.

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Amicus curiae American Council on Education states that it has no parent corporation and no publicly held company owns 10 percent or more of its stock.

Amicus curiae Association of American Medical Colleges states that it has no parent corporation and no publicly held company owns 10 percent or more of its stock.

Amicus curiae Association of American Universities states that it has no parent corporation and no publicly held company owns 10 percent or more of its stock.

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Pursuant to Federal Rule of Appellate Procedure 29, and with the
consent of all parties, amici curiae Cornell University, Duke University, Emory

University, the George Washington University, Johns Hopkins University, Mayo Clinic, Stanford University, the University of Michigan, the University of Minnesota, the University of Pittsburgh, the University of Rochester (collectively, the “Institutional Amici”), American Council on Education, Association of American Medical Colleges, and Association of American Universities (collectively, the “Association Amici”) respectfully submit this brief in support of plaintiff-appellee, Washington University, and affirmance.

INTEREST OF AMICI CURIAE

Amici include higher education and research institutions at the forefront of biomedical research and associations that represent them. All of the Institutional Amici maintain biorepositories, like that maintained by Washington University, which collectively contain hundreds of thousands of donated biological specimens. The scientists whom Amici employ depend on these biological materials for current and planned research projects in areas of crucial scientific inquiry.

For example, the George Washington University Medical Center houses the East Coast AIDS and Cancer Specimen Bank, a biorepository established by the National Cancer Institute in 1994 as part of the national AIDS and Cancer Specimen Resource. Its goal is to collect, preserve, and maintain for national research a comprehensive, confidential, state-of-the-art bank of malignant

and other specimens and clinical data from HIV-infected individuals. As other examples, Amici Emory University and the University of Michigan maintain an Alzheimer’s Disease Center funded by the National Institute on Aging. Each Center is a brain tissue bank that provides tissue samples and related data for Alzheimer’s researchers nationwide.

Amici’s ability to conduct important biomedical research—which has already produced remarkable advances and holds the promise of immeasurable benefit for mankind—would be profoundly hampered by the unprecedented rule that Appellants urge the Court to adopt. As the District Court recognized, “[m]edical research can only advance if access to these materials to the scientific community is not thwarted by private agendas,” and public policy requires that these materials not become “chattel going to the highest bidder.” Dist. Ct. Op. 27.

The Institutional Amici are joined in this brief by the Association Amici, which support and foster the biomedical research their members conduct. The American Council on Education, founded in 1918, is the major coordinating body for the Nation’s higher education institutions. It seeks to provide leadership and a unifying voice on key higher education issues and to influence public policy through advocacy, research, and program initiatives. The Association of American Universities was founded in 1900 to advance the international standing of American research universities. It focuses on issues of importance to research-

intensive universities. The Association of American Medical Colleges includes as members all 125 accredited United States medical schools, the 17 accredited Canadian medical schools, approximately 400 teaching hospitals and health systems, 94 academic and professional societies representing 109,000 faculty members, and the Nation's 64,000 medical students and 104,000 medical residents. Founded in 1876, it assists its members in medical research, medical education, patient care and community service.

Amici submit that affirmance of the District Court judgment will protect the integrity and utility of biorepositories for the academic medical community. It will also, in turn, protect the progress and promise of medical research. By contrast, the ruling that Appellants seek would be an unprecedented judicial intrusion on the delicate balance that Federal policy has struck between protection of research participants and the enormous human benefits of biomedical research.

Amici respectfully request that this Court affirm the decision of the District Court.

SUMMARY OF ARGUMENT

Appellants ask this Court to create a new rule of property law that would permit donors of human biological materials for research to exercise perpetual ownership rights over the materials—including an open-ended right to

direct transfer at the donor's discretion—where the donors never reserved such rights and the University never granted them. As shown in Washington University's brief, such a rule is not supportable as a matter of law or on the evidence in this case. As leading practitioners of biomedical research, Amici know that adoption of Appellants' unprecedented proposal would imperil crucial pending and future scientific research.

Biorepositories represent a well-established and scientifically promising resource for research. Today, research using human specimens is indispensable; cutting edge work for human well-being depends on it. Academic institutions safeguard biorepositories for the scientific community, using a peer review process to determine the best scientific use of stored specimens and promoting shared access among collaborating institutions. Federal policy strongly supports biospecimen research and the peer-review system.

Appellants' proposed rule would severely impede vital research using biospecimens. Permitting donors to transfer their biological samples while studies are ongoing would skew or invalidate research results. In addition, Appellants' proposal would introduce confusion among researchers about the continuing availability of specimens, create disincentives for institutions to establish and maintain biorepositories, and promote morally dubious practices, such as luring donors to transfer samples based on promises of cash or cures.

