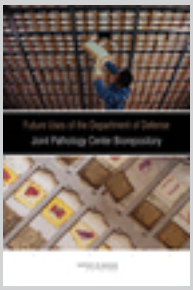

Future Uses of the Department of Defense Joint Pathology Center Biorepository

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Tissue Repository Following Its Transfer to the Joint Pathology Center

Board on the Health of Select Populations

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

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"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Harold C. Sox,** Professor of Medicine, Dartmouth Medical School and Associate Director for Faculty, The Dartmouth Institute, and **Jeremy Sugarman,** Harvey M. Meyerhoff Professor of Bioethics and Medicine, Berman Institute of Bioethics and Department of Medicine, Johns Hopkins University School of Medicine. Appointed by the National Research Council and Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Acknowledgments

This report could not have been prepared without the guidance and expertise of numerous persons. Although it is not possible to mention by name all those who contributed to the committee's work, the committee wants to express its gratitude to a number of them for their special contributions.

Sincere thanks go to all the participants at the public meetings convened on April 21, July 11, and September 8, 2011. The intent of the workshops was to gather information regarding issues related to the topics addressed in the committee's statement of task. The speakers, who are listed in Appendix A, gave generously of their time and expertise to help to inform and guide the committee's work. Many of them also provided additional information in response to the committee's questions. Pilar Ossorio and Jeffrey Mason supplied important detail and insight on issues before the committee in their role as consultants.

The committee extends special thanks to the dedicated and hard-working staff of the Institute of Medicine's Board on the Health of Select Populations, who supported and facilitated its work. Board Director Rick Erdtmann helped to ensure that this report met the highest standards of quality.

Finally, James Childress, chair, thanks David Butler, director of the study, for his fine work in drafting and editing materials for the report, and he thanks the members of the committee for their excellent ideas, helpful drafts, and vigorous and valuable participation in the deliberative process. He is also grateful to Alexander Capron for filling in as chair when he was unable to participate in committee meetings.

Contents

Summary

In May 1862, the Army Surgeon General, Brigadier General William Hammond, undertook an initiative to try to learn from the carnage of the Civil War. He ordered the establishment of the Army Medical Museum as a research institution that would collect and catalog specimens obtained from medical and surgical procedures performed by Army physicians and others and make them available for study (Stone, 2011). The museum expanded and diversified in the years that followed, setting up a Pathology Department and Instructional Laboratory in 1910 and undertaking an extensive effort to document the medical consequences of combat during World War I. Several registries—collections of rare or representative biospecimens from a particular organ system or representing a specific medical condition—were established in the early decades of the 20th century, and new departments were founded as science advanced and the demand for professional education and expert pathology advice increased. By the end of the 20th century, the institution, which was renamed the Armed Forces Institute of Pathology (AFIP) in 1949, had accumulated the largest collection of human pathology specimens in the world and established itself as a premier consultation, education, and research facility. Perhaps its best known contribution to science was as the source of some of the biospecimens used to sequence the genome of the 1918 influenza virus that killed over 40 million people worldwide and as the home institution of the lead investigator in the research (Morens et al., 2008; Taubenberger et al., 2007).

The federal Base Realignment and Closure (BRAC) Commission recommended in 2005 that AFIP be disestablished except for some components,

including the biorepository. The National Defense Authorization Act of 2008 (PL 110-181, § 722) later created the Joint Pathology Center (JPC) to absorb the AFIP biorepository and continue its duties.

As the transition to the JPC was taking place in 2010, the Department of Defense (DoD) asked the Institute of Medicine (IOM) to convene an expert committee to offer advice on several issues related to the operation of the biorepository and the management of its collection. The questions posed in its statement of task (Box S-1) were focused on issues related to the appropriate future use of the specimens in consultation, education, and research. This report, prepared by the IOM Committee on the Review of

BOX S-1
Questions Posed in the Committee's Statement of Task

- Given the defined mission and vision of the Joint Pathology Center, should access to repository materials be limited to the federal government or open to a larger pool of potential users? What advantages and disadvantages should be considered in defining the potential users of the repository in research?
- What are the ethical and legal considerations regarding utilization of the tissue repository in support of clinical care and education?
- The tissue repository currently contains paraffin embedded tissue, glass slides, wet (formalin-fixed tissue) and frozen tissue; some of it is not usable for consultation, education, and research given current technology. Should material not deemed currently usable for consultation, education, and research be stored indefinitely or should the JPC develop a plan for disposal of unusable or nonviable specimens and are there any legal considerations with disposal of said specimens?
- Should the BRAC Collection of materials be maintained indefinitely?
- Can tissue collected for clinical use be used for research (i.e., from patients not specifically consented for use of tissue in research)?
- What are the ethical considerations regarding use of tissues originally submitted for clinical use for research and can this be accomplished within current accepted guidelines for clinical research?
- The tissue repository currently contains consult material from both federal facilities as well as that submitted for consultation by civilian providers. Can tissue within the repository from civilian providers be utilized in the same manner as that from federal facilities?
- What considerations should be given to utilization for research of unique, one-of-a-kind material within the Central Collection of the tissue repository?
- What existing or emerging technologies (either as an intrinsic function or through partnership) should be considered in developing a plan for utilization of the tissue repository in research and how would they potentially affect the mission of the JPC?

the Appropriate Use of AFIP's Tissue Repository Following Its Transfer to the Joint Pathology Center, provides responses to those questions.

FRAMEWORK AND ORGANIZATION

The committee organized its response to its statement of task in three primary chapters addressing the following topics:

- A brief history of the biorepository that is now under the aegis of the JPC; a description of the current status of its collection, an explication of the committee's statement of task, the methodologic considerations that informed the committee's evaluation of the literature, and summary information on earlier reports addressing AFIP and JPC operations and on related National Academy of Sciences reports (Chapter 1).
- The means of preserving biospecimens, methods for analyzing and assessing their research value, and how the details of the specimen's preservation, storage, and documentation, and the uses to which they are put may affect prospects for their future use (Chapter 2).
- The ethical, legal, and regulatory considerations underlying the committee's responses to the questions posed by the DoD with particular attention to the federal laws and regulations, DoD rules, and AFIP and JPC regulations regarding research on biospecimens and their associated data (Chapter 3).

Those chapters contain the detailed literature reviews and analysis of their relevance to the JPC biorepository that build the foundation for the committee's findings, conclusions, and recommendations presented in Chapter 4.

Background information on the biorepository's collection is summarized below.

THE STATE OF THE BIOREPOSITORY'S COLLECTION

As of 2011, the JPC tissue repository comprised some 7.4 million accessions that contained specimens or data from about 3.2 million people (Baker personal communication, 2011). About 3.2 million of the accessions are in the Central Collection, which is composed primarily of biologic materials submitted for consultation by military, other government, and civilian medical providers. Most of the remaining 4.2 million accessions are from military medical facilities closed under BRAC Commission proceedings. They differ from those in the Central Collection in that they include the complete array of data and specimens collected in the course of the provision of routine medical care. About two-thirds of the so-called BRAC Col-

lection cases have both specimens and data; the remaining one-third have only data (Baker personal communication, 2011). In addition, a series of war and cohort registries that were created at the direction of Congress or on the initiative of the Department of Veterans Affairs or DoD comprise collections of specimens and data from military personnel who shared a military experience (such as participation in Operation Iraqi Freedom or time spent as prisoners of war) or wartime exposure (such as exposure to Agent Orange or depleted uranium) (JPC, 2011).

All told, the repository includes

- 55 million glass slides.
- 31 million paraffin-embedded tissue blocks.
- 500,000–700,000 wet tissue samples.
- 29 tissue microarray assays, each of which may contain hundreds of specimens.
- over 23 million digitized images of specimens.
- an unknown number of digitized radiologic images.
- other pathology and diagnosis-related holdings, including medico-legal materials and veterinary specimens.
- associated medical records or other data (Baker, 2011).

There are also 18 freezers that contain frozen samples that were still being cataloged in early 2012. The materials are housed in climate-controlled storage facilities in an annex of the Walter Reed Army Medical Center in Forest Glen, Maryland.

The amount of data associated with specimens depends on when they were sent to the repository. In recent decades, information accompanying most accessions in the Central Collection includes patient name, Social Security number, date of birth, repository accession number, surgical number, type of specimen, contributor's[1] health care facility, and specialty branch numbers associated with the consultation. Other information that may also be associated with a sample includes age, sex, race, ethnicity, contributor's working diagnosis, and details of the patient's clinical history (such as location and size of tumor, symptoms, duration of illness, physical and laboratory findings, type and date of surgery, and treatments). Data related to specimens in the BRAC Collection vary because the submitting military base, rather than the repository, determined which information was collected, but is typically more limited than in the Central Collection.

[1] *Contributor*, in the repository's parlance, is the medical professional (often, a pathologist) who submits the specimen for consultation or storage. It is not the person from whom the specimen was obtained.

It usually includes patient name, where the specimen originated, surgical number, and diagnosis.

A 2008 assessment of the accuracy and completeness of the AFIP databases and analysis of the state of the repository's specimens found that about 75 percent of retrievals of specimens from the Central Collection cases yielded the records that were requested (Asterand, 2008). The assessment concluded that the utility of Central Collection specimens for research purposes depended on the age of the specimen, with the most recently acquired specimens having the fewest aberrations and the largest amount of associated clinical data. The vast majority of wet tissue specimens examined were desiccated and thus of impaired research value. However, tests suggested that at least one pathology research tool (immunohistochemistry analysis) could be successfully used with even the oldest of specimens.

The JPC does not have documentation regarding any consent forms signed by patients or research participants whose data or specimens were submitted to the repository (Baker personal communication, 2011). Such consents may have been obtained for the clinical procedures used to excise the specimens at the facilities where the individuals received medical care, but it is highly unlikely that they included notification that the specimens could be sent to a remote repository or later used for education or research purposes. Consents for research use may have been obtained for some materials gathered for the war or cohort registries, but the JPC has no documentation on these (Baker personal communication, 2011).

CONCLUSIONS AND RECOMMENDATIONS

The committee structured the results of its work into three broad categories. It first offers general observations based on its overall evaluation of the JPC's future challenges. It then responds to the questions posed in the DoD's statement of task, dividing them into questions related to the retention and maintenance of biospecimens and those addressing the future use of the biospecimens and associated data and medical records in clinical care, education, and research.

This summary covers the major findings of the committee; more detailed advice is offered in Chapter 4.

General Observations

The JPC faces major challenges as it transforms into a modern biorepository that provides clinical consultation, education, and research services. Many of these arise from the way in which much of the existing collection of biospecimens and associated clinical data was obtained. The challenges include determining the utility of the collection—which consists

of materials collected, handled, and stored under a variety of conditions—and establishing appropriate ethical and legal standards for using the materials, especially in research, inasmuch as they were generally collected without source individuals'[2] consent for use in research.

The threshold issue that the JPC must confront in facilitating use of the repository is the uncertainty regarding the utility of its collection of biospecimens. Experience with other biorepositories that, like the JPC, are composed of samples collected in the absence of a purposefully designed protocol indicates that their value may be severely limited by the state of specimens and their associated documentation (Compton et al., 2009). Variations in the preanalytic handling of specimens, in specimen preparation and fixation, in postfixation handling and storage, and in accompanying documentation greatly affect their suitability for some forms of analysis. That is not to say that such specimens lack value—almost all have utility in at least some applications—but it indicates that the operators of such a repository must be circumspect in their expectations and representations. Advances in technology will undoubtedly change the criteria for determining whether particular specimens are fit for purpose in ways that may make fewer or more of them useful.

The committee recommends that the JPC, as part of its plan for improving the use of repository materials in research, evaluate the strengths and limitations of the collection to the extent permitted by its resources and current science and technology, consider how to enhance the repository's value given the JPC's organizational and budgetary constraints, and formulate its retention policy and dissemination management and marketing strategies accordingly. In this regard, the committee believes that it is crucial for the JPC to find ways to engage the professional community in discussion concerning future use of the repository so that it can understand better the potential demand for collection materials and how to facilitate their use.

