

INTRODUCTION

The Past, Present, and Future of Informed Consent in Research and Translational Medicine

Susan M. Wolf, Ellen Wright Clayton and Frances Lawrenz

The last century has seen a remarkable evolution of the notion of informed consent, first in medical care, then in research, and now in the domain of translational science linking the two. Yet, a century after Justice Benjamin Cardozo's famous declaration in the *Schloendorff* case that a competent adult "has a right to determine what shall be done with his own body,"¹ enormous challenges remain, especially in research. Debate continues on the core purposes of informed consent,² how best to design and effectuate an informed consent process,³ how those processes should be tailored for vulnerable populations and challenging circumstances,⁴ the utility of alternatives such as broad consent (endorsed by the recent revision to the Common Rule) and innovations such as electronic consent,⁵ and when informed consent may be waived or avoided altogether.⁶ While these debates over research consent persist, new debates are emerging over how to design consent in fast-moving realms such as translational genomics,⁷ how to seek electronic consent by smartphone or computer in large population studies (such as the National Institutes of Health (NIH) "All of Us" Research Program⁸), and the role

of ongoing governance strategies in research projects and biobanks to supplement informed consent in protecting individual interests.

In this highly dynamic context, we convened a conference of national experts from multiple disciplines to pool insights on the past, present, and future of informed consent in research and translational medicine. Our goal was to look back on a century of law, ethics, and innovation in order to learn the lessons of the past. We aimed then to examine the pressing consent issues currently upon us as well as issues now emerging. Finally, we sought to look forward to the cutting-edge of innovation in informed consent and looming challenges. This critical examination of the past, present, and future yields new insights and fresh possibilities for the deeply challenging concept and practice of informed consent.

The Past

The very term "consent" reveals a built-in tension. Though an often-stated goal of informed consent is to effectuate the decision maker's autonomy and choice, the origins of the word suggest a different goal

Susan M. Wolf, J.D., is McKnight Presidential Professor of Law, Medicine & Public Policy; Faegre Baker Daniels Professor of Law; Professor of Medicine; and Chair of the Consortium on Law and Values in Health, Environment & the Life Sciences, University of Minnesota. She is a Principal Investigator (PI) on NIH/NHGRI/NCI grant 1R01HG008605 on "LawSeqSM: Building a Sound Legal Foundation for Translating Genomics into Clinical Application." She was also a PI on NIH/NCI/NHGRI grant 1R01CA154517 on return of genomic results to family members, including after the death of the proband. **Ellen Wright Clayton, M.D., J.D.**, is Craig-Weaver Professor of Pediatrics, Vanderbilt University Medical Center, and Professor of Law, Vanderbilt University. She is a Principal Investigator (PI) on NIH/NHGRI/NCI grant 1R01HG008605 on "LawSeqSM: Building a Sound Legal Foundation for Translating Genomics into Clinical Application." She is also PI on "GetPreCiSe: The Center for Genetic Privacy and Identity in Community Settings," an NIH-funded Center of Excellence in ELSI Research. **Frances Lawrenz, Ph.D.**, is Professor of Educational Psychology and Associate Vice President for Research at the University of Minnesota. Her research focuses on science and mathematics program evaluation, utilizing a variety of techniques and usually involving mixed methodologies. She is a Principal Investigator (PI) on NIH/NHGRI/NCI grant 1R01HG008605 on "LawSeqSM: Building a Sound Legal Foundation for Translating Genomics into Clinical Application."

— agreement with the person seeking the decision maker’s consent. Thus, the Latin source “consentire” means not to feel one’s own sentiment or choice, but to feel together (con- “together” and “sentire” feel).⁹ And the Latin term reaches us through the Old French “consentir” (meaning “agree” or “comply”).¹⁰

It is fitting, then, that the case most-cited in American law for the proposition that the patient’s consent is needed, is a case in which the patient’s failure to agree and comply was paternalistically overridden. In January of 1908, Mary Schloendorff arrived at New York Hospital complaining of a stomach disorder.¹¹ Physicians discovered a mass and proposed an examination under ether. Mrs. Schloendorff agreed to the ether examination, but insisted on no operation — no excision of any mass or tumor discovered. Surgeons proceeded with the examination, discovered a fibroid mass in her uterus, and performed a hysterectomy despite the patient’s refusal.