Further, Appellants' proposed ownership rule is unneeded because a comprehensive Federal regulatory policy already protects the interests of specimen donors and other research participants. The Common Rule ensures that covered human subjects research at academic institutions is subject to an assurance of compliance, Institutional Review Board ("IRB") review, informed consent, and ongoing oversight by the Department of Health and Human Services ("HHS") and other Federal agencies. Nothing in the Common Rule assigns property rights to research participants. Instead, Congress and the Federal agencies adopted an approach that regulates the use of donated specimens. The ruling that Appellants seek would wreck the delicate balance that Federal policy has struck.

Appellants rely on two regulatory provisions, but neither establishes the ownership or transfer rights that Appellants seek. First, they cite a regulation that permits research participants to discontinue participation in research; but that provision does not address ownership or transfer. Rather, Federal guidance establishes that where a specimen donor wishes to discontinue participation, a biorepository may either destroy or de-identify the donor's specimen; it need not return or transfer it. Second, Appellants rely on a provision that prohibits "exculpatory language" in research consent forms. That provision, however, addresses waiver of claims and rights a research participant already has; it does not create substantive property rights in donated research samples.

The judgment below should be affirmed.

ARGUMENT

I. **PERMITTING RESEARCH PARTICIPANTS TO EXERCISE PERPETUAL OWNERSHIP RIGHTS IN THEIR DONATED BIOLOGICAL MATERIALS WOULD HAVE PROFOUNDLY HARMFUL CONSEQUENCES FOR BIOMEDICAL RESEARCH.**

A. **Research Using Human Biospecimens Is A National Imperative.**

The fruits of research using human biological materials include landmark health discoveries of our time. Thanks to such research we know, for example, of the links between smoking and lung disease, atherosclerosis and diet and exercise, the pregnancy drug DES and tumors in children, and certain environmental substances and cancer. See National Bioethics Advisory Commission, Research Involving Human Biological Materials: Ethical Issues and Policy Guidance Vol. I (“NBAC 1999 Guidance”) at 19 (Aug. 1999). As the District Court in this case recognized, the rule that Appellants advocate would threaten future research, to the detriment of mankind.

The practice of collecting, storing, and conducting research using donated biological materials is a deeply established and broadly accepted method of medical discovery. “Human tissue has been collected and stored at institutions in the United States for more than 100 years.” RAND Corporation, Case Studies of Existing Human Tissue Repositories: “Best Practices” for a Biospecimen Resource for the Genomic and Proteomic Era (“RAND Corp. Report”) iii (2003).

Today, biospecimen research is indispensable. As of 1999, an estimated 307 million tissue specimens were being stored in the United States, growing at more than 20 million per year. Id. at 1. The “pathology departments at academic medical centers and community hospitals collectively constitute the largest and some of the oldest stores of biospecimens in the United States, with some specimens more than a century old.” Id. at 2.

“The collection and storage of human biological samples has become integral to clinical research.” D. Wendler, “One-Time General Consent for Research on Biological Samples,” 166 *Arch. Intern. Med.* 1449, 1449 (2006). Tissue banks and repositories “have enormous potential” to advance medical knowledge. Id. Researchers use specimens to explore prevention, detection and treatment of breast, ovarian, prostate, gastrointestinal, brain, skin, and neck cancers, blood disorders, lung diseases, diseases of the cardiovascular system, and lymphoma, to name just a few. RAND Corp. Report 13-21. Federal policy justifiably prizes this essential source of knowledge for human well-being. The National Institutes of Health (“NIH”) is the largest funding source for U.S. tissue repositories. The National Cancer Institute (“NCI”) alone has invested more than \$50 million annually in biorepository programs supporting four million human specimens. NCI, NIH & HHS, First-Generation Guidelines for NCI-Supported Biorepositories, 71 *Fed. Reg.* 25184, 25184 (Apr. 28, 2006) (herein, “NCI

Guidelines”). As HHS, NIH and NCI have found, “biorepositories serve as critical resources to the research community * * * .” Id.

B. The Threat Of Research Participants Transferring Their Donated Samples Among Studies, Investigators And Institutions Would Impede Crucial Biomedical Research.

Appellants ask this Court to create for research participants a perpetual right to own and to direct the transfer of previously donated specimens. Adoption of such a rule would threaten the availability and utility of crucial research resources in the Nation’s biorepositories.

1. Institutional biorepository ownership promotes scientific collaboration.

The prevailing system of biorepositories in the United States—in which individuals voluntarily provide informed consent to donate biospecimens, and recipient institutions exercise ownership and stewardship of the donated samples—has enabled research collaboration and spurred medical progress for over half a century. Biorepository contents are generally available to collaborating researchers at other institutions under a peer-review system. See, e.g., NCI Guidelines, 71 Fed. Reg. at 25195 (stating that all 125 NCI-supported biorepositories should rely on a peer-review system and should grant access based on scientific merit). For example, working with twelve academic medical centers, NCI has established breast and colon cancer family registries. The biospecimens and related data that these institutions collect “are available to the scientific

community at large through a process predicated on the establishment of collaborative studies that are subject to external peer review.” NCI, Cancer Family Registries, Mission Statement Overview.