The JPC may also wish to consider means such as the "honest broker" model for providing specimens and data to researchers while protecting the interests of specimen sources. An honest broker is an individual, organization or system that serves as neutral intermediary between a provider of materials (a source individual or biorepository, for example) and researchers, collating pertinent specimens and data, replacing identifying information with a code, and releasing only coded information to the researchers (Eiseman et al., 2003; NCI, 2011). The notion of an honest broker, which has been adopted

[2]The term *source individual* (sometimes abbreviated to *source*) is used in this report to refer to the person from whom biospecimens and data were obtained. Unlike the term *donor*, it does not imply that the person necessarily made a decision about the storage and use of the materials—such an implication would be mistaken in the case of almost all the materials held in the JPC repository.

by some biorepositories, has been applied more generally in facilitating the dissemination of materials to life-science researchers.

The JPC indicated to the committee that it would like to make repository materials available for research on a cost-neutral basis (Baker, 2011). Because the federal government is in general prohibited from charging nongovernment entities for such services,[3] **the committee recommends that the JPC immediately determine whether it has the statutory ability to recover the costs of providing specimens and data for approved research projects. If it does not, the JPC should work with Department of Defense (DoD) leadership to determine the best way to establish such an ability.** The committee notes that other government agencies have used such mechanisms as partnering with nonprofit organizations (which may accept nongovernment funds) to provide services that they cannot charge for or to receive funds from outside parties.

Retention and Maintenance of Biospecimens

General Retention and Maintenance Issues

Advances in tissue-analysis technology continue to be made and no one can confidently predict the potential future scientific value of particular repository specimens. However, the possibility that some currently unusable material might become useful does not mean that all of the material that the JPC holds must be stored indefinitely to safeguard against losing something of possible prospective value. **The committee recommends that the JPC develop protocols for determining when to retain potentially useful materials and when to dispose of specimens that have no special research or educational value and are past the point of required retention for clinical use. The committee recommends that the criteria for determining when specimens should be disposed of** include whether the specimens fall into any of these categories:

- Wet tissue specimens and slides that have been obviously contaminated, desiccated, or otherwise damaged.
- Tissue blocks that have been contaminated, exhausted, dried out, or have otherwise deteriorated.
- Frozen specimens that show evidence of freezer burn or of having been melted and refrozen.
- Specimens of any type that cannot be associated with a data record in the system.

[3]Federal organizations can recover such costs from other parts of the federal government through interagency transfers (31 U.S.C. § 1535).

Auditing the vast holdings of the JPC repository to determine the condition of specimens would be a long and expensive undertaking. **The committee recommends that as long as it is less expensive to retain specimens than it is to assess their condition comprehensively, specimens be evaluated only when they are retrieved for clinical, education, or research purposes. If a specimen is found to satisfy the disposal criteria, it should be removed from the collection. If and when the cost of retaining specimens exceeds the estimated cost of auditing the collection, a procedure for setting priorities for review and systematically removing specimens that are not usable for clinical, education, or research purposes from the collection should be implemented.**

Statutory requirements for retention change, and **the committee recommends that the JPC seek the advice of the DoD Office of the General Counsel regarding the procedures it should have in place to conform to the laws in force when implementing disposal policies.**

Retention of BRAC Collection Materials

The specimens and data in the BRAC Collection appear no different from ones that can be obtained from other sources, such as hospital and university pathology departments and currently open military healthcare facilities. The information available to the committee suggests that the BRAC Collection of materials has no greater value for education or research purposes than the collections of pathology materials found in hospitals comparable with the facilities that transferred them. Therefore, **the committee recommends that the JPC retain materials in the BRAC Collection for potential clinical consultation only for as long as required by CAP or CLIP–CLIA guidelines[4] and requirements, whichever specifies the longer period.**

Use of Biospecimens in Clinical Care, Education, and Research

Ethical and Legal Considerations

Use in clinical care and education The use of the stored biospecimens and other clinical data in the JPC repository for clinical care of the person from whom they were obtained is subject to the same ethical and legal

[4]The guidelines set forth in the College of American Pathologists (CAP) Laboratory Accreditation Program (CAP, 2010) and DoD's Clinical Laboratory Improvement Program (CLIP)—which conform to the Centers for Medicare and Medicaid Services Clinical Laboratory Improvement Amendments (CLIA) certification requirements (42 CFR § 493.1105)—specify how long biospecimens must be retained to satisfy reasonably anticipatable clinical needs.

considerations as arise in the management of any clinical pathology collection. Generally speaking, educational use of repository materials that have been stripped of all information that would allow sources to be identified poses no ethical or legal issues and should continue to be facilitated by the JPC. **The committee recommends that dissemination of biospecimens by the JPC for educational purposes should be subject to strict compliance with rules and procedures to protect source identity.** Those requirements should be developed and updated to ensure that reidentification of source individuals cannot readily be accomplished. In addition, material-transfer agreements and other documents offered to individuals and institutions seeking access to JPC repository materials (whether for education or other purposes) should explicitly forbid reidentification efforts.

Use of repository materials for the medical care of other persons—notably, genetically related persons and persons who have a life experience (such as an exposure or service in a military unit) in common with the source—presents special issues that require careful consideration of the relevant ethical and legal issues as well as the circumstances of the request. **The committee recommends that the JPC develop a policy for evaluating such requests and, when it is appropriate, fulfill them in a manner that protects the privacy of persons from whom the specimens were obtained. The policy should include consideration of whether the material can be provided in a deidentified manner, whether access is necessary to address a medical need that cannot be equally well met by another available means, and applicable legal constraints.**

Use in research The policy landscape governing research on clinically collected specimens that are assembled by pathologists and then made available for research use is in transition. It is important to consider which approaches for using archived clinical data and specimens in research and which approaches for accessioning new data and specimens accomplish the goals of protecting and respecting source individuals, meeting public expectations, and supporting the efficient functioning of the repository. **The committee recommends that the JPC adopt a policy regarding research use of tissues originally submitted for clinical consultation that places transparency and respect for source individuals and populations at its core. The procedures adopted should remain flexible enough to adapt to the changing legal, regulatory, and ethics landscape.** The policy should include the elements listed below:

- Establishment of a Data Access Committee (DAC) that would examine requests to use repository materials (both specimens and data) and that would operate in addition to the Research Review

Committee and IRB that the JPC already uses.[5] It would be composed of persons in and outside the JPC who have expertise in research ethics, military research, and research on biospecimens. The DAC's responsibilities should comprise

- — evaluating whether proposed research meets the JPC's goals for the use of its materials.
- — determining whether the researcher's credentials and specimen- and data-handling protocols satisfy the JPC, DoD, and current legal and regulatory requirements.
- — reviewing and providing guidance on the proper management of any ethical issues raised by the proposed research.
- — ensuring that data use and material transfer agreements made with researchers protect the privacy of source individuals and obligate the researchers to keep information secure, to avoid efforts to identify data or specimen sources, and to otherwise protect the interests of specimen sources and the DoD.

- Solicitation of input from the community of people—in particular, active-duty military, veterans, and their family members—whose specimens are held by the repository through, for example, representation on the DAC or creation of a community advisory board.
- Notification through public means—for example, posting on its website, in newsletters, and in other media that reach the military community and the general public—of the JPC's intention to allow repository materials to be used for research purposes, including

  - — examples of the kinds of research that have been done with repository specimens in the past.
  - — a description of the oversight and review mechanisms governing access to the materials that can be easily understood by the general public.
  - — a clear statement that no access will be allowed without the review and approval of an IRB.
  - — user-friendly means by which people may ask questions or request that a good-faith effort be made to determine whether the repository holds specimens from them with the option to request

[5]The most current repository protocol regarding review of research proposals available at the time of this report was contained in AFIP Regulation 70-1, *AFIP Research Program*, dated June 7, 2005. The protocol called for review of proposals by a research committee and an IRB and specified the composition and function of these bodies. The committee understands that this regulation is being followed by the JPC.

that any specimens be withheld from research use (through, for example, a Web form, e-mail address, or telephone number for inquiries).

- Posting, in a forum such as the JPC website, of the active research projects that are using repository materials. This will promote accountability to specimen sources and citizens regarding how repository materials are being used; it will also help to inform the research community about the repository's collection and potential research uses.
- Regular review of JPC forms, protocols, and procedures to ensure that they meet evolving legal and regulatory requirements and reflect best practices for biorepository operations and management, as defined by, for example, the National Cancer Institute (NCI, 2011) and the International Society for Biological and Environmental Repositories (ISBER, 2012).

Protocols and procedures regarding research use of materials should be public documents and should be regularly updated on the JPC website.

Use of Consultation Materials from Federal Facilities and Civilian Providers

Access by researchers to human materials that entered the JPC repository from federal facilities and from civilian providers[6] is generally governed by the same legal requirements and ethical standards. Additional protections regarding research on human subjects, especially requirements regarding informed consent, do apply to U.S. military service members, and these impose additional review and procedural responsibilities on the repository. The JPC has an ethical obligation to ensure *all* materials (as well as data) in its repository are utilized in a manner that respects the privacy of the specimen sources, prevents misuse by researchers who obtain access to them, and protects the security and other interests of the government.

Scientific Considerations

Current and emerging technologies Several existing and emerging technologies in protein and gene-expression profiling and advances in DNA, elemental, and chemical studies hold the potential for making the JPC

[6]The *providers* are the physicians who and medical facilities that submitted materials for consultation or educational purposes, not the persons from whom the samples were derived. When the provider is a medical professional, this person is also a *contributor* as defined above.

repository materials more useful by permitting specimens previously considered unusable to be analyzed or by allowing more information to be extracted from specimens. However, although the technical ability to extract and analyze biomolecules from archived specimens has improved and is likely to increase, the many unknown types and degrees of preanalytic variation to which the specimens have been subjected before stabilization will affect the validity of analytic results and may limit many types of research studies.

If the JPC is to fulfill its stated mission to provide "world class" research services, it will need to establish procedures that minimize the adverse consequences of inconsistent preanalytic handling of specimens. **The committee therefore recommends that the JPC adopt a set of best practices for the collection, processing, and storage of all incoming specimens, either by developing its own standards or by using one developed by another entity—for example, NCI's *Best Practices for Biospecimen Resources* (NCI, 2011).** As the JPC takes steps to enhance its laboratory information management system by improving basic search and analytic functionality, its system should include fields that detail how specimens were collected and handled before accessioning in the repository, quality-control data, and what record there is of consent to future research use. There may also be merit in digitizing all new cases coming to the repository and the committee suggests that the JPC consider whether it is feasible given economic and logistical circumstances. And, the committee believes that the JPC would derive value from pursuing research partnerships with the Department of Veterans Affairs to examine questions regarding the health consequences of military service and the determinants of disease and wellness.

Use of rare and unique materials Rare and unique materials in the Central Collection of the repository are a resource for the JPC, the country, and the global scientific community. However, the question of what constitutes rare and unique material is complex: even relatively common diseases have rare subtypes, for example. Moreover, particular collections of specimens may be "unique" in the aggregate, although until a particular set of desired material characteristics is defined it may not be possible to determine whether or not other similar collections are available elsewhere. It is also difficult to predict what may prove to be valuable at some future time or under particular circumstances.

The committee recommends that the following considerations be taken in account in evaluating whether *any* given specimen should be made available for research:

- the age of the specimen.
- the disease state that it represents.

- the specimen's medical, scientific, and historical[7] significance.
- the condition of the specimen and its fitness for the proposed use.
- whether a proposed use would exhaust the research potential of the specimen.
- whether the same research need might be met by another, less rare specimen or another source of specimens.
- the importance of the public health or military need the proposed use aims to meet.

The JPC should also develop criteria for determining when a collection of specimens—rather than an individual sample—is unique or has special medical, scientific, or historic value, and for managing access to such collections.