As the subsequent judicial opinion recounts, the consequences for Mrs. Schloendorff were horrific: “gangrene developed in her left arm, some of her fingers had to be amputated, and her sufferings were intense.” Not reflected in the court’s opinion is the full

would award damages and that the hospital could not be liable for the acts of physicians whom the court found to be independent contractors rather than hospital employees. Yet the notion that a layperson with no medical training — a patient burdened with pain and worry — was the ultimate decision maker, began to inscribe in American law the necessity of consent.

Jay Katz, the great analyst of the doctor-patient relationship, has written of the judicial silence that followed Cardozo’s declaration.¹³ It was not until the *Salgo* case in 1957 that courts again took up the project of elucidating the requirement of consent and its implication — that the patient needed to be told the information material to the decision.¹⁴ But all of this developing law was in the realm of clinical care. Professor Alexander Capron’s article in this issue argues that this important line of cases provides only part of the history of informed consent in research.¹⁵

He finds a second pivotal source in the Nazi physicians’ torture and killing of concentration camp victims in the name of medical experimentation. This atrocity led to the Medical Trial of those Nazi physicians at Nuremberg and pronouncement of the Nuremberg Code. The third equally pivotal source

That history illuminates current challenges. Five articles in this issue focus on a range of difficult challenges — creating a respectful and appropriate consent process in research with historically underrepresented and underserved minorities, exploitation in Phase I clinical trials, consent in pediatric oncology trials, and coping with issues of capacity and vulnerability.

extent of her suffering. Based on review of Mrs. Schloendorff’s testimony, Paul Lombardo relates more details.¹² Her cries of pain were so anguished that she was moved to the hospital basement. “My mouth was torn to pieces inside; ...I suffered with pains in my arm and hand, coldness and numbness in my left hand.” She was hospitalized for months, requiring a second operation on her hand due to an embolism resulting from the surgery.

Mrs. Schloendorff sued, complaining that the surgery was performed with no consent and, indeed, over her express refusal. It was in this context that Justice Benjamin Cardozo penned what has become the most famous line in health law jurisprudence: “Every human being of adult years and sound mind has a right to determine what shall be done with his own body...” This was dictum, as Mrs. Schloendorff lost her suit; the court ruled that the doctrine of charitable immunity shielded New York Hospital from a judgment that

derives from the racist horrors of the Tuskegee Syphilis Study, leading to the formulation of federal regulations that became the Common Rule.

Professor Capron argues that attention to all three sources of informed consent in research is crucial. He maintains that an overwhelming emphasis on regulatory requirements and compliance with the Common Rule threatens to obscure the full set of values that should be vindicated through informed consent, including human rights.

The Present

That history illuminates current challenges. Five articles in this issue focus on a range of difficult challenges — creating a respectful and appropriate consent process in research with historically underrepresented and underserved minorities, exploitation in Phase I clinical trials, consent in pediatric oncology trials, and coping with issues of capacity and vulnerability.

Professors Sarah Gehlert and Jessica Mozersky analyze the barriers to research participation facing members of racial and ethnic minorities, as well as individuals of low socioeconomic status and people of low educational attainment resulting in low literacy and numeracy.¹⁶ They analyze the vulnerability of these groups, their underrepresentation in research, and the harms that flow from their exclusion. The authors then turn to informed consent to examine techniques for increasing comprehension, trust, and uptake in vulnerable populations. They also critically examine newer models of informed consent, such as broad consent and models stressing governance, including the challenges these models pose for different groups.

Professor Neil Henderson zeroes in on the experience of Native American tribes with research involving human participants.¹⁷ He reflects on more than thirty years of research experience with tribal members. He argues that effective protection of research participants requires seeing such research as an inter-cultural process. Though tribal Institutional Review Boards (IRBs) are trained based on the *Belmont Report*, he argues that the document is a culturally specific one, taking an American approach to autonomy (for instance) that may not be shared by other societies, such as members of sovereign tribal nations. Professor Henderson illuminates the cultural conflict that may arise in research involving tribal members and what is required for a balanced and mutually respectful process.