Recognizing that an institution owns a biorepository thus does not mean that the materials are monopolized for its own use. To the contrary, academic research institutions are well situated to make biospecimens available for collaborative research and to assure the best scientific use of the materials. In this case, the record shows that Washington University uses a Peer Review Panel to consider requests for use of biorepository samples from researchers at the University and at other institutions, and that the University has widely shared the materials in its biorepository. The record contains eight material transfer agreements and cites Washington University’s attempt to share its materials with NCI (before Dr. Catalona blocked the effort). See Br. of Washington University at 11.

2. Appellants’ proposal would skew research results.

Research using biological materials often depends on continued availability of the same set of samples over time, to ensure that studies can be completed and results are valid. This is especially important in the longitudinal and long-term studies on which much important health science is based. See NBAC 1999 Guidance, supra, at 20-21; E. Eiseman & S. Haga, The Handbook of

Human Tissue Resources, Chapter 5, “Tissue Collections Created from Longitudinal and Individual Research Studies,” RAND Corporation Monograph Report (2000); see, e.g., S. Khosla, et al., “Incidence of Childhood Distal Forearm Fractures Over 30 Years,” 290 *Journal of the Am. Med. Ass’n* 1479 (2003) (research study based on data sets from 1969-1971, 1979-1981, 1989-1991, and 1999-2001). These studies would be impossible or severely compromised if donors were empowered to invoke an ownership right—years after donation—to order the transfer of their samples. The resulting shifts in data sets would distort the validity of, for example, longitudinal studies involving sample collection and long-term follow-up.¹

Transfer of samples can introduce systemic, sample, or selection bias in data sets. Such statistical bias—studying subjects not representative of a population—arises if the samples that remain in a study systematically differ from those transferred out. For example, if female donors are induced to transfer their samples from a study on malignant liver tissue to a study on the link between liver and breast cancers, the results of the first study may be gender-biased. Statistical

¹ For an example of a study based on long-term follow-up of research participants, see R. Kyle, et al., “A Long-Term Study of Prognosis in Monoclonal Gammopathy of Undetermined Significance,” 346 *New Eng. J. of Med.* 564 (2002) (research study, exploring how a disease progresses and what are valid predictors of outcomes, followed individuals with the disease from 1960-1994 and drew conclusions based on the disease state at 10, 20, and 25 years post-diagnosis).

bias can skew study outcomes, making research results less useful or even invalid. See, e.g., S. Jacobsen, et al., “Potential Effect of Authorization Bias on Medical Record Research,” 74 Mayo Clin. Proc. 330 (1999).

Although existing Federal rules allow specimen donors to discontinue participation in such studies, see infra 27-29, the historical incidence of such requests has been low. Adoption of the Appellants’ proposed perpetual ownership rule would dramatically change the incentive structure. It would give research institutions and commercially owned tissue banks enormous incentives to seek authorization for valuable biospecimens to be transferred to them. See infra 15-17. The resulting movement of samples would threaten the integrity of research studies, and in some cases would make it impossible to complete the study.

3. Appellants’ proposal is unworkable.

The ownership rule that Appellants propose is unworkable. See Greenberg v. Miami Children’s Hosp. Research Inst., Inc., 264 F. Supp. 2d 1064, 1070-71 (S.D. Fla. 2003) (noting that it would be “unworkable” and “chill medical research” to allow individual donors “to dictate how medical research progresses”). Allowing donors to dictate transfer of their samples would greatly confuse the question of stewardship over biospecimens and would threaten to disrupt collaboration among researchers and across institutions.

A collaborating institution would have no way of knowing whether specimens provided by another institution's biorepository might imminently be "recalled" by the donor. Clear property rights are the bedrock of any efficient system of exchange, including collaborative research. For that reason, in 1995 NIH promulgated the Uniform Biological Material Transfer Agreement (UBMTA), which clarifies those circumstances in which the provider, and those in which the recipient, of biomaterials retains ownership. Over 290 institutions have signed this Agreement. See Association of University Technology Managers, Signatories to the March 8, 1995, Master UBMTA Agreement. Appellants' proposed rule would sow uncertainty, directly undercutting Federal policy that aims to promote collaboration and scientific progress by enabling unambiguous transfer of rights in biological materials.

In addition, administering the flood of transfer requests that would come if donors were induced to shift their samples between biorepositories would be extraordinarily burdensome. Honoring such requests would be infeasible in many cases. Since many participants donate multiple tissue samples, or diseased tissue in conjunction with non-diseased matching tissue, a heavy burden would fall on the biorepository to determine which samples (or portions of samples), and what accompanying data or records, to transfer. And for samples that have been

de-identified in accordance with Federal regulations, a transfer request would be impossible to honor.