The JPC does not have any specific policy regarding how the depletion of a repository specimen should be factored into decisions regarding access to it, beyond ensuring that all applicable retention requirements are met. That should change to ensure that the repository remains a resource for otherwise unobtainable material. **The committee recommends that the JPC establish criteria for deciding whether to deplete a specimen to exhaustion. The criteria should be determined in close consultation with pathology subspecialty experts in and outside the JPC.** Detailed recommendations are beyond the scope of the present committee's task but the criteria may include such considerations as the following:

- retaining a set percentage of the tissue-containing portion of a tissue block unless a designated repository officer authorizes its use.
- retaining a set number of stained or unstained tissue sections from a specimen.
- not permitting any specimens collected before a given date to be used for research without specific review of whether the need justifies depletion of the resource and without explicit authorization by a designated repository officer.
- not disposing of any specimen collected before a given date, no matter its condition.

Access to Repository Materials

Permitting wide access to the JPC repository materials promotes the public good through the advancement of medical and scientific knowledge.

[7]The National Museum of Health and Medicine (http://www.medicalmuseum.mil) houses military pathology specimens with historical value and would be the authority on this question.

It also benefits the DoD by fostering the development of information on the determinants of disease and good health in service members and veterans.

The JPC's mission and vision are focused on the DoD and the rest of the federal government but do not preclude working with other entities. The committee does not believe that there are any intrinsic advantages or disadvantages to any particular set of potential users of the repository's resources. **The committee recommends that there be no a priori restrictions on which applicants may apply for access to the repository's specimens and data.**

When data or specimens are disseminated to outside investigators, the JPC must be especially attentive to employing mechanisms to manage privacy and security issues properly. **The committee recommends that the JPC condition its provision of repository materials to researchers outside of the federal government on**

- **Participation of a DoD-affiliated monitor trained in and assigned the responsibility of ensuring the appropriate use of repository specimens and data and safeguarding the interests of its sources, the repository, and the federal government.** The monitor would also facilitate research by helping outside investigators to identify and gain access to the most appropriate JPC resources for a particular project.
- **Implementation of data-use agreements and material-transfer agreements, as appropriate, to help to protect the identified interests.** Data-use and material-transfer agreements were used by AFIP and are widely used by other research biorepositories and by the federal government to inform investigators of their responsibilities and to gain their agreement to abide by a set of requirements.

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1

Introduction and Background

This chapter provides basic information about the motivation for and the conduct of the study summarized in this report, beginning with a brief history of the biorepository currently under the aegis of the Joint Pathology Center (JPC) and a description of the status of its collection. It then presents the statement of task for the Institute of Medicine (IOM) committee responsible for the report and discusses the committee's approach to its task. The methodologic considerations that informed the committee's evaluation of the literature are addressed, and summary information on related National Academy of Sciences reports is presented. The chapter concludes with a description of the present report's organization.

ESTABLISHMENT AND HISTORY OF THE ARMED FORCES INSTITUTE OF PATHOLOGY AND THE JOINT PATHOLOGY CENTER

The collection of biospecimens currently held by the JPC had its origins in the U.S. Civil War. The Army Medical Museum was founded in 1862 by Army Surgeon General Brigadier General William Hammond (AFIP, 2011). It was given the task of collecting and cataloging all specimens of morbid anatomy that would be of interest in military medicine. The museum served primarily as a reference collection, but it also accommodated the visiting public. One of its earliest products was *The Medical and Surgical History of the War of the Rebellion*, a six-volume publication that cataloged the types of diseases and injuries that a military physician might encounter during service (U.S. Army Surgeon General's Office, 1861–1865).

The Museum was divided into the Pathology Department and Instruction Laboratory in 1910, beginning its transformation from a storehouse to a consultation, research, and education facility. An extensive effort to document the medical consequences of combat was conducted during World War I and prompted a decision to split the institution's collection into two groupings: Series A, consisting of all specimens received before the U.S. declaration of war against Germany on April 2, 1917, and Series B, all specimens accessioned from that date on (Stone, 2011).

The 1920 U.S. surgeon general's report made a strong statement in favor of general access to the nascent repository's materials (U.S. Surgeon General, 1920, p. 247):

> The Army Medical Museum is a very valuable connecting link between the Medical Department of the United States Army and the general medical profession of the United States, from the standpoint of scientific medicine and surgery. It has been the policy of the museum during the past year to encourage the use of its collections by civilian physicians and it is believed that only in this way will the museum fulfill its larger function of being not only a place for the exhibition of pathological and other material, but a great instruction center in pathology and epidemiology.

With that endorsement, the museum created the first of the registries in the repository in cooperation with the Academy of Ophthalmology and Otolaryngology. Registries provided a means by which medical societies representing various specialties could donate materials, thereby strengthening and diversifying the museum's collection while preserving valuable specimens for the medical community and creating links between civilian researchers and museum staff (Stone, 2011). Several other registries were established in the following years, including those for lymphatic tumors (1925), bladder tumors (1927), dental and oral pathology (1933), and dermatology (1937). Diagnosis and consultation services also expanded, particularly after a 1929 circular from the U.S. Army surgeon general called attention to this work (Henry, 1964).

The introduction of the registries and the continued accession of thousands of pathologic specimens per month led to the museum's being renamed the Army Institute of Pathology in 1946 (Stone, 2011). Series A accessions were assigned to the museum, and Series B became known as the Central Repository (Henry, 1964).

World War II brought another influx of specimens to the repository and with them a new mandate to serve all the U.S. armed forces and the Veterans Administration (VA, now the Department of Veterans Affairs) as their central pathology laboratory (Stone, 2011). In recognition of that enlargement of mission, the institute was renamed the Armed Forces Institute

of Pathology (AFIP) in 1949. The number of new accessions continued to increase through the 1950s, reaching about 75,000 per year (Asterand, 2008). Institutional growth during the period included the introduction of branches in laboratory animals and in aerospace, forensic, and geographic aerospace pathology and expansions in military and civilian consultations and in educational and research programs (Stone, 2011). Over 200 research studies using biorepository materials were conducted in 1955–1960 alone (Stone, 2011).

Congress chartered the American Registry of Pathology (ARP) in 1976 (PL 94-361; 10 U.S.C. 177) to facilitate the Armed Forces Institute of Pathology's (AFIP's) interactions with the civilian medical community. A provision of the charter permitted ARP to receive fees for such services as education courses and consultations, with AFIP staff holding joint appointments with the two institutions (Stone, 2011). That cost-offsetting mechanism, which is not available to government entities, allowed further expansions in AFIP's clinical care (in the form of consultations), education, and research activities and attracted a number of clinicians and investigators to its staff.

Scientific and technologic advances in such fields as DNA analysis, microscopy, and digital image processing spurred AFIP's work in the 1980s and 1990s. The AFIP Department of Forensic Sciences became the Armed Forces Medical Examiner System (AFMES) in 1988. The Armed Forces DNA Identification Laboratory was absorbed into the AFMES 3 years later. That centralized system allowed surveillance of active-duty deaths and led to research into improvements in protective gear and emergency medicine.

The era also saw the establishment of the first of a series of war and cohort registries that were created at the direction of Congress or on the initiative of VA or the Department of Defense DoD (Baker personal communication, 2011a). They include registries addressing military personnel who participated in the Persian Gulf War, Operation Iraqi Freedom, and Operation Enduring Freedom; former prisoners of war; those who received a diagnosis of leishmaniasis; and those exposed to Agent Orange, depleted uranium, nerve agents, or embedded metal fragments (JPC, 2011). Unlike almost all the other material in the repository, data and specimens in the registries were collected according to research protocols that were reviewed by an institutional review board (Baker personal communication, 2011a).

As it entered the 21st century, the AFIP repository continued to serve as a major resource for the medical community, with its staff supplying education and diagnostic services and improving knowledge through research. Residency training, fellowships, postgraduate short courses, continuing education, and lectures were provided to both domestic and international medical professionals, while state-of-the-art technologies were utilized in making advances in pathology and other sciences (Stone, 2011). Notably, a team of

more than 50 repository personnel used DNA analysis and other means to identify remains recovered from the September 11, 2001, terrorist attacks on the Pentagon and at the Shanksville, Pennsylvania, crash site—one of the most comprehensive forensic investigations in U.S. history (Stone, 2011).

The Base Realignment and Closure (BRAC) Act of 1990 (PL 101-510) formalized a mechanism for improving the efficiency of the military by closing and consolidating operations. Several DoD hospitals and other health facilities were shuttered as part of various rounds of evaluations by an independent entity known as the BRAC Commission that was formed to implement the law. Pathology specimens and other diagnostic materials and data in 27 of the closed facilities were transferred to the AFIP repository to satisfy accreditation requirements for specimen retention (Baker, 2011). The 2005 BRAC Commission recommendation called for the disestablishment of AFIP with the exception of the National Museum of Health and Medicine and the tissue repository and for the relocation of the AFMES and the DNA registry (Defense Base Closure and Realignment Commission, 2005). In response, the DoD undertook a re-evaluation of the administration and scope of its pathology services.

AFIP's disestablishment raised concerns in the clinical diagnostic and research pathology communities that were centered on the loss of ready access to the staff's expertise (McCook, 2011). The National Defense Authorization Act of 2008 (PL 110-181, § 722) created the Joint Pathology Center to absorb the AFIP repository collections and continue consultation services, education, and research. The DoD later formed a working group that developed a concept of operations for the organization. It defined the JPC's vision and mission as follows (JPC, 2012):

> **Vision:** The Joint Pathology Center (JPC) is the federal government's premier pathology reference center supporting the Military Health System (MHS), DoD and other federal agencies.
>
> **Mission:** The JPC provides world class diagnostic subspecialty pathology consultation, education and research services to federal agencies and operates the National Pathology Tissue Repository in support of the mission of the Department of Defense and other federal agencies.

AFIP's civilian consultation mission was discontinued in September 2010, and the JPC took over from AFIP formal responsibility for accepting cases from the Military Health System and other federal government entities on April 1, 2011 (JPC, 2011). The JPC became fully operational in September 2011.

A more detailed history of the repository can be found in *Legacy of Excellence. The Armed Forces Institute of Pathology, 1862–2011* (Stone,

2011), on which this section is based. Box 1-1 cites some examples of how repository materials have been used to advance scientific knowledge.

THE JOINT PATHOLOGY CENTER BIOREPOSITORY

As of 2011, the JPC tissue repository comprised some 7.4 million accessions[1] containing specimens or data from about 3.2 million people (Baker personal communication, 2011a), making it the largest collection of human pathologic specimens in the world. About 3.2 million of the accessions are part of the Central Repository (also referred to as the Central Collection), which is composed primarily of biologic materials submitted for consultation by military, other government, and civilian medical providers.

Over the years, some of the materials were organized into collections of rare or otherwise interesting specimens. Those and the war and cohort registries noted above were flagged in the inventory database rather than separated from the rest of the collection.

The remaining 4.2 million accessions are from the facilities that were closed under the BRAC process. They differ from the Central Collection in that they include the complete array of data and specimens collected in the course of provision of routine medical care. About two-thirds of the so-called BRAC Collection cases have both specimens and data; the remaining one-third have only data (Baker personal communication, 2011a).

All told, the repository includes

- 55 million glass slides.
- 31 million paraffin-embedded tissue blocks.
- 500,000–700,000 wet tissue samples.[2]
- 29 tissue microarray assays, each of which may contain hundreds of specimens.
- over 23 million digitized images of specimens.
- an unknown quantity of digitized radiologic images.
- other pathology and diagnosis-related holdings, including medicolegal materials and veterinary specimens (Baker, 2011).

There are also 18 freezers with frozen samples that were still being cataloged in early 2012. The samples include tissue, urine, and other bodily fluids submitted for testing environmental exposures in the depleted-

[1]The terms *accession* and *case* are used interchangeably in the literature and in this report to refer to a submission of material to a repository that is cataloged into its inventory. A particular patient may have multiple accessions in a repository. In addition, an accession may include multiple types of material, such as a macroscropic specimen, paraffin blocks, and glass slides.

