The American Journal of Pathology, Vol. ■, No. ■, ■ 2017

ELSEVIER

The American Journal of PATHOLOGY

ajp.amjpathol.org

PERSPECTIVES

Disruptive Influences on Research in Academic Pathology Departments

Proposed Changes to the Common Rule Governing Informed Consent for Research Use of Biospecimens and to Rules Governing Return of Research Results

Mark E. Sobel* and Jennifer C. Dreyfus†

From the American Society for Investigative Pathology, Bethesda; and the Dreyfus Consulting, LLC,† Takoma Park, Maryland*

Accepted for publication November 3, 2016.

Address correspondence to Mark E. Sobel, M.D., Ph.D., American Society for Investigative Pathology, 9650 Rockville Pike, Ste E130, Bethesda, MD 20814. E-mail: mesobel@asip.org.

Academic pathology departments will be dramatically affected by proposed United States federal government regulatory initiatives. Pathology research will be substantially altered if proposed changes to the Common Rule (Code of Federal Regulations: Protection of Human Subjects title 45 CFR 46) and regulations governing the return of individual research results are approved and finalized, even more so now that the Precision Medicine initiative has been launched. Together, these changes are disruptive influences on academic pathology research as we know it, straining limited resources and compromising advances in diagnostic and academic pathology. Academic research pathologists will be challenged over the coming years and must demonstrate leadership to ensure the continued availability of and the ethical use of research pathology specimens. *(Am J Pathol 2017, ■: 1–5; http://dx.doi.org/10.1016/j.ajpath.2016.11.001)*

History

The conduct of pathology research has been governed by a variety of ethical considerations. The 1974 National Research Act generated the first national bioethics committee in the United States—the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Commission is best known for publishing The Belmont Report (1979),[1] which established the key principles of respect for persons (autonomy), beneficence, and justice. These principles have their roots in the 1964 Declaration of Helsinki,[2] which established the basis for research ethics.

In 1981, the Common Rule[3] generated a baseline ethical standard for government-funded research in the United States, with nearly all academic institutions holding their researchers to these statements of rights regardless of funding source. The Common Rule applied to government-funded research from 15 federal agencies (later expanded to 17 and finally 19 agencies in 2015), and led to the requirement for informed consent for human subjects research and the generation of institutional review boards (IRBs) for the oversight of that research in the United States. The Common Rule was subsequently revised in 1991.

Beginning in the mid-1990s, the issue of biospecimen use in research and the Common Rule regulations were moved to the fore. When the National Center for Human Genome Research was launched, its Ethical, Legal, and Social Issues Working Group was tasked with proactively considering the

Supported by the American Society for Investigative Pathology.

Disclosures: M.E.S. is employed as the Executive Officer of the American Society for Investigative Pathology. J.C.D. is a Science Policy Consultant for the American Society for Investigative Pathology.

This article is partly based on a presentation given by Mark E. Sobel at the Association of Pathology Chairs Annual Meeting in San Bernardo, California, on July 12, 2016.

http://dx.doi.org/10.1016/j.ajpath.2016.11.001

rights of subjects participating in research studies, including a recognition that an individual's biospecimens, whether obtained through clinical intervention (biopsy, surgical resection of diseased tissue, or body fluids for laboratory testing) or through a research study, should be included under the umbrella of human research subjects protections. A seminal *Journal of the American Medical Association* article in 1995[4] raised concerns about lack of informed consent for research use of human biospecimens. A consortium of 17 national organizations responded in 1999 with recommendations for responsible conduct of research on human biospecimens.[5]

A central concept of the Common Rule is exemption from the regulations based on the definition of human subject: "A living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual, or identifiable private information."[3] As a result, several types of research fall outside the definition of human subjects research, including research conducted on deceased persons (ie, autopsy specimens), studies using publicly available information, and research using nonidentified biospecimens. Such research has been exempt from Common Rule regulatory oversight. Nonidentified biospecimens include so-called anonymous samples that were originally collected without any data that could reveal the identity of the donor (although they can be associated with some demographic data), as well as anonymized samples that were originally collected with an identifier but the identifier has since been permanently stripped from the sample, rendering it anonymous. Examples of identifiers include name, medical record chart number, and social security number. In contrast, the definition of an identified sample refers to a biospecimen that can be identified by any one person at any time or location. Coded or linked biospecimens are used in research with a random identifier developed to disconnect the specimen from identifiable information. However, if there is a method for linking the random identifier to the specimen that can be accessed by the researcher, even if under lock and key or encryption, the biospecimen is considered identifiable.

A key component of the Common Rule is the ability of an IRB to grant a waiver of informed consent if the proposed research meets four criteria: i) minimal risk, ii) respect for autonomy and the rights of the individual, iii) impracticability of obtaining consent, and iv) notification. Using an algorithm developed by the Office of Human Research Protections, IRBs generally follow a rule that informed consent is not waived for the use of identified samples, and is rarely, if ever, waived for coded (linked) samples.

A 2008 Guidance[6] from the Office of Human Research Protections, US Department of Health and Human Services, clarified that research on biological specimens is not considered human research if the following two criteria are met: the specimen was not collected specifically for a current proposed research project through an interaction or intervention with a living individual; and the investigator is not able to readily ascertain the identity of the individual(s). In essence, by signing an agreement that the researcher has no intention to break the code of a linked biospecimen or to discern the identity of the donor, a pathologist or other biomedical researcher may more readily obtain a waiver of informed consent from the IRB to conduct research using nonidentified biological specimens.

In 2011, two components of the US Department of Health and Human Services (Office of the Secretary and the Food and Drug Administration) issued an Advanced Notice of Proposed Rulemaking,[7] proposing a variety of changes to update the Common Rule. A central premise of the Advanced Notice of Proposed Rulemaking was that the application of new technologies, such as next-generation sequencing, makes it possible for any sample to be identified and that there is, in fact, no such thing as an anonymous or nonidentified sample. Indeed, a research report by Gymrek et al[8] in 2013 demonstrated that sequencing a significant portion of the genome may result in the specimen being considered identifiable and therefore worthy of appropriate protections under human subjects research regulations. This research study further heightened concern as to whether the ability to inexpensively and rapidly sequence the genome of an individual from a single cell of a biospecimen nullifies the concept of an anonymous or anonymized sample.

No further regulatory action was taken for 4 years. In September 2015, the US federal agencies covered under the Common Rule, now 19 in number, jointly issued a Notice of Proposed Rulemaking (NPRM).[9] Notably, the NPRM broadened the definition of a human subject to include nonidentified biospecimens. As a result, research use of nonidentified biospecimens would no longer be exempt from human subject research protections, as they are currently under the Common Rule. The NPRM also set such strict criteria for IRB waivers of informed consent that they would be granted only under rare circumstances.

Response to the Common Rule NPRM

By the end of the most recent comment period on the proposed regulatory changes, the US federal government had received well over 2100 comments from researchers, research institutions, research participants, the general public, and others. Currently, federal regulators are reviewing these comments and determining which, if any, will be incorporated into a final rule. As of the last update in May 2016, finalizing the proposed changes to the Common Rule remains on the Unified Agenda,[10] and thus a topic of ongoing regulatory activity.

The 2015 NPRM[9] emphasized the concept of autonomy, recommending that research using nonidentified biospecimens would now be considered human subjects research requiring informed consent. The NPRM proposed

REV 5.4.0 DTD ■ AJPA2515_proof ■ 30 November 2016 ■ 4:54 pm ■ EO: AJP16_0460