4. Appellants' proposal would eliminate incentives to build scientifically valuable biorepositories.

The ownership rule that Appellants propose would create disincentives for investment in biorepositories. Building a biorepository entails considerable capital outlays, including significant costs to collect, store, maintain, and retrieve tissue samples. RAND Corp. Report 36-37. A substantial staff must be employed. For example, one of Amici's biorepositories—the University of Pittsburgh Health Sciences Tissue Bank—employs a medical director, a laboratory manager, seven tissue bankers, three cancer registrars, two laboratory technicians, two cancer biomarker technicians, a medical fellow, a director of Oncology and Pathology Informatics, a director of Research Informatics and a team of bioinformaticians. Id. at 38. A staff of 75 runs the National Pathology Repository of the Armed Forces Institute of Pathology, the Nation's largest biorepository, which contains over three million disease specimens and accompanying case histories dating back over 150 years. See id. at 17, 38. A significant portion of the Institute's \$100 million annual budget supports the repository. See GAO Report 05-615, "Armed Forces Institute of Pathology," at 6, 8 (June 2005).

Biorepositories incur substantial costs for specimen processing, quality control testing, auditing, verification of tissue morphology and

characteristics, collection of basic pathology data about each specimen, standardization, electronic tracking systems, longitudinal data collection, database maintenance, shipment of specimens from collection sites to the repository and from the repository to researchers, training collection personnel, and developing standard protocols for them to follow. See RAND Corp. Report 39-59, 78-83 (describing best practices related to each of these aspects of maintaining a biorepository); American Society for Investigative Pathology, International Society for Biological and Environmental Repositories, Best Practices for Repositories I: Collection, Storage, and Retrieval of Human Biological Materials for Research, 3 Cell Preservation Tech. 5, 12-43 (Mar. 2005) (same). Research institutions would be discouraged from making these substantial investments if the samples they collect and maintain could be transferred at the whim of research participants. See Moore v. Regents of Univ. of California, 51 Cal.3d 120, 146, 793 P.2d 479, 496 (1990) (finding that recognition of a continuing ownership interest in donated cells would give donors a “ticket in a litigation lottery” and would reduce institutional investment because of the “uncertainty” as to whether clear title exists).

In addition, tissue donors are willing to provide samples for research because they believe that they are contributing to a collection of samples that will be used productively. Uncertainty about whether a biorepository will remain intact

in the future, and whether studies using that biorepository can be completed, would undoubtedly dissuade many would-be donors from providing tissue samples.

5. Appellants' proposal would promote morally dubious practices.

Appellants' proposed rule would produce morally dubious results.

Research participants could expect to be solicited, with false or misleading promises about therapeutic benefits, or cash rewards, in exchange for authorization to transfer their samples. Many donors who suffer from serious and debilitating diseases are vulnerable to suggestions that, for example, a researcher is on the verge of a breakthrough discovery. The prospect of competition, or a cash market, for donated specimens is anathema to scientific research norms. Where, as here, the interested researcher is also a treating physician, and the transfer of specimens is linked to donors' therapeutic care, the inducement to transfer can be particularly coercive. See 45 C.F.R. § 46.116(a)(8) (requiring research participants to be informed that non-participation "will involve no penalty or loss of benefits to which the subject is otherwise entitled").

Other troubling consequences are predictable. Some donors may seek to control the research itself, by threatening to send their tissue elsewhere if their demands are not met. See, e.g., T. Ashburn, "Human Tissue Research in the Genomic Era of Medicine," 160 *Archives of Internal Medicine* 3377, 3380 (Dec. 11, 2000). In addition, research participants could demand (additional)

compensation from a repository for the right to continue using their samples, potentially resulting in bidding for specimens, or could place unreasonable or counter-scientific limitations on the continued use of samples. Scientifically rich research resources currently stored at academic institutions—and available to the academic research community through peer-review access—could be lost if individuals were empowered to direct transfer of specimens to private, commercially owned tissue banks.²

Appellants' proposal thus would threaten the progress of biospecimen research at a time when this mode of discovery is increasingly vital. In addition, as shown below, their proposal is unnecessary and contrary to the comprehensive Federal policy already in place to protect the interests of specimen donors and other research participants.

II. A PERPETUAL-OWNERSHIP RULE IS NOT NEEDED TO PROTECT RESEARCH PARTICIPANTS AND WOULD DISRUPT THE EXISTING COMPREHENSIVE FEDERAL HUMAN RESEARCH PROTECTION POLICY.

Appellants argue that a perpetual-ownership rule is needed to protect research participants from unauthorized and unethical use of donated biological materials. They raise the specter, absent such a rule, of research institutions having

² Transfer to commercially owned tissue banks also would have the troubling consequence of removing these materials from the reach of the Common Rule, which does not apply to non-Federally funded research. See 45 C.F.R. § 46.101.

unfettered discretion to perform morally objectionable experiments or breaching donors' confidentiality. However, despite the fact that no court or Federal agency has adopted Appellants' proposal, Appellants cite no example of the abuses they imagine may occur. Their extreme remedy—inventing ownership and transfer rights—is unnecessary, because research institutions are already subject to strict accountability under a comprehensive Federal regulatory policy characterized by multiple layers of oversight.