[2]Wet tissue samples are fixed in formalin or some other preserving agent but not otherwise processed. They typically are stored in sealed, airtight containers.

BOX 1-1
Past Uses of the Joint Pathology Center Biorepository

One of the primary reasons offered for preserving the Joint Pathology Center (JPC) biorepository is that specimens from this collection are instrumental in addressing public health issues (Auburn Health Strategies, 2005). The most prominent instance of this entails the use of tissue specimens in the repository to sequence the 1918 influenza virus, which killed more than 40 million people worldwide. That research was of great importance in that it may provide clues for avoiding future influenza outbreaks. In 1995, a research team led by Jeffery Taubenberger, chief of the Division of Molecular Pathology of the Armed Forces Institute of Pathology (AFIP), used technology that could extract RNA fragments from formalin-fixed, paraffin-embedded tissue to sequence the 1918 influenza virus. The researchers examined more than 100 autopsy cases from the pandemic that were stored in the AFIP biorepository and found one case that tested positive for the presence of influenza RNA. From that sample, they sequenced four gene segments, which revealed that the pathogen was an H1N1 influenza A virus. It was feared that there would not be enough material to sequence the entire genome. Fortunately, another scientist, Johan Hultin, provided AFIP with an infected lung sample from a 1918 influenza victim in Brevig Mission, Alaska, whom he exhumed (Taubenberger et al., 2007). The investigators compared the sequences of one gene segment from both samples with the sequence of a third 1918 influenza sample—which was found in the AFIP biorepository after a second round of screening in 1997—and discovered that the three were almost identical. The researchers decided to sequence the rest of the genome by using the sample that contained the most material, the Alaska case. In the end, tissue samples from the AFIP repository were instrumental in sequencing 4 of 11 gene segments from the 1918 influenza virus. In 2008, Taubenberger's team followed up their study by examining 58 cases from 1918 influenza pandemic from the AFIP repository and 8,335 other cases to determine that the primary cause of death from the pandemic was secondary bacterial pneumonia (Morens et al., 2008). The data also correlate with findings from the 1957 and 1968 influenza pandemics and will aid in planning for future outbreaks.

uranium registry program and other circumstances and frozen tissue left over from neuromuscular biopsies submitted for clinical diagnosis (Baker personal communication, 2011b).

Slides are held in an automated storage and retrieval mechanism. Paraffin blocks, wet tissue samples, veterinary specimens, and other pathologic materials—including all the BRAC Collection—are stored in cardboard boxes in high-density storage units. The materials are housed in climate-controlled storage facilities in an annex of the Walter Reed Army Medical Center in Forest Glen, Maryland.

Data associated with accessions vary according to when they were

Specimens from the AFIP biorepository have also been important for other less notable discoveries. U.S. Army Lt. Col. Joseph Woodward was the first pathologist at AFIP, which was then called the Army Medical Museum. In 1862, he generated tissue sections from autopsies of Civil War victims who suffered from chronic diarrhea. Woodward used those sections to revolutionize the field of histology in the United States by establishing the use of synthetic aniline dyes to stain particular parts of tissue (Woodward, 1865)—a practice that had been independently developed 2 years earlier in Germany but had not yet reached the United States (Saunders and Barron, 1970).

Another important AFIP study occurred in 1983, when researchers examined biorepository cases of children who had Reye's syndrome, which causes damage to the brain and liver. They found that the syndrome was linked to the use of salicylate (aspirin) to treat chickenpox and upper respiratory infections (Starko and Mullick, 1983). After that discovery, the Food and Drug Administration issued a warning about the use of aspirin in children and infants who had influenza or chickenpox, and the warning has correlated with a decline in the occurrence of Reye's syndrome.

AFIP researchers reviewed and performed autopsies from 2003 to 2005 on U.S. marines who died in Iraq and Afghanistan. The data obtained have been influential in protecting and treating our troops. For example, researchers determined that having armor that protected the shoulder, back, chest, and side can prevent most fatal injuries (Global Security, 2006; Gutierrez, 2009); this resulted in the development of more efficient body armor for military personnel by the Department of Defense (DoD) (GAO, 2007). Body scans of those subjects revealed that the needles and tubes inserted into soldiers suffering from collapsed lungs were too small for about half of military personnel. That finding led the DoD to switch to thicker tubing to penetrate collapsed lungs for treatment (GAO, 2007; *New York Times*, 2009). Finally, specimens that have been archived at AFIP have been used to describe rare diseases, such as papillomatosis (Antila et al., 2008) and hibernoma (Murphey et al., 2004), so that they can be diagnosed more readily.

sent to the repository. In recent decades, information accompanying most accessions in the Central Collection includes patient name, Social Security number,[3] date of birth, repository accession number, surgical number, type of specimen, contributor's[4] health care facility, and specialty branch num-

[3]Social Security numbers were first assigned in late 1936 (Social Security Administration, 2012).

[4]*Contributor*, in the repository's parlance, is the medical professional (often, a pathologist) who submits the specimen for consultation or storage, not the person from whom the specimen was obtained.

bers associated with the consultation. The specimens themselves typically are labeled with at least two identifiers: the surgical number and the accession number (Baker personal communication, 2011a). Other information that may also be associated with the sample includes age, sex, race, ethnicity, the contributor's working diagnosis, and details of the patient's clinical history—location and size of tumor, symptoms, duration of illness, physical and laboratory findings, type and date of surgeries, and other treatments (Baker personal communication, 2011a).

Data related to specimens in the BRAC Collection vary because the submitting military treatment facility, rather than the repository, determined which information was collected. It usually includes patient name, facility where the specimen originated, surgical number, and diagnosis (Baker personal communication, 2011a). Some of that information has been entered into the repository's database; other parts are available only in paper records, almost all of which had been captured in portable document format (PDF) by late 2011 (Baker personal communication, 2011a). Those data were received in paper form and then, in more recent years, either coded electronically or stored in image form. The database that contains them allows records to be searched for information on a particular person and for research, statistical, and inventory-management purposes.

For the last several years, material submission has been routinized through the use of a Contributor's Consultation Request Form (JPC, 2011). The most recent version of the form, a PDF with a March 31, 2011, date stamp, is reproduced in Appendix C. It includes two items pertinent to the future use of specimens. The first is the biorepository's specimen-retention policy:

1. MICROSCOPIC SLIDES SUBMITTED WITH EACH CASE ARE RETAINED PERMANENTLY. Under certain circumstances original slides may be returned to the Contributor if requested by the Contributor and approved by the JPC. If slides are returned, then each slide will be digitized at the expense of the Contributor.
2. Blocks are retained for a minimum of ten (10) years, unless return is requested by the Contributor at the time the case is submitted. Contributors may request return or loan of blocks at some later time. If blocks are returned, then JPC will retain representative diagnostic material.
3. Other pathologic material, X-rays, CT scans, MRI scans, echograms, angiograms, photographs, and similar diagnostic studies *may be retained for education and research* or discarded. [emphasis added]

The second is a Privacy Act Statement, which includes notification that submitted material may be used for research:

1. AUTHORITY: 5 U.S.C. 301 and 10 U.S.C. 176, 5 U.S.C. 552a, 10 U.S.C. 1079b.
2. PRINCIPAL PURPOSES: Medical information received is considered during the consultative process and is used to form a database for education and research in pathology. Other patient information is used for filing and retrieval of consultation records. Information concerning the contributor is used to maintain contributor mailing lists.
3. ROUTINE USES:
   a. In addition to those disclosures generally permitted under 5 U.S.C. 552a(b) of the Privacy Act, these records or information contained therein may specifically be disclosed outside the DoD as a routine use as follows.
   b. Pathology consultation records are tracked in the Pathology Information Management System database for filing and retrieval of records, medical research, and statistical purposes. Individual consultation records may be released to the contributing medical care provider (physician, veterinarian), when required by law or as otherwise permitted by 45 C.F.R. 164.
   c. The DoD 'Blanket Routine Uses' set forth at the beginning of the Army's compilation of systems of records notices also apply to this system.
   d. Pathology consultation records contain individually identifiable health information. The DoD Health Information Privacy Regulation (DoD 6025.18-R) issued pursuant to the Health Insurance Portability and Accountability Act of 1996, applies to most such health information. DoD 6025.18-R may place additional procedural requirements on the uses and disclosures of such information beyond those found in the Privacy Act of 1974 or mentioned in this Privacy Act Notice.
4. PROVISION OF INFORMATION: The provision of patient information requested on this form is voluntary. However, if the information is not furnished, a consultation may not be possible. If so, the material submitted may be returned at the discretion of the JPC without a consultation. [capitalization in original]

The committee was able to locate versions of the Contributor's Consultation Request Form dated as far back as July 1995 that contain similar language; the JPC was unable to say how long before then such notifications to contributors had been in place.

The JPC does not have documentation regarding any consent forms signed by patients or research participants whose data or specimens were submitted to the repository (Baker personal communication, 2011a). Such consents may have been obtained for clinical procedures used to excise specimens at facilities where people received medical care, but it is highly unlikely that they included notification that the specimens could be sent to a remote repository or used later for education or research purposes. Consents for research use may have been obtained for some materials gathered for the war or cohort registries, but the JPC has no documentation on these (Baker personal communication, 2011a).

The repository has a long history of conducting and collaborating on research, examples of which are highlighted in Box 1-1. In 2009, AFIP had 145 active research protocols (Baker personal communication, 2011b). Seventy-three (73) of these were internal to the institute, with no external collaborators. The remaining 72 protocols were collaborations with investigators in a wide variety of settings:

- 3 U.S. Air Force
- 21 U.S. Army
- 17 Uniformed Services University of the Health Sciences (USUHS)
- 13 multi-agency collaboration (all federal agencies)
- 11 civilian academic universities
- 4 private-sector pharmaceutical or medical device companies
- 3 civilian hospitals

ORIGIN OF THE STUDY AND STATEMENT OF TASK

The DoD in 2010 asked IOM to conduct a study of the appropriate use of the biospecimens to be maintained by the JPC. It noted that the mission of the center includes support of two primary collections—the pathology material accumulated by AFIP in the course of its clinical, education, and research activities (the Central Collection) and pathology material from DoD military treatment facilities closed under the BRAC program (the BRAC Collection)—and other materials, such as the war and cohort registries (Baker, 2011).

The DoD tasked the committee with addressing several questions:

- Given the defined mission and vision of the Joint Pathology Center, should access to repository materials be limited to the federal government or open to a larger pool of potential users? What advantages and disadvantages should be considered in defining the potential users of the repository in research?

- What are the ethical and legal considerations regarding utilization of the tissue repository in support of clinical care and education?
- The tissue repository currently contains paraffin embedded tissue, glass slides, wet (formalin-fixed tissue) and frozen tissue; some of it is not usable for consultation, education, and research given current technology. Should material not deemed currently usable for consultation, education, and research be stored indefinitely or should the JPC develop a plan for disposal of unusable or non-viable specimens and are there any legal considerations with disposal of said specimens?
- Should the BRAC Collection of materials be maintained indefinitely?
- Can tissue collected for clinical use be used for research (i.e., from patients not specifically consented for use of tissue in research)?
- What are the ethical considerations regarding use of tissues originally submitted for clinical use for research and can this be accomplished within current accepted guidelines for clinical research?
- The tissue repository currently contains consult material from both federal facilities as well as that submitted for consultation by civilian providers. Can tissue within the repository from civilian providers be utilized in the same manner as that from federal facilities?
- What considerations should be given to utilization for research of unique, one-of-a-kind, material within the Central Collection of the tissue repository?
- What existing or emerging technologies (either as an intrinsic function or through partnership) should be considered in developing a plan for utilization of the tissue repository in research and how would they potentially affect the mission of the JPC?

The DoD indicated that it would use the committee's input to inform future policy.