Professors Matt Lamkin and Carl Elliott challenge traditional approaches to protecting human research participants that focus on securing voluntary consent by keeping financial compensation low to avoid undue inducement.¹⁸ The authors argue that avoiding exploitation actually requires higher compensation, health insurance and compensation for injuries resulting from the research, and ensuring conditions that are not degrading. Especially in Phase I clinical trials, whose purpose is to assess an intervention's safety in healthy volunteers, making sure that prospective research participants truly understand the risks and are treated with fairness and respect is essential.

Dr. Amy Porter and Professor Eric Kodish turn to pediatric trials involving children with cancer.¹⁹ They confront the question of what to do when families reveal use of chemical complementary medicines (including vitamins, herbs, and cannabis) along with the therapeutic agents being tested. Family candor during the medication-reconciliation process risks disqualifying the child from the research trial. The authors offer an analysis that balances the importance of data integrity with the welfare of the child, in an effort to harmonize the research commitment to generate knowledge for the benefit of future children with

the clinical commitment to serve the needs of the individual child facing cancer.

Professor Michelle Biros focuses on another set of issues at the intersection of research and clinical care — research on patient-participants lacking decisional capacity or otherwise vulnerable and not fully able to protect themselves.²⁰ These have long been recognized as difficult problems. However, effective strategies to assess capacity, evaluate vulnerability, and create adequate protections remain elusive. The author argues for a range of disclosure, consent, and assent procedures depending on capacity, vulnerability, and clinical circumstances.

Emerging Issues

Two articles face emerging issues in genomic research. Professor Wylie Burke and colleagues examine the limits of informed consent in translational genomic research.²¹ Such research increasingly includes return of individual genomic research results to participants and the long-term storage of data and specimens for future research uses. The authors argue that both of these features challenge traditional approaches to informed consent, because the range of potential results and range of future research uses cannot be fully predicted at the time of the initial informed consent. In addition, participants who enroll in the research are effectively agreeing to a series of decisions to be made by others on return of results and future research uses of data and specimens. The article urges reforms to the consent process that would make clear to prospective participants what governance process is proposed. In addition, the authors recommend strategies to ensure trustworthy governance and actively involve stakeholders.

Professor Susan Wolf and colleagues focus on return of results in genomic research, by addressing the often-neglected question of what to tell the participant's family members.²² Researchers may discover pathogenic and clinically actionable findings with potential health implications for relatives, including after the research participant's loss of decisional capacity or death. The authors previously published a consensus paper offering a detailed analysis and recommendations to guide the research team. In their new article, they offer practical tools to guide researchers facing this complex issue, including decision flow charts and template documents that researchers can customize. This toolkit can streamline the process of responsibly addressing the issue of return of results to relatives.

The Future

Finally, two articles look forward to the future of informed consent in research and translational medi-

cine. John Wilbanks, Chief Commons Officer at Sage Bionetworks and leader of the Consent to Research Project, is a pioneer who has worked to develop models of online informed consent now being used in Apple ResearchKit and the federal “All of Us” Research Program. He describes the process of developing a fully electronic informed consent process (often called “e-consent”) that is not dependent on personal interaction.²³ By showing how design choices incorporate ethical concerns, he reveals fundamentally new ways of thinking about consent and new options. He points to future possibilities, including the use of online gaming methods to create vivid and effective consent processes.

Professor Effy Vayena and Dr. Alessandro Blasimme address the evolving ecosystem of data collection and use.²⁴ They point to the growing integration of phenotypic, biological, and behavioral data in enormous data sets that may include information on location, purchasing, and social media. Analysis of these data may use opaque algorithms, neural networks, and artificial intelligence. This convergence of fast-evolving technologies defies conventional approaches to informed consent, which the authors find entirely inadequate to the challenges posed by this big data research. They argue for the necessity of oversight systems that themselves evolve. Looking across national borders and models of new governance, they propose development of a systemic oversight pipeline, whose features they outline.