A. Congressionally Authorized Federal Policy Strikes A Delicate Balance That Protects Research Participants And Promotes Medical Research.

The rule Appellants seek would disrupt the careful balance struck in the Federal Policy for the Protection of Human Subjects, generally referred to as the Common Rule, which 17 Federal agencies have adopted. See 45 C.F.R. Part 46 (the Common Rule); see also 21 C.F.R. Parts 50 and 56 (U.S. Food and Drug Administration regulations on protection of human subjects).³ Notably, the Common Rule says nothing about continuing ownership rights of research participants and provides no basis for the asserted right to direct transfer of previously donated tissue samples. Rather, it provides multiple levels of protection

³ For a list of the Federal agencies that have adopted the Common Rule, see Office for Human Research Protections, IRB Guidebook, Chapter II, Part A.

for research participants by regulating how institutions may use donated tissues, thus taking into account donors' interests and advancement of medical research.

1. Assurance of compliance.

Institutions that receive Public Health Service (including NIH) funds to conduct human subjects research must file an assurance of compliance with HHS. 45 C.F.R. § 46.103. This Assurance certifies that the institution complies with the Common Rule and with ethical principles. See Federalwide Assurance (FWA) for the Protection of Human Subjects for Institutions Within the United States. Although not required, many research institutions also voluntarily certify compliance with the Common Rule in all human subjects research they conduct, whether or not Federally funded. See, e.g., Stanford University, Federalwide Assurance of Protection for Human Subjects; University of Michigan, Federalwide Assurance of Protection for Human Subjects. In addition, institutions that file an FWA must certify that all human subjects research will be conducted in accord with the seminal ethical document known as the Belmont Report or an analogous set of ethical standards.⁴

⁴ The Belmont Report was issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1979. See HHS, OHRP, Policy Guidance, "The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research."

2. Institutional Review Boards.

The Common Rule provides that no covered human subjects research may be conducted without review and approval by an authorized Institutional Review Board. IRBs are responsible for safeguarding research participants' welfare and ensuring compliance with regulations. See 45 C.F.R. § 46.109. They must follow specified procedures and assess research protocols against a yardstick of rigorous standards before approving research. No human subjects research may commence until the IRB has conducted initial review and given its approval. After a study commences, the IRB must re-review it at least annually. Id. §§ 46.109(e), 46.111(a)(6). The Common Rule prescribes the qualifications of IRB members (id. § 46.107), standards for approval of research (id. § 46.111), and IRB authority to suspend or terminate research (id. § 46.113) and to ensure that informed consent requirements are met (id. §§ 46.116, 46.117). Heightened standards govern IRB review of studies involving groups such as pregnant women, prisoners or children. 45 C.F.R. Part 46, Subparts B, C and D.⁵ While IRBs include institutional

⁵ In addition to the Federal regulations, additional layers of oversight help ensure that IRB decisions are made appropriately and objectively. For example, there are certification programs for IRB members, and accreditation for human research protection programs. See National Bioethics Advisory Commission, "Methods for Ensuring Protection: Education, Certification, and Accreditation," Ethical and Policy Issues in Research Involving Human Participants, Vol. I 48-50 (2001); see also, e.g., Association for the Accreditation of Human Research Protection Programs, "Accreditation Standards"; Public Responsibility in Medicine and Research, Council for Certification of IRB Professionals, "Certification."

scientists and ethicists, they must also include unaffiliated community members.

Id. § 46.107. An IRB decision to disapprove research cannot be overridden by the institution. See id. § 46.112.

The requirement of IRB approval and ongoing review provides robust protection for donors of research samples. See id. §§ 46.102, 46.109; see generally E. Heath, “The History, Function, and Future of Independent Institutional Review Boards,” published in National Bioethics Advisory Commission, Ethical and Policy Issues in Research Involving Human Participants, Vol. II (2001). In addition, even secondary uses of samples are generally subject to IRB review if they are identifiable (i.e., the researcher is able to discover the identity of a sample’s donor) or the research involves more than minimal risk to the donor. See 45 C.F.R. § 46.102(f).

3. Informed consent.

Human subjects research generally may not be conducted without participants’ informed consent. 45 C.F.R. § 46.116. In the context of donation of research samples, the informed consent process ensures that those choosing to provide biological materials for scientific research do so voluntarily and with full information about the risks and benefits of the research. Informed consent must comply with detailed requirements set out in 45 C.F.R. § 46.116, and the IRB must review the proposed consent process and consent document to ensure compliance

with regulatory and ethical standards. Before consenting, research participants must be provided an explanation and description of: the purposes of the research, procedures, risks and benefits, extent of any confidentiality protections, whether any compensation is involved (for research involving more than minimal risk), whom to contact with questions about the research or the research participant's rights and the voluntary nature of participation. Id. § 46.116(a)(1)-(8); see also NBAC 1999 Guidance, supra, at 48 (describing elements of informed consent). Informed consent must be documented on an IRB-approved form that meets substantive standards set forth in 45 C.F.R. § 46.116.