THE COMMITTEE'S APPROACH TO ITS TASK

The committee conducted an extensive examination of research on the scientific, legal, and ethical issues surrounding the management and use of biorepository resources in the course of its work. It did not review all such literature but attempted to cover the work that it believed to have been influential in shaping policy and practice at the time when it completed its task in mid-2012. Papers and reports reviewed were identified through extensive searches of relevant databases. Committee staff also inspected the reference lists of major papers, books, and reports for relevant citations, and committee members independently identified potential citations on the basis of their expertise. Three public meetings were held in April–September

2011 at which JPC staff, invited experts, and other participants presented information for the committee's consideration. The committee visited the biorepository in conjunction with the first of those meetings. Appendix A lists the agendas for the public meetings, the speakers, and their topics.

The committee also commissioned an analysis of property and other legal issues as they pertain to human biospecimens (Ossorio, 2012). The resulting paper was a helpful source of references and perspectives for the committee to consider.

EARLIER REPORTS ADDRESSING ARMED FORCES INSTITUTE OF PATHOLOGY AND JOINT PATHOLOGY CENTER OPERATIONS

Four outside reviews of the tissue repository's operation have been conducted since the BRAC Commission recommendation for disestablishment was promulgated. Salient results of the reviews are summarized below.

2005 Consensus Conference

Shortly after the AFIP disestablishment announcement was released to the public in May 2005, a consensus conference was convened to evaluate the status and prospects of the repository (Auburn Health Strategies, 2005). Conference panelists at the 2-day August 2005 meeting included representatives of government, the private sector, and academic clinical and research pathology communities. The panelists offered a series of observations on the future of the repository. They agreed that it "should be maintained as a vibrant, living entity that permits appropriate access" and stated that

> a scientific review process should be instituted for obtaining materials from the Repository. The process should assure the quality of the proposed scientific study and the need for the Repository tissue. The review process should be cognizant of present and future needs of military medicine. It is critical to the public health that the Repository should be widely accessible and responsive to the needs of the research community.

2007 U.S. Government Accountability Office Report

In response to a request by the Senate Committee on Health, Education, Labor, and Pensions, the Government Accountability Office (GAO) conducted an analysis of the possible effects of implementation of the BRAC recommendation to disestablish AFIP (GAO, 2007). Although AFIP was tasked to be a central resource for key pathology services, GAO concluded that its disestablishment would have a minimal effect on the DoD, VA, and civilian medical communities because the pathology consultation

services that AFIP provided could be obtained from other institutions. It asserted that the DoD—although recognizing that there would be challenges in finding new ways for government entities to obtain pathology consultations and in managing the repository assets to ensure their continued use in military and civilian research—had yet to formulate strategies to address these issues. GAO noted that the DoD had contracted for an assessment of the repository's assets and their potential for research; the contract resulted in the Asterand (2008) report discussed below.

2008 Asterand Report

Asterand, a commercial supplier of human tissue and biofluids, was contracted by the DoD's Uniformed Services University of the Health Sciences in September 2007 to assess the accuracy and completeness of the AFIP databases and to analyze the state of the repository's specimens. As part of the effort, the firm offered an estimate of the research and commercial value of the specimens and recommendations to improve the collections. Its report was delivered in December 2008 (Asterand, 2008).

Asterand's survey found that about 75 percent of requested retrievals of Central Collection cases yielded the correct records and matched the diagnoses that were requested. The information associated with the cases varied (Asterand, 2008, p. 52):

> All have summary diagnostic sheets with basic clinical information. All include an AFIP diagnostic report, and most include the standard pathology report from the submitting institution. Autopsy cases almost invariably include complete clinical history, pertinent laboratory studies, gross and microscopic descriptions, and diagnostic summaries. Some cases have X-ray images as well.

In general, older samples had fewer data associated with them. Asterand also found that some of the documentation associated with some older samples—which exist as microfiches derived from paper records[5]—was illegible because of the poor quality of the media. Limitations in the readability of materials that have been scanned into digital form and changes in pathology nomenclature over the decades also affected the ability to access older specimens with particular characteristics.

Asterand's examination of the utility of Central Collection specimens for research purposes yielded mixed results. Over 50 percent of sampled cases had tumor (primary, metastatic, or both) and normal tissue from the same patient—a characteristic beneficial for research on the role of genetics

[5]Many of these fiche have been converted to digital (PDF) format.

in disease. About 97 percent of 2,773 sampled cases had at least one readable slide; the most common readability problems in the remainder were dried or cracked mounting media and faded stains. Accompanying records identified the correct lesion in 94 percent of the roughly 2,700 slides that were spot-checked by pathologists. The state of formalin-fixed, paraffin-embedded (FFPE) tissue blocks depended on the age of the samples. Three-fourths of specimens from 1917–1969 (541 examined), about half of those from 1970–1999 (505 examined), and one-fourth of those from 1999–2002 (83 examined) had at least one aberration that impaired analysis; desiccation was identified as a problem in most of the aberrant samples. That may have been a result of storage conditions. Until the mid-1980s, the collection was housed in facilities without climate controls, and this led Asterand to comment that "considering the typical Washington DC summer weather, there were detrimental effects of heat and humidity on some samples stored under these conditions" (p. 9).

Immunohistochemical analysis—performed on 377 samples representing the period 1917–2002—found that a high level of simple antigenicity had been preserved with "no evidence of time-dependent decrease in specific staining" (p. 91). The vast majority of wet tissue specimens examined were in poor condition. More than 99 percent of the 338 specimens from 1917–1969 were completely desiccated, as were over 72 percent of the 218 from 1970–2002. Asterand observed that "it is unclear whether desiccated tissue samples can be rehydrated to restore cellular architecture and ready the tissues for future studies" (p. 92). It noted that the volume of tissue stored with a case decreased over time and that although "many samples have sufficient volume to provide tissues for various research projects" (p. 89), "limits in sample size or retention [in materials collected after 1980] may preclude further study" (p. 116).

The BRAC Collection of materials, consisting of medical records and tissue specimens transferred to the repository for storage and maintenance from closed military health facilities, were evaluated separately. Documentation related to these materials consists primarily of digitized copies of paper case reports, and there may be multiple discrete reports for a given person. The type and amount of information available varies from between records and between facilities. Importantly, there is no diagnosis field coded in the collection database. Those characteristics make it relatively difficult and time-consuming to retrieve specific information from the collection and limit its potential for research use.

Asterand's analysis of BRAC Collection specimens was limited to 13 of the 24 closed facilities stored in the repository at the time of the survey. It found that 99 percent of the roughly 9,000 slides examined were readable and that 98 percent of diagnoses associated with the slides were correctly linked with their pathology record. Of the 617 FFPE blocks that were

evaluated, 64 percent had at least one aberration that would limit research utility; air bubbles in the paraffin were the most prevalent aberrations. By and large, Asterand found "sufficient tissue for a variety of experimental procedures" (p. 110).

Asterand estimated the commercial value of the collections by extrapolating survey results regarding the accessibility of relevant data and viability of tissues to the entire repository and applying its knowledge of the market for specimens. Its most conservative estimate—based on the current state of the collection, accessibility of the materials to requesting parties without restriction, and the provision of complete tissue blocks (that is, without preservation of any portion for future use)—was about $1.4 billion.[6]

The report concluded that "the greatest strengths of the Central Repository for research and educational purposes lie in the breadth and depth of its materials and in the potential for developing cohorts for rare and unusual diseases" but that both it and the BRAC Collection "are in need of better data organization and enrichment of patient clinical information (particularly follow-up) [and that] each would benefit from selection and development of disease-based cohorts of cases with adequate amounts of representative stored tissues" (pp. 117–118).

Asterand offered several recommendations for maximizing the value of the repositories, indicating that these were predicated on "the understanding that the value of the collections can only be realized through permitting widespread access" (p. 133). They included assessing "the retrievability and quality of the RNA of tissues in both the Central and BRAC repositories to further refine the precise value and potential utility of the repositories for research" and discarding samples that have no usable tissue or have deteriorated to the point where they can no longer be used.

2008 Defense Health Board Review

In June 2008, the DoD asked the Defense Health Board (DHB)—an independent federal advisory committee tasked with providing the military with advice and recommendations on health-related issues—to review its strategic plan for the establishment of the JPC and offer its opinion on the plan's appropriateness and feasibility (Parisi, 2008). The board delivered its conclusions in December of that year (DHB, 2008).

The DHB offered a series of observations and recommendations regarding the JPC's scope of service, governance, and organizational structure. It expressed the strong belief that "the Tissue Repository is a national treasure

[6]This estimate should be viewed skeptically because the anecdotal experience of other biorepositories indicates that their presumed value as research materials sources was not borne out in practice (Silberman, 2010).

and resource from which significant potential for research and advances in medical care will result" (p. 8). However, the report counseled the DoD "to consider the legal issues that may arise in situations where non-DoD entities may have access to and utilize some of these assets," stating (DHB, 2008, p. 5) that

> it is essential that the plan clearly delineate the access and usage limits of the resources available through the Tissue Repository. The Board advises DoD to thoroughly define the route of access to specimens for civilian sector research and include a direct communication mechanism to ensure a facilitated process for interagency and civilian avenues of approach.

NATIONAL ACADEMY OF SCIENCES REPORTS ADDRESSING RELATED TOPICS

A number of National Academy of Sciences reports have addressed topics relevant to the issues under consideration here. Salient publications are summarized below.

Monitoring Human Tissues for Toxic Substances (NRC, 1991) described the benefits of using tissue specimens to evaluate the health effects of exposures to chemicals in the environment. The report described the need for quality control in maintaining biospecimens in the short term and the long term. It noted that "access to specimens in an archive must be carefully controlled" and that "in each case, it must be determined whether a projected use will provide useful data and its value must be balanced against the need to maintain specimens for future studies" (p. 106).

Effect of the HIPAA Privacy Rule on Health Research (IOM, 2006), the proceedings of a workshop, evaluated the rule's impact on research, including considerations regarding the bureaucracy, informed consent, and clinical trials. A participant observed that the Common Rule has been interpreted to permit broad research consents whereas the Privacy Rule requires study-specific consents and that this often led to confusion in the research community. A resulting suggestion was to allow both broad and specific consent of biospecimen preservation, maintenance, and use under HIPAA.

Beyond the HIPAA Privacy Rule: Enhancing Privacy, Improving Health Through Research (IOM, 2009) assessed whether the HIPAA Privacy Rule was having an effect on health research and offered recommendations to promote efficient health research while maintaining the privacy of personally identifiable health information. The report stated that the Privacy Rule did not protect privacy as well as it should and that it was hindering effec-

tive and efficient health research. Its recommendations included improving data and privacy security and the proper application of privacy protections.

Conducting Biosocial Surveys: Collecting, Storing, Accessing, and Protecting Biospecimens and Biodata (NRC, 2010) evaluated the best approaches to the collection, storage, use, and sharing of biospecimens gathered in social-science surveys and studies. The committee recommended that potentially sensitive data or data that could be used to identify a particular research subject should be shared only under very restricted circumstances and only if the data have been encrypted. The report also recommended that the National Institutes of Health develop procedural standards that would maintain the privacy of data held in repositories, including the use of informed consents.

Establishing Precompetitive Collaborations to Stimulate Genomics-Driven Drug Development (IOM, 2011) summarized the results of a July 2010 workshop convened to elucidate a conceptual framework for the sharing of stored biospecimens and associated data by academe, industry, government, and other stakeholders. Speakers emphasized that high-quality data can be derived only from high-quality biospecimens. Workshop participant Carolyn Compton, a member of the present committee, noted that the salient question was not "Can I get access to existing samples?" but "Do I want them?" Highly variable specimen quality and lack of consent for research use were among the other identified barriers to effective research.

ORGANIZATION OF THIS REPORT

The remainder of this report is divided into three chapters and supporting appendixes. Chapter 2 addresses the determinants of the research value of biospecimens held in repositories, concentrating on scientific and technical considerations. It begins with a summary of the means by which specimens are preserved and an explication of the education, clinical care, and research uses to which they are put. The text then describes the technologies used to manage specimen and data acquisition and to maintain and analyze specimens and data. It concludes with a discussion of the scientific and technical limitations on using in research samples that were originally obtained for pathology purposes.