Analyzing a Century of Innovation

This collection of articles, coming roughly a century after Justice Cardozo’s famous proclamation in *Schloendorff* of the individual’s right to decide the fate of her own body, traces an arc of innovation. We have progressed from the question of a patient’s right to refuse bodily invasion to defining the scope of a source individual’s authority over biospecimens and data that may be archived for use in complex research analyses long into the future. Verbal exchange and written consent are yielding to new models of online and electronic consent. And dyadic focus on the doctor and patient, and later the researcher and participant, are yielding to a more systemic and longitudinal vision of the research enterprise.

Throughout it all, the question remains how best to protect the role of choice, communicate the information essential to that choice, and embed choice in an oversight system designed to safeguard core values. In the real world of 21st-century research and translational science blending research and clinical care, the old definition of “consent” as agreement or compliance with another no longer suffices. Instead, choice based

in transparency, partnership, and shared governance is today’s challenge.

Acknowledgments

Preparation of this article and symposium was supported in part by the National Institutes of Health (NIH), National Human Genome Research Institute (NHGRI) and National Cancer Institute (NCI) grant 1R01HG008605 on “LawSeqSM: Building a Sound Legal Foundation for Translating Genomics into Clinical Application” (Susan M. Wolf, Ellen Wright Clayton, Frances Lawrenz, Principal Investigators). The contents of this article are solely the responsibility of the authors and do not necessarily represent the views of NIH, NHGRI, or NCI.

The articles in this symposium grow out of a conference on March 8, 2017, on “The Future of Informed Consent in Research and Translational Medicine: A Century of Law, Ethics & Innovation” and a conference the following day on “The Challenges of Informed Consent in Research with Children, Adolescents & Adults,” both held at the University of Minnesota. The first conference was sponsored by the University’s Consortium on Law and Values in Health, Environment & the Life Sciences and supported in part by NIH, NHGRI/NCI grant 1R01HG008605, as noted above. The second conference was sponsored by the University’s Consortium on Law and Values, Office of the Vice President for Research, Human Research Protection Program, and Masonic Cancer Center. Both conferences are archived on the Consortium’s website at <https://consortium.umn.edu/news-events/events>. Thanks to Audrey Boyle for outstanding coordination of this published symposium.

References

1. *Schloendorff v. New York Hospital*, 211 N.Y. 125, 129 (1914).
2. Compare N. W. Dickert et al., “Reframing Consent for Clinical Research: A Function-Based Approach,” *American Journal of Bioethics* 17, no. 12 (2017): 3-11, with T. L. Beauchamp, “The Idea of a ‘Standard View’ of Informed Consent,” *American Journal of Bioethics* 17, no. 12 (2017): 1-2.
3. See, e.g., G. J. Annas, “Informed Consent: Charade or Choice?,” *Journal of Law, Medicine & Ethics* 45, no. 1 (2017): 10-11; L. M. Beskow, L. Lin, C. B. Dombeck, E. Gao, and K. P. Weinfurt, “Improving Biobank Consent Comprehension: A National Randomized Survey to Assess the Effect of a Simplified Form and Review/Retest Intervention,” *Genetics in Medicine* 19, no. 5 (2017): 505-512.
4. See, e.g., D. Bracken-Roche, E. Bell, M. E. Macdonald, and E. Racine, “The Concept of ‘Vulnerability’ in Research Ethics: An In-Depth Analysis of Policies and Guidelines,” *Health Research Policy and Systems* 15, no. 8 (2017): DOI 10.1186/s12961-016-0164-6, available at <<https://health-policy-systems.biomedcentral.com/articles/10.1186/s12961-016-0164-6>> (last visited January 10, 2018).
5. See, e.g., C. Grady, S. R. Cummings, M. C. Rowbotham, M. V. McConnell, E. A. Ashley, and G. Kang, “Informed Consent,” *New England Journal of Medicine* 376, no. 9 (2017): 856-867; E. E. Anderson, S. B. Newman, and A. K. Matthews, “Improving Informed Consent: Stakeholder Views,” *AJOB Empirical Bioethics* 8, no. 3 (2017): 178-188.
6. See, e.g., S. Kalkman, S. Y. H. Kim, G. J. M. W. van Thiel, D. E. Grobbee, and J. J. M. Delden, “Ethics of Informed Consent for Pragmatic Trials with New Interventions,” *Value in Health* 20, no. 7 (2017): 902-908.
7. See, e.g., G. E. Henderson et al., “The Challenge of Informed Consent and Return of Results in Translational Genomics: Empirical Analysis and Recommendations,” *Journal of Law, Medicine & Ethics* 42, no. 3 (2014): 344-355.
8. National Institutes of Health, All of Us Research Program, available at <<https://allofus.nih.gov/>> (last visited January 10, 2018).