4. Federal agency oversight.

Human subjects research at academic institutions is subject to oversight vested in several agencies. The Office for Human Research Protections (“OHRP”) is authorized to exercise an array of enforcement powers, including investigations of written complaints and not-for-cause investigations. See HHS, OHRP, “OHRP’s Compliance Oversight Procedures for Evaluating Institutions” 1-5 (Oct. 19, 2005); see also National Bioethics Advisory Commission, Ethical and Policy Issues in Research Involving Human Participants, 54-56 (2001) (summarizing major OPRR Compliance Oversight Investigations of research institutions from January 1990-June 2000).

If an OHRP investigation finds noncompliance, OHRP has authority to impose a wide range of sanctions, including requiring corrective action, special reporting to OHRP, training of IRB members, prior OHRP review of research projects, suspending research projects, recommending that HHS temporarily or permanently remove investigators or institutions from specific studies or from all HHS-supported research, recommending that HHS scientific-peer-review groups be notified of past noncompliance issues prior to approval of any new projects and recommending that institutions or investigators be debarred from all government funded studies. See HHS, OHRP, “OHRP’s Compliance Oversight Procedures for Evaluating Institutions,” supra, 5-7.

In addition to OHRP oversight, other Federal regulations and guidelines protect specimen donors’ confidentiality and welfare. For example, the FDA has its own set of regulations that closely track the Common Rule in most respects, including the requirements of IRB approval and informed consent. See generally 21 C.F.R. Parts 50 and 56. Institutions and investigators that conduct clinical investigations are subject to inspections and enforcement by the FDA to ensure compliance with those regulations. See, e.g., FDA, Office of Regulatory Affairs, Bioresearch Monitoring Program Coordination, Background (describing

Bioresearch Monitoring Program that “provide[s] for protection of the rights and welfare of the thousands of human subjects involved in FDA regulated research”).⁶

The Health Insurance Portability and Accountability Act (“HIPAA”) further protects privacy and confidentiality of tissue donors’ health information. The HIPAA Privacy Rule generally requires a covered entity to obtain the donor’s written authorization to use or transfer identifiable samples. 45 C.F.R. Parts 160 and 164. Like the Common Rule, however, HIPAA does not give the donor any ownership right in the sample. And notably, if the sample becomes de-identified in accordance with HIPAA standards, the donor has no remaining HIPAA rights at all with respect to the sample. See 45 C.F.R. § 160.103 (protected health information is limited to individually identifiable information).

Finally, biorepositories supported by NCI are subject to additional, specific guidelines. NCI guidelines include standards on, for example, maintaining

⁶ FDA recently issued a Guidance document explaining its current stance on balancing public health and privacy risks for studies involving investigational use of leftover biospecimens that were previously collected for other research purposes and are not individually identifiable. See FDA, Guidance for Sponsors, Institutional Review Boards, Clinical Investigators and FDA Staff, “Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable” (Apr. 25, 2006). In this Guidance, FDA clarified that leftover biospecimens previously collected for other purposes may be used for investigational purposes without additional informed consent so long as the biospecimens are not identifiable. Id. at 7.

confidentiality, informed consent and requests to discontinue participation. See NCI Guidelines, 71 Fed. Reg. at 25194, 25194-96.

B. Appellants' Proposed Rule Would Disrupt Federal Policy.

Appellants suggest that if research participants are not given perpetual rights to own and transfer their research samples, research institutions will have unfettered discretion to misuse those samples. However, the stringent limits on human subjects research imposed by Federal regulations demonstrate that Appellants' concerns are unfounded.

The Common Rule protects donors of research samples in at least three specific ways. First, donors can decline to provide informed consent for donation of a research sample; participation is thus truly voluntary. Second, later research using identifiable samples is subject to IRB approval and agency oversight. And third, regulations allow research participants to discontinue participation in research, which means that the biospecimen would either be destroyed or de-identified (depending on which method the institution chooses). See, e.g., NCI Guidelines, 71 Fed. Reg. at 25194.

To be sure, the Common Rule permits research using previously collected specimens without additional informed consent in three specific circumstances, where: (1) no identifiable private information nor intervention with a human subject is involved (45 C.F.R. § 46.102(f)); (2) the research involves

“collection or study of * * * pathological specimens, or diagnostic specimens, * * * 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” (id. § 46.101(b)(4)); or (3) the IRB waives informed consent after determining that the research involves minimal risk, subjects’ welfare will not be adversely affected and informed consent is not practicable (id. § 46.116(d)). These provisions represent the Federal agencies’ judgment regarding the appropriate balance between the important interests of informed consent and permitting biomedical research to be conducted without inappropriate impediment.