Legal, ethical, and regulatory considerations regarding the use of repository specimens in clinical care, education, and research activities are taken up in Chapter 3. It begins with a general discussion of these considerations and previous scholarly work concerning them. The text then addresses considerations regarding the source of specimens, before finishing with an examination of the federal laws and regulations, DoD rules, and

AFIP and JPC regulations regarding research on biospecimens and their associated data.

Chapter 4, the final chapter, builds on the foundation of the foregoing to draw out the overarching themes of the report and presents the committee's findings, conclusions, and recommendations related to its statement of task.

Agendas of the public meetings held by the committee are provided in Appendix A. Appendix B contains a reproduction of the latest (as of the time this report was completed) version of JPC's Contributor's Consultation Request Form. DoD Instruction 3216.02, which delineates the military's rules regarding the protection of human subjects and adherence to ethical standards in DoD-supported research, is reproduced in Appendix C. Biographic information on the committee members and staff responsible for this study are provided in Appendix D.

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2

Determinants of the Research Value of Biospecimens

Pathology is the study of the structural and functional changes brought about by disease or injury. Pathologists analyze biospecimens for such changes and thereby attempt to discern their causes. The present committee's statement of task poses a number of questions regarding the future use of the Joint Pathology Center (JPC) repository's biospecimens collection in clinical care, education, and research activities. This chapter lays the groundwork for addressing those questions by providing information on the means of preserving biospecimens, on methods for analyzing and assessing their research value, and on how the details of preservation, storage, documentation, and the applications for which they are intended may affect prospects for their use. It focuses on scientific and technical considerations; legal and ethical issues are addressed in Chapter 3.

COLLECTION AND PRESERVATION OF BIOSPECIMENS

Three types of biologic material may be collected during pathologic investigations: tissues and cells removed during surgery or obtained specifically for diagnosis via biopsy; cytologic material, including that from fine-needle aspiration biopsy, brushings, or swabs; and whole blood. The main objective in diagnostic pathology and pathology laboratories is to provide accurate diagnosis of a disease and additional pathologic information needed to define a prognosis and determine appropriate therapeutic strategies. Clinical data—including information about the patient and her or his medical history, physical examination, and diagnostic imaging, such as X-rays, CT scans, and the like—are also collected to inform evaluations.

This section briefly addresses how specimens are handled after collection, focusing on the types of samples found in the JPC repository. Figure 2-1 shows the relationship between the various materials collected and their forms of preservation for pathologic analysis.

The pathology workflow for tissues comprises collection or excision from the patient; visual examination of the macroscopic specimen (called a gross specimen); initial stabilization; transfer to a laboratory; selection of material from the gross specimen for further analysis; fixation; further visual examination; histopathologic, biochemical, or molecular analyses; and storage.

After collection or excision and any initial diagnostic evaluation, specimens are typically either frozen or chemically stabilized for transport. The essential processing steps for laboratory preparation of samples that are not maintained in a frozen state are summarized below.

Fixation. Fixative solutions stabilize tissue structure and biochemical constituents by coagulating (cross-linking, denaturing, and precipitating) proteins and thereby prevent cellular hydrolytic enzymes, which are released when cells die, from degrading tissue components and rendering tissues inadequate for microscopy. Fixation also immobilizes fats and carbohydrates, reduces or eliminates enzymatic and immunologic reactivity,

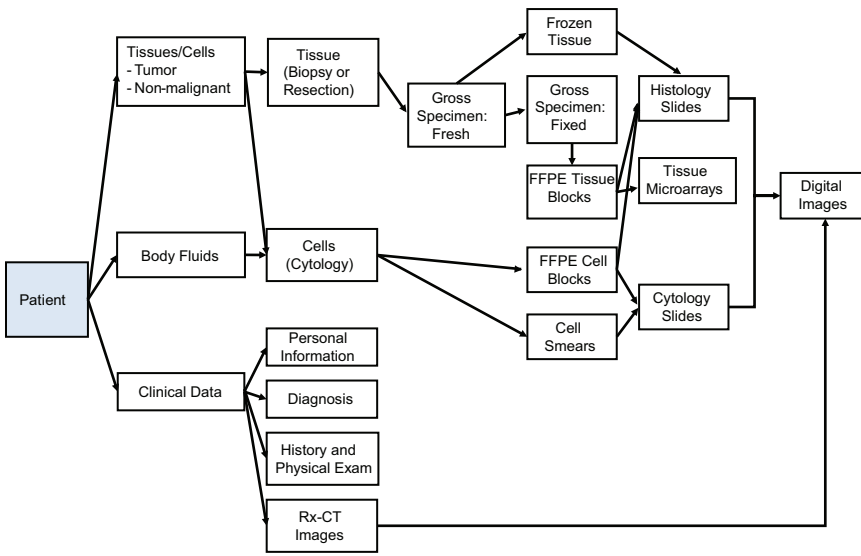

FIGURE 2-1 Relationship between pathologic materials collected and form in which they are preserved for analysis.

and kills microorganisms that are present in tissues. The fixative routinely used in pathology is 10 percent neutral buffered formalin, a buffered aqueous solution of formaldehyde. Fixation yields "wet tissue" that is either stored in an air-tight container or processed further as delineated below.

Embedding. Specimen water (about 70 percent of tissue mass) is replaced with paraffin wax, and the specimen is surrounded by paraffin in a mold to provide support during sectioning and to aid in preservation. Formalin-fixed paraffin-embedded (FFPE) tissue is one of the predominant forms in which pathologic specimens are stored.

Sectioning. Sections are cut on a microtome, which has a blade similar to a single-edge razor blade, that is advanced through a block of paraffin-embedded tissue. The shavings—about 5 μm thick, about twice the thickness of a human hair—are placed in water, and the floating shavings are picked up on 1 × 3-in. glass slides. A given tissue block can be recut many times, although specific slices may differ in the amounts and types of tissues (for example, primary tumor vs. normal tissue) present.

Staining. Tissue components can be distinguished with selective absorption of dyes to facilitate viewing under a microscope. The stain routinely used in histology is hematoxylin and eosin. There are special methods for highlighting components (such as microorganisms) that do not stain well with the customary preparations. Pathologists commonly use tissue sections prepared in this manner in their analyses.

Researchers use tissue microarrays (TMAs) constructed from diagnostic blocks of FFPE tissue to permit simultaneous evaluation of expression of specific pathologic features—proteins by immunohistochemistry, for example—in hundreds of individual tissue samples from different patients on a single slide (Rimm et al., 2011; Voduc et al., 2008). TMAs are assembled by using a needle to core an FFPE tissue block and extract a 0.5- to 2.0-mm piece that is placed into a predrilled master paraffin block that may contain up to 400 cores. Sections from the resulting block may be cut with a microtome, placed on a slide, stained, and analyzed. In cancer research, TMAs are used to analyze the frequency of a molecular alteration in different tumor subtypes, as detected by immunohistochemical and molecular techniques, to enable evaluation of potential diagnostic and prognostic markers by correlating staining patterns with light microscopy and clinical information, which may also contain outcome measures (Camp et al., 2008; Kapur, 2011). Advantages of using TMAs include minimal tissue use, lower reagent costs, faster results, and the ability to define a set of cases that

have related diseases and clinical annotations and to use many such cases in direct parallel analysis on the same slide.

Advances in technology also permit high-fidelity capture of the information contained on slides and in diagnostic images in digital form. Digitization removes the opportunity for further biologic analysis but facilitates storage, sharing, and, if desired, deidentification of specimens.

USES OF BIOSPECIMENS

Educational, clinical consultation, and research uses impose different demands on the physical state of a specimen and the documentation that accompanies it. This section presents a brief summary of the considerations that influence the assessment of fitness for those uses.

Educational Uses

Educational uses have the lowest bar for molecular quality and physical integrity of material and therefore can, in principle, permit the greatest variety of samples. However, it is uncommon to keep fresh, frozen, or even preserved samples in a manner that would allow ready distribution beyond the location at which they were generated. Indeed, unfixed tissue poses a risk of infection and should be handled only by persons who are trained in handling potentially infectious agents. The risk associated with fixed tissues is much lower, but such agents as prions are not inactivated by normal fixation methods. Fixed specimens can be encased in plastic to facilitate handling, eliminate the risk of contagion, and enhance the educational value, but this is not commonly done. For those reasons, in most contexts, gross specimens are likely to have their most effective and widespread educational use in image form.

Microscope slides are extremely useful for education, are easy to ship and return, and carry a very low risk of contagion. They have a long but finite shelf-life. However, there is little need for samples of extremely rare entities, except in advanced residency and fellowship training, and slides of common entities are abundantly available. The current trend is toward archiving of teaching slides digitally and viewing them with virtual microscopy. That avoids the problems of image or slide degradation and of slide distribution. Digital microscopy allows a teacher and a student to collaborate as though they are at the same microscope even though they may be separated by large distances.

Accompanying clinical information often improves the pedagogic value of specimens, but it is not always required.

Clinical Consultation Uses

Clinical consultation was a major function of the Armed Forces Institute of Pathology, and the JPC continues to serve this function for the Military Health System, the Department of Defense, and other federal agencies. In the past, it was common to limit the materials for consultation to stained microscopic sections. Advances in diagnostic procedures now require the ability to extend the histopathologic description with immunohistochemical and molecular probes. That may require that unstained slides be included in the materials for consultation and, less often, that the tissue block or fresh-frozen tissue be available. Consultation also requires that detailed clinical information be provided to the consulting physician. Large medical centers can often carry out the more advanced procedures on their own and need only send appropriately stained slides to the consultant, whereas smaller centers might require that the consultant carry out the procedures. In general, fresher, unfixed tissues give better results in assays than do samples that have had longer intervals at room temperature or long periods in fixatives. When consultation is limited to examination of slides, digital (or "virtual") microscopy via scanning of glass slides (Pantanowitz et al., 2011) allows rapid, interactive consultation without the need to transport and retrieve slides.

Research Uses

Research comprises a broad array of activities and a correspondingly broad array of requirements for pathologic specimens. Case reports and historical studies might need slides alone and be limited only by the condition of the slides, but more extensive studies of the mechanism of disease require the freshest materials possible with cryopreservation, snap freezing in liquid nitrogen, or relatively brief times in fixatives to obtain the best results. That means not that older materials or materials that have not been obtained under those conditions are without value—DNA sequences have been obtained even from Neanderthal bones—but simply that they make studies technically more difficult and limited in scope and preclude some studies as the signal-to-noise ratio tilts toward the noise.

In most cases, the more complete the accompanying clinical information is, the more valuable the sample. Nonetheless, many otherwise undocumented samples that have been well characterized histopathologically can be of value in genetic, microRNA (miRNA), and other functional studies. Studying diseases that have a high incidence, such as breast cancer, need not depend on suboptimal tissues or special collections inasmuch as specimens are readily available, whereas studying rare diseases may require greater

compromises with respect to sample quality and rely critically on special collections and repositories.

Limitations on the use of pathologic samples in research are addressed in greater detail later in this chapter.

TECHNOLOGIES USED TO MANAGE SPECIMEN ACQUISITION AND MANAGEMENT

Over the last two decades, technology development has created both challenges to and opportunities for human biospecimen resources. The sensitivity, specificity, multiplexing capability, and speed of operation of technologies for molecular analysis of all classes of biomolecules in human specimens have undergone transformative improvements, and further refinements are developed at ever-increasing rates. However, this greatly augmented analytic power has raised the bar for the quality of the biospecimens that serve as the source of analytes for the technology platforms, which are increasingly used in research and clinical care. Biospecimens acquired in the setting of standard clinical practice that formerly served as adequate sources of research material despite the varied, undocumented, and uncontrolled sources of preanalytic variation[1] to which they were exposed are no longer adequate, let alone optimal, for new molecular-assessment platforms. Technology development specifically directed to the challenges related to biorepository operation in this environment has been essential in addressing the gap between the demand for and supply of high-quality human specimens for molecular research.