9. Oxford Living Dictionaries, "consent," available at <<https://en.oxforddictionaries.com/definition/consent>> (last visited January 10, 2018).
10. Online Etymology Dictionary, "consent," available at <<https://www.etymonline.com/word/consent>> (last visited January 10, 2018).
11. *Schloendorff v. New York Hospital*, 211 N.Y. 125 (1914).
12. P. A. Lombardo, "Phantom Tumors and Hysterical Women: Revising our View of the Schloendorff Case," *Journal of Law, Medicine & Ethics* 33, no. 4 (2005): 791-801.
13. J. Katz, *The Silent World of Doctor and Patient* (New York: Free Press, 1984).
14. *Salgo v. Leland Stanford Jr. University Board of Trustees*, 154 Cal.App.2d 560.
15. A. M. Capron, "Where Did Informed Consent for Research Come From?" *Journal of Law, Medicine & Ethics* 46, no. 1 (2018): 12-29.
16. S. Gehlert and J. Mozersky, "Seeing Beyond the Margins: Challenges to Informed Inclusion of Vulnerable Populations in Research," *Journal of Law, Medicine & Ethics* 46, no. 1 (2018): 30-43.
17. J. N. Henderson, "Personal Experiences with Tribal IRBs, Hidden Hegemony of Researchers, and the Need for an Inter-cultural Approach: Views from an American Indian Researcher," *Journal of Law, Medicine & Ethics* 46, no. 1 (2018): 44-51.
18. M. Lamkin and C. Elliott, "Avoiding Exploitation in Phase I Clinical Trials: More than (Un)Just Compensation," *Journal of Law, Medicine & Ethics* 46, no. 1 (2018): 52-63.
19. A. S. Porter and E. Kodish, "The Ethics of Using Complementary Medicine in Pediatric Oncology Trials: Reconciling Challenges," *Journal of Law, Medicine & Ethics* 46, no. 1 (2018): 64-71.
20. M. H. Biros, "Capacity, Vulnerability, and Informed Consent for Research," *Journal of Law, Medicine & Ethics* 46, no. 1 (2018): 72-78.
21. W. Burke, L. M. Beskow, S. B. Trinidad, S. M. Fullerton, and K. Brelsford, "Informed Consent in Translational Genomics: Insufficient Without Trustworthy Governance," *Journal of Law, Medicine & Ethics* 46, no. 1 (2018): 79-86.
22. S. M. Wolf, E. Scholtes, B. A. Koenig, G. M. Petersen, S. A. Berry, L. M. Beskow, M. B. Daly, C. V. Fernandez, R. C. Green, B. S. LeRoy, N. M. Lindor, P. P. O'Rourke, C. R. Breitkopf, M. A. Rothstein, B. Van Ness, and B. S. Wilfond, "Pragmatic Tools for Sharing Genomic Research Results with the Relatives of Living and Deceased Research Participants," *Journal of Law, Medicine & Ethics* 46, no. 1 (2018): 87-109.
23. J. Wilbanks, "Design Issues in E-Consent," *Journal of Law, Medicine & Ethics* 46, no. 1 (2018): 110-118.
24. E. Vayena and A. Blasimme, "Health Research with Big Data: Time for Systemic Oversight," *Journal of Law, Medicine & Ethics* 46, no. 1 (2018): 119-129.