Appellants ask this Court to find that the Federal agencies struck this balance incorrectly—but it is not up to the Court to rewrite the Federal regulations. Such a substantial departure from the current regulatory framework is not needed and, if it were, should be effected through the regulatory or legislative process—not by judicial fiat. If an adjustment were needed to recalibrate the balance between human subjects protection and the interests of conducting biomedical research, HHS has the authority to promulgate new substantive regulations, and has done so in the past. For example, in 1991, HHS adopted additional protections in research involving children. See 45 C.F.R. Part 46, Subpart D. Or, if HHS failed to act, Congress could step in, as it has in the past, to recalibrate the delicate balance of interests and rights struck in the regulations. See, e.g., 42 U.S.C.

§ 289(b)(1) (requiring HHS to establish a program to provide guidance on ethical issues in human subjects research).

C. The Regulatory Provision On Discontinuing Participation In Research Does Not Create A Right To Direct The Transfer Of Previously Donated Research Samples.

Appellants cite a Common Rule provision requiring informed consent documents to state that “the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.” 45 C.F.R. § 46.116(a)(8). Appellants’ attempt to distort this provision into an ownership right in previously donated tissue is unavailing.

First, nothing in this regulatory language suggests a right of transfer or ownership. The provision speaks only of discontinuing participation.⁷ Second, Federal guidelines for biorepositories hold that discontinuing participation requires only that identifiable biospecimens be destroyed or de-identified. NCI Guidelines, 71 Fed. Reg. at 25194. Third, the clear purpose of the regulatory language—to preserve an individual’s autonomy and avoid coercing participation in research—is

⁷ In the vast majority of human subjects research projects, the right to discontinue participation means that a research participant can discontinue the “intervention or interaction” with researchers or sharing of personal and private information that constitute human subjects research. See 45 C.F.R. § 46.102(f). It has nothing to do with property rights.

not advanced by the right Appellants assert here—an alleged ownership right to transfer their tissue samples from one biorepository to another.⁸

Appellants suggest that the right to discontinue participation casts doubt on whether research institutions have any ownership rights over research specimens. That is incorrect. Appellants are conflating an individual’s right to autonomy in deciding whether to participate in a research project with a continuing property right in physical specimens that were previously donated. The fact that Federal regulations allow donors a limited right to authorize certain uses of confidential information does not mean that the donor “owns” the tangible specimen.

Examples from other contexts show that the use of personal property may be regulated, including requiring authorization to use or disclose personal information, without divesting the institutional owner of its ownership interest. For instance, although HIPAA requires hospitals to obtain patients’ permission to

⁸ The right to discontinue participation in research applies only to personally identifiable biological material. See HHS, OHRP, “Guidance on Research Involving Coded Private Information or Biological Specimens” 3 (Aug. 10, 2004); see also id. at 5 (“If the investigators are not obtaining either data through intervention or interaction with living individuals, or identifiable private information, then the research activity does not involve human subjects.”). If the right to discontinue participation were any sort of property right in donated biological material, it would apply to all such material—including material that had been de-identified. That the right to discontinue participation applies only to personally identifiable material confirms the error of Appellants’ property rights argument.

use or disclose personal health information, the hospital nonetheless owns the records. See P. Stearns, Access to and Cost of Reproduction of Patient Medical Records: A Comparison of State Laws, 21 J. Legal Med. 79, 98-99 (2000) (citing state laws codifying “the ownership of patient medical records as being the property of the hospital or health care provider”). Similar restrictions on use arise in many other contexts, without affecting property rights. See, e.g., 20 U.S.C. § 1232g(b), (d) (giving students and parents a right to block disclosure of school records although the school continues to own such records). As in those contexts, an institution may own certain materials (here, research specimens) even though an individual retains specific rights over their use.

D. The District Court Correctly Found The Regulatory Prohibition Against “Exculpatory Language” In Informed Consent Documents Not Pertinent To This Case.

The Common Rule protects research subjects against coercion and “undue influence” in recruitment into research studies. It provides: “No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject’s legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.” 45 C.F.R. § 46.116. Appellants argue that this provision negates language in certain consent forms used by Washington University and, in effect, barred the research

participants from “waiving” their claimed right to continuing ownership of their donated samples. Appellants greatly distort this provision’s meaning.

First, and most obviously, the regulation’s reference to exculpatory language does not assign ownership rights to the donor. Indeed, it does not assign any rights. It only prohibits the consent document from making the donor waive whatever rights he already has. Thus, the issue in this case—who owns the tangible research samples—is simply not addressed. The cited provision would be pertinent only if the Court decided that the research participants continued to own their samples after they donated them to Washington University. If the Court agrees with the District Court that the ordinary state-law rules apply to vest ownership in the University, then the research participants waived no ownership right, because they had no such right.