Biorepositories, such as the JPC, that comprise clinically derived samples collected in diverse settings and referred for pathologic consultation on disease, typically face greater complexities in ensuring that their collections meet quality standards for sensitive analytic platforms than do biobanks that were established for the express purpose of collecting specimens for research. Clinical consultation biorepositories have difficulty in controlling, recording, or assessing the sources of preanalytic variation that may compromise the molecular quality of their collections. Thus, technologic solutions for controlling processing and environmental variation and for assessing the molecular quality of processed or stored specimens have been essential for the continued evolution and usefulness of clinical consultation biorepositories for biomedical research.

[1]Preanalytic variation refers to any of the many biospecimen acquisition, handling, or processing procedures and environmental characteristics (such as temperature and humidity) to which a specimen may be exposed before analysis takes place. Preanalytic variation may alter the molecular quality or composition of a biospecimen and render it unsuitable for a specific type of analysis.

Technologic solutions for the problems in specimen acquisition, preservation, and management include the following:

- *Shipping technologies* that maintain specific environments during transport of samples and thus help to maintain the molecular quality of the samples for analysis at remote sites.
- *Specimen fixation and other stabilization technologies* that preserve the quality of labile biomolecules, allow optimal molecular preservation and histopathologic quality, or allow in situ stabilization of the specimen to preclude preanalytic variation incurred during specimen acquisition (for example, through surgical resection and pathologic handling).
- *Information technology solutions* that allow annotation of specimen collections with clinical data about the individual from whom the specimen is derived; consent to specimen collection, transfer, storage, and use; authorization of use of protected health information; pathologic data on the specimen (such as gross description and accompanying diagnosis); collection, processing, transportation, and storage data; quality-control data; specimen analysis data; radiologic imaging data; inventory tracking; overall (system-wide) quality-management data; and molecular analysis data.
- *Specimen or molecular storage technologies*, such as ambient-temperature ("dry-state") storage.
- *Molecular quality-assessment technologies* for RNA, DNA, and proteins.
- *Digital imaging and image analysis technologies* for precise structure-based data associated with each specimen.

Those categories of technologies are not all equally developed, but all continue to improve rapidly and decrease in cost. Nevertheless, the rate of obsolescence of many of the technologies and the increasing knowledge of the effects of specific preanalytic factors on molecular analysis data require continual reassessment of the adequacy and functionality of technologies that are in place in light of the repository's mission.

TECHNOLOGIES USED TO ANALYZE SPECIMENS

Researchers have several tools at their disposal for deriving clinical and research information from specimens. This section—which is based on review articles by West (2010) and Beck and colleagues (2010)—identifies some of the technologies used in analysis and discusses how preservation technique influences the ability to perform various types of analysis.

Table 2-1 summarizes the results of some recent research on the influ-

TABLE 2-1 Recent Research on the Influence of Preservation Method on Specimen Analysis Outcomes

Collection or Preservation Methods	Tissue Types	Attributes
Fresh-frozen (Snap-frozen)	Pancreatic cancer specimens	RNA integrity was determined with microcapillary electrophoresis, using RNA integrity number (RIN) algorithm and results of laser-capture microdissection (LCM). Various ex-vivo procurement times (up to 10 min, 11–30 min, 31–60 min, over 1 h); banked over three periods (2001–2004, 2004–2006, 2006–2008)
Fresh-frozen	Invasive breast cancer tissues	Manual method: subjective evaluation of electropherogram; ratio method: ratio between 28S and 18S peaks; RIN
Room temperature, iced, saline solution, RNA-stabilizing buffer, snap-frozen (after 0.5, 1, 3, 6, 16 h)	Normal tonsil Normal colon	Structural RNA integrity via microchip electrophoresis
Snap-frozen (unfixed and immersed in RNA-stabilizing buffer), thawed for 0, 5, and 45 min, 1, 3, 6, and 16 h	Tonsil	Microchip gel electrophoresis and gene expression level via PCR
Snap-frozen, formalin-fixed paraffin-embedded (FFPE)		RNA quality
FFPE	Diffuse large B-cell lymphoma	Gene expression

Effects	Source
• 42 percent of human pancreas cancer specimens banked under a dedicated protocol yielded RNA with a RIN of ≥7 • Brief warm ex-vivo ischemia times did not adversely affect RNA quality (percentage of tissue with total RNA with RIN of ≥7 for ≤10 min, 42 percent; 11–30 min, 58 percent; 31–60 min, 33 percent; >60 min, 42 percent) • Long-term storage of banked pancreas cancer biospecimens did not adversely affect RNA quality (total RNA with RIN of ≥7 banked in 2001–2004, 44 percent; 2004–2006, 38 percent; 2006–2008, 50 percent); RNA retrieved from pancreatic cancer samples with RIN of C7 subject to LCM yielded RNA suitable for further downstream applications • Fresh-frozen pancreas tissue banked according to a standardized research protocol yields high-quality RNA in about 50 percent of specimens and can be used for enrichment with LCM; quality of tissues in the biobank was not adversely affected by slight variations in warm-ischemia times or different storage periods	Rudloff et al., 2010
• Comparison between RNA quality (RIN) and gene expression analysis shows dense clustering of high-quality samples but weak clustering of low-quality samples • Manual and RIN methods are superior to ratio method	Strand et al., 2007
• RNA stable in both tissues under all conditions for up to 6–16 h • Expression levels essentially stable when samples kept on ice • Marked regulation of single genes observed during room-temperature storage in normal saline and RNA-stabilizing buffer • RNA from 54 of 47 samples had proper ribosomal peaks • Nonfixed specimens may be transported on ice for hours with minimal influence	Micke et al., 2006
• Minimal RNA degradation after 30 min • Relevant changes in some gene-expression levels at 45 min • Repetitive thawing cycles had similar effects on RNA integrity • Incubation in RNA-stabilizing buffer prevents RNA degradation	Botling et al., 2009
• Introduced heating into extraction protocol to improve quality; incubation at 70°C for 20 min was applied to disrupt cross-links in FFPE without compromising RNA integrity • TaqMan detection influenced by master mix, amplicon size, and use of preamplification step • Comparable results in frozen and FFPE tissue	Li et al., 2007
• Provided PCR protocol for gene-expression analysis • 62 of 65 samples “successfully” analyzed	Votavová et al., 2009

continued

TABLE 2-1 Continued

Collection or Preservation Methods	Tissue Types	Attributes
FFPE	Parathyroid	Proteome quality
Fresh-frozen, FFPE	Colon adenoma	Proteome quality Liquid chromatography
Frozen, FFPE	Frozen/optimal cutting temperature (OCT)-embedded livers (rats)	Proteome quality Liquid chromatography

Effects	Source
• 163 unique proteins identified via mass spectrometry • Similar results via sodium dodecyl sulfate (SDS)-out in gel-free method • Antigenicity not always preserved in Western blot • Despite some limitations due to extensive formalin-induced covalent cross-linking, results suggest that FFPE extracts may be an alternative source for large-cohort samples when frozen samples are unavailable	Donadio et al., 2011
• "The major difference between frozen and FFPE proteomes was a decrease in the proportions of lysine C-terminal to arginine C-terminal peptides observed, but these differences had little effect on the proteins identified." • "Analysis of archival colon adenoma FFPE specimens indicated equivalent numbers of MS/MS spectral counts and protein group identifications from specimens stored for 1, 3, 5, and 10 years." • "Analysis of the combined frozen and FFPE data showed a 92 percent overlap in the protein groups identified. Comparison of gene ontology categories of identified proteins revealed no bias in protein identification based on subcellular localization." • "Archival samples displayed a modest increase in methionine oxidation, from approximately 17 percent after one year of storage to approximately 25 percent after 10 years." • "These data demonstrate the equivalence of proteome inventories obtained from FFPE and frozen tissue specimens and provide support for retrospective proteomic analysis of FFPE tissues for biomarker discovery."	Sprung et al., 2009
• "Comparable molecular mass representation was found in extracts from FFPE and OCT-frozen tissue sections, whereas protein yields were slightly less for the FFPE sample." • "The numbers of shared proteins identified indicated that robust proteomic representation from FFPE tissue and LCM [laser capture microdissection] did not negatively affect the number of identified proteins from either OCT-frozen or FFPE samples." • "Subcellular representation in FFPE samples was similar to OCT-frozen, with predominantly cytoplasmic proteins identified. Biologically relevant protein changes were detected in atorvastatin-treated FFPE liver samples, and selected atorvastatin-related proteins identified by MS were confirmed by Western blot analysis. These findings demonstrate that formalin fixation, paraffin processing, and LCM do not negatively impact protein quality and quantity as determined by MS and that FFPE samples are amenable to global proteomic analysis."	Scicchitano et al., 2009

continued

TABLE 2-1 Continued

Collection or Preservation Methods	Tissue Types	Attributes
FFPE	Heart tissue (mice)	Proteome quality
FFPE	Liver (mouse)	Proteome quality
FFPE (different temperatures [4, 20–25, 37°C] and storage times [0–12 months])	Liver, kidney, heart, brain, lung, spleen (rat)	RNA quality
FFPE (different fixation periods)		RNA quality

ence of preservation method on specimen analysis outcomes. It is intended not as a comprehensive survey of the literature but as an illustration of work in this field.

Protein Expression

Immunohistochemistry

Most gene-expression profiling studies aim to address clinical questions with biologic insight. Conventional gene-expression profiling, in which thousands of measurements are made, is not yet an efficient clinical tool. It is expensive, is technically demanding, and requires arduous tissue-handling protocols for optimal results (for example, rapidly freezing fresh tissue and maintaining it frozen at well-controlled, very low temperatures). However, such approaches as multiplex polymerase chain reaction (PCR) are emerging as useful options (Parker et al., 2009). Such techniques offer important

Effects	Source
• "Incubation of tissue sections at high temperature with a novel extraction buffer . . . resulted in improved protein recovery." • "This is an indication of the formation of protein-protein complexes by cross-linking, and of protein fragmentation due to prolonged sample storage."	Azimzadeh et al., 2010
• "It was found that incubation of tissue in a lysis buffer containing 6 M guanidine hydrochloride at high temperature led to the highest protein yield and the largest number of proteins identified. The peptides and proteins identified from formalin-fixed tissue were first comprehensively compared with those identified from frozen-fresh tissue. It was found that a majority of peptides identified from fixed tissue were unmodified and proteome coverage for the analysis of fixed tissue was not obviously compromised by the formalin fixation process."	Jiang et al., 2007
• RIN 7 for 1–3 days of storage at 4°C • RIN 5–6 for 1 year at 4°C • 20°C and above yielded poorer results (and poor RNA amplification) • RNA quality not adversely affected by long interaction with fixative • RT–PCR quality is affected by long interaction with fixative • Sample size influences quality: the thicker the sample, the longer it takes for fixative penetration and the lower the RNA quality; similarly for RT–PCR	von Ahlfen et al., 2007
• Optimal fixation period 12–24 h, yielded best RNA.	Chung et al., 2008

improvements in reproducibility and dynamic range, but more traditional immunohistochemistry for protein detection still has a great role in diagnostic pathology.

A strength of immunohistochemistry is the ability to perform single-cell identification and functional analysis in the context of an archival specimen. Immunohistochemistry is robust for use with a wide variety of materials obtained for pathologic analysis. Its utility is independent of the size of the specimen, working well with very small biopsies, and is often robust in non-ideal conditions. For example, the method can often identify signal in tissue that shows extensive necrosis or is contaminated with normal, inflammatory, or cancer tissue. Although it has been in clinical use for decades (Warnke et al., 1983), the field of immunohistochemistry is not stagnant. For example, a technique that uses multiple antibody stains on a single slide with different reporter dyes has been developed clinically in the last decade and now has a number of clinical applications (West, 2010). These multidimensional assays can be useful in identifying relationships between different cell types (such

as breast luminal and myoepithelial cells) or distinguishing a subgroup of a single cell type (such as proliferating lymphocytes).

Immunohistochemistry requires expert interpretation, though, and this can lead to variations in results from one laboratory to another. Another limitation of the technique is that it can be difficult to control for variation in tissue quality or stain quality. That can be a problem in dealing with clinical specimens because ischemic time, fixation time, and variations in tissue processing can decrease signal-to-noise ratio and may lead to false-negative or false-positive results. Morphology often supplies the necessary backup to a single protein biomarker but requires expert interpretation. Although poor tissue preservation is easily recognizable when underfixation is the problem, the more subtle tissue degradation due to overfixation—which preserves tissue architecture but destroys the macromolecules because of extensive cross-linking—may not be evident in morphology alone (Werner et al., 2000).

Immunofluorescence

Immunohistochemistry using immunofluorescence is an emerging technology for protein detection that is likely to have an important impact on both medical clinical work and research. Several reports of improved immunofluorescence in FFPE sections have been published (Bataille et al., 2006; Ferri et al., 1997; Mason et al., 2000; Niki et al., 2004), but the techniques have yet to become widely used because of the dearth of the needed specialized microscopic technology in most laboratories and the lack of operators who are comfortable with the techniques and their challenges. Difficult features in FFPE material, such as autofluorescence, can be reduced with the use of new reagents, such as Sudan Black B. New tools, such as confocal microscopes, can also largely reduce the problem of autofluorescence. Data obtained with these techniques are likely to be incorporated into the clinical workflow as image analysis migrates from the microscope to the computer.

Proteome Analysis

The emergence of proteomic methods has enabled researchers to interrogate expressed proteins from a number of different tissue types systematically. That allows exploratory studies as opposed to studies that depend on prior knowledge of the proteins that are being studied, as do immunohistochemical studies (Hanash et al., 2008). Proteomic methods generally require high-quality tissue because changes in protein composition can lead to difficulties with identification of specific peptides due to the features of mass spectrometry (Aebersold and Mann, 2003).

The study of proteins extracted from FFPE material is particularly challenging owing to intraprotein and interprotein cross-linking that results

from the interaction with formaldehyde, the active ingredient in formalin. This issue is difficult to bypass in that the practical goal of fixation is to preserve the morphologic features of the tissue for pathologic analysis. The preservation is achieved by strengthening the integrity of the tissue with fixation. The protein cross-linking properties of formaldehyde are well suited for this whereas other fixatives that are more gentle on protein quality fail to preserve tissue structure to the standards generally expected in patient-care settings. Recent progress has been made in using FFPE tissue for proteomics. A number of groups have used steps to reverse the covalent interactions caused by formaldehyde cross-linking, including incubation at high temperatures (Prieto et al., 2005; Shi et al., 2006). These methods have allowed novel protein identifications in FFPE material.

Gene-Expression Profiling

Since the method of gene-expression microarrays was developed in the mid-1990s, genomewide expression profiling has been used widely in research (Janssens and van Duijn, 2008; Kraft et al., 2009; van der Net et al., 2009; Xu et al., 2009). Experiments with gene-expression profiling have led to important advances in our understanding of a wide variety of human conditions, but research efforts with clinically derived specimens have been frustrated by lack of specimens amenable to the biochemistry of the technique. A major obstacle to the translation of gene-expression profiling to specimens gathered for clinical purposes has been the fact that such analyses are best performed on fresh-frozen tissue, and few specimens are stored as fresh-frozen. Indeed, essentially all clinical tumor specimens are stored as FFPE (Hewitt et al., 2008). That fixation and storage technique results in extensive RNA fragmentation and alteration of hybridization qualities (Hewitt et al., 2008). Several groups have attempted to use clinical specimens in FFPE for gene-expression profiling with microarrays (Coudry et al., 2007; Farragher et al., 2008; Frank et al., 2007; Linton et al., 2008; Penland et al., 2007; Scicchitano et al., 2009) with less than ideal results.

Multiplex Real-Time Polymerase Chain Reaction[2]

Multiplex PCR has recently been shown to be robust in archival material. It is able to provide quantitative information compared with the typically qualitative information supplied with immunohistochemistry. The clinical utility of multiplex PCR has been shown in connection with a number of diseases, such as breast cancer. A multiplex kit is already available for clinical use in the quantitative measurement of prognosis of

[2]PCR is a technique used to reproduce pieces of DNA or RNA for analysis.

primary breast cancers. In addition, multiplex real-time (RT) PCR has been demonstrated to outperform immunohistochemistry in the characterization of breast carcinomas into their molecular subtypes (Parker et al., 2009).

cDNA-Mediated Annealing, Selection, Extension, and Ligation

Multiplex RT–CR has been shown to be useful in analyzing the expression levels of tens of genes. Other molecular approaches allow the analysis of thousands of genes. One of these is complementary DNA-mediated annealing, selection, extension, and ligation (DASL) (Ravo et al., 2008), which uses a two-probe oligonucleotide pair to measure each complementary DNA (cDNA) target. DASL uses two small oligonucleotides placed 1–20 nucleotides apart on the annealed target cDNA. Extension and ligation steps fuse these two oligonucleotides and the ligation event indicates identification of the presence of the target RNA. The technique provides high sensitivity and accuracy for measuring RNA expression in archival material. One major drawback is that the probe pairs must be synthesized, so few gene probe pairs (typically fewer than 10,000) are available for target interrogation (West, 2010).

RNA-Seq for Archival Material: 3SEQ and SAGE-Seq

RNA-seq refers to methods that use high-throughput "next-generation" sequencing to produce reads of transcripts from each gene in a sample. A typical RNA-seq experiment generates tens of millions of sequencing reads. An expression level of each gene can be generated by counting how many reads have mapped to any given transcript.

Two novel RNA-seq protocols—3′-end sequencing for expression quantification (3SEQ) and serial analysis of gene expression-seq (SAGE-seq)—have been designed to work with mRNA extracted from FFPE tissue (Beck et al., 2010; Wu et al., 2010). As noted above, RNA purified from archival tissue does not work well with microarray methods. However, the small RNA fragments purified from archival tissue, typically 100–500 nucleotides, are well suited for small libraries for short-read (50–100 nt) sequencing.

Degraded mRNA from FFPE material can be purified with polyA selection, and reads can then be obtained from the ends (either single or paired) of the fragments. The reads are short but contain more than enough unique sequence to be confidently mapped to the reference genome. Transcript counts can thus be obtained in that the reads usually are in the three-prime untranslated region (3′-UTR) abutting the polyA tail, which leads to a convenient aggregation of signal that increases the power of the later statistical analysis. An important advantage over microarray profiling, which predefines the transcripts that will be measured by choices made in

the spotting of sequences in the array construction, is that the 3SEQ and SAGE-Seq methods generate reads from all polyA RNA molecules, including those from unannotated genes and transcripts and alternative 3′-UTRs.

RNA in situ Hybridization

An alternative method for evaluating gene expression in paraffin-embedded tissue is to use RNA in situ hybridization (ISH). The ISH technique is particularly useful for the examination of newly found genes of interest. Rather than waiting 4–6 months for a conventional antipeptide antiserum that has a success rate of 5–10 percent, ISH probes can be generated in less than a month. A number of methods are being developed. The ISH technique for archival material used most widely was developed by St. Croix and colleagues (2000) and Iacobuzio-Donahue and colleagues (2003). It uses RNA probes that are 400–600 nucleotides long. The signal is amplified with a tyramide-based system, and this is followed by development with traditional markers, either chromogenic or fluorescent substrates. The advantage of RNA ISH probes over antisera or antibodies is that one can include so-called sense strands or mis-sense probes as controls (Clarke and Shimono, 2011). Moreover, specificity of the probes is highly likely inasmuch as the probes are designed to hybridize with the 3′-UTR of each gene, an area that is highly specific for individual genes.

Despite the capabilities of ISH, immunohistochemistry appears to be more useful with very old specimens; RNA in specimens more than 20 years old appears to be less well preserved for detection with ISH. Although antigens for immunohistochemistry diminish over time, they are more resistant to deterioration than is mRNA. This issue becomes important for clinical studies that use cases with long followup.

miRNA Studies

In contrast with DNA and mRNA, the quality of miRNA does not change substantially with fixation. The key feature is the length of the miRNA molecules. These molecules are typically quite short, averaging 22 nucleotides, and so are less susceptible to fragmentation by formaldehyde (Li et al., 2007; Liu et al., 2009). The isolation of mRNA compared with miRNA can be complicated by substantial RNA degradation.

DNA Studies

Many of the studies performed with RNA can be applied equally to DNA, but high-throughput sequencing is an emerging technique specifically for use with archival DNA. The presence of mutations in multiple

cancer-related genes is being applied to DNA extracted from FFPE tumor-tissue specimens with PCR-based approaches. Recent advances in high-throughput next-generation sequencing methods permit the analysis of mutations in 200–400 genes from small amounts of FFPE-extracted DNA. DNA, in general, is much more stable that RNA. However, all nucleic acids are susceptible to depurination in highly acidic environments, and the preservation of DNA in archival tissues depends heavily on the quality of the fixative used. Depurination can lead to strand cleavage, which would create problems for many of the modern molecular techniques. Thus, if unbuffered formalin was used originally to fix the archival material—as might be the case for older specimens in the JPC repository—it could lead to substantial degradation of the DNA (Akalu and Reichardt, 1999; Bonin et al., 2010). There are few published data on the quality of reads generated from high-throughput sequencing of archival DNA.

Elemental and Chemical Studies

Tissues are routinely analyzed for trace minerals in clinical pathology laboratories for diagnostic purposes. Trace minerals are preserved and can easily be localized and measured in FFPE tissues. For example, hepatic iron concentrations are essentially the same whether assessed in fresh tissues or in paraffin-embedded tissues (Torbenson, 2011). However, the alterations in tissue quality, such as a change in weight due to the replacement of water with less-dense paraffin, can necessitate correction factors (Bischoff et al., 2008). The routine fixation process, with numerous alcohol washes to dehydrate the tissue, results in the removal of many lipophilic small molecules. Elemental concentrations were studied in the past largely with atomic absorption spectroscopy or energy-dispersive X-ray analysis, but new methods are available now (Becker and Jakubowski, 2009; Harrington et al., 2010; Mizuhira et al., 2000).

LIMITATIONS IN THE USE OF PATHOLOGIC SAMPLES IN RESEARCH

Several factors influence whether pathologic samples obtained for clinical consultation purposes will be fit for use in research. This section identifies the major issues that limit the research use of such specimens and addresses how the details of collection, preservation, storage, and documentation can affect fitness for research use.

The specimen preservation–stabilization process might be inappropriate for or incompatible with the technologic or scientific demands of the research analysis.

The suitability of any specific specimen for analysis depends on the analyte that is to be assessed and the technique to be used for the analysis—that is, whether it is "fit for purpose." As previously noted, the most common stabilization method used in pathologic practice is 10 percent neutral buffered-formalin fixation followed by dehydration with graded alcohols, xylene exchange, impregnation by liquid paraffin, and permanent preservation in paraffin. While the paraffin is maintained in liquid state, the specimen is spatially oriented in a small, thin rectangular container and then rapidly cooled until the paraffin is solidified. Adequacy of fixation of a pathologic specimen is determined largely according to the dimensions of the tissue (when it is submerged in formalin in the gross state and when it is sampled for single aliquots to be individually processed into tissue blocks, formalin penetrates about 1 cm into tissue) and the total time in fixative. In general, inadequate preservation due to underfixation is far more deleterious to samples than is prolonged fixation. Both fixation in a molecular cross-linking fixative, such as formalin, and paraffin embedding with exposure to high temperatures may compromise the molecular quality of samples.

Other related issues concern variations in concentration, pH, or buffering of formalin or the use of fixatives other than 10 percent neutral buffered formalin. The optimal formaldehyde