This is evident from the plain meaning of the regulatory provision at issue. “Exculpatory” means “[c]learing or tending to clear from alleged fault or guilt; excusing.” Black’s Law Dictionary 566 (6th ed. 1990). By advising research participants that they no longer had ownership rights in their samples after they conveyed them, Washington University was not clearing itself from alleged fault or guilt; it was stating its understanding of the law—an understanding that was upheld by the District Court. Nor has the University ever relied on the cited informed consent language to assert that Appellants Ward *et al.* waived any claim

in this case. Further, Appellants' argument conflicts with the plain meaning of "waive". One can only "waive" rights one otherwise would have absent waiver. As the District Court properly found, under state law the research participants had no continuing ownership right in the samples they freely donated to Washington University. If this Court were to disagree with the District Court, it would need to find a substantive ownership right; any invalid "waiver" could not itself be the basis for the claimed underlying right.

The clause in question is similar to other language in consent documents that advises research participants of what rights they do and do not have. The regulations expressly permit such statements, and in some instances require them. For example, a consent document may advise that a research participant will not receive free treatment for injuries resulting from the research. See 45 C.F.R. § 46.116(a)(6) (requiring "an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs"). Such statements serve the important function of informing research participants of those rights and benefits they are, and those they are not, acquiring by signing up for research. This type of clarification is fully consistent with regulations and helps participants make fully informed choices about whether to participate in a research study.

Appellants Ward et al.'s reliance on a 1996 Cooperative Oncology Group Chairpersons Meeting document, posted on the OHRP website and cited in two OHRP enforcement letters, is unavailing.⁹ That document does not purport to assign continuing property rights in anything to anyone. Instead, it cites—as an example of what OHRP's predecessor agency thought was prohibited “exculpatory language”—words that make a participant, as a condition of participating in research, “give up any property rights I may have” in collected biological samples.” Cooperative Oncology Group Chairpersons Meeting, November 15, 1996, “Exculpatory Language” in Informed Consent. At most, this document suggests that if a participant otherwise retained property rights in his tissue samples (for example, by operation of a state statute), he could not be made to waive such rights as a condition of participation in the research.¹⁰ The 1996

⁹ The amicus brief filed by the People's Medical Society notes that some university policies, such as Amicus Stanford University's, cite the 1996 document's examples of exculpatory language. Amicus Br. of People's Med. Soc'y 20 n.12. As the Stanford policy explains, these examples are “taken from a document on exculpatory language * * * included on the OHRP website.” Stanford University IRB Guidance, “Basic Research Consent Requirements.” That a university seeks to ensure consistency with OHRP guidance does not imbue research participants with ownership rights. It is the policy of all of the Institutional Amici that tissue provided for research is the property of the institution. Because this is a straightforward issue under state law, there is no need for a waiver of property rights in the informed consent document; once the tissue is provided, the research participant has no ownership right to waive.

¹⁰ Even if OHRP took the view that 45 C.F.R. § 46.116 gives research participants ownership rights—and it has not done so—such a departure from the

document does not address the question of what property rights the participant has, nor does it suggest that ordinary state-law personal property rules must be suspended.

CONCLUSION

For the foregoing reasons and the reasons in Washington University's brief, the decision of the District Court should be affirmed.

Respectfully submitted,

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plain language of the regulation would be entitled to no deference. Here, there has never been any contention—nor could there be—that 45 C.F.R. § 46.116 is ambiguous on the claimed point. The meaning of the regulation is plain on its face: the informed consent document may not waive any legal rights that the subject has nor may it release those involved in the study from negligence claims. The 1996 document does not imbue research participants with ownership rights. See Glover v. Standard Fed. Bank, 283 F.3d 953, 962 (8th Cir. 2002) (agency policy statements are entitled to deference only when the regulation being interpreted is ambiguous).

CERTIFICATE OF COMPLIANCE

Pursuant to Fed. R. App. P. 29(d), the attached Brief for Amici Curiae Cornell University, Duke University, Emory University, the George Washington University, Johns Hopkins University, Mayo Clinic, the Board of Trustees of the Leland Stanford Junior University, the University of Michigan, the University of Minnesota, the University of Pittsburgh, the University of Rochester, American Council on Education, Association of American Medical Colleges and Association of American Universities in Support of Plaintiff-Appellee and Affirmance is proportionally spaced, has a typeface of 14 point and contains 6961 words according to the word count function of Microsoft Word 2003.

Alexander E. Dreier

CERTIFICATE OF SERVICE

I hereby certify that on this 31st day of August 2006, two copies of the foregoing Brief for Amici Curiae Cornell University, Duke University, Emory University, the George Washington University, Johns Hopkins University, Mayo Clinic, the Board of Trustees of the Leland Stanford Junior University, the University of Michigan, the University of Minnesota, the University of Pittsburgh, the University of Rochester, American Council on Education, Association of American Medical Colleges and Association of American Universities in Support of Plaintiff-Appellee and Affirmance were served by overnight delivery on the following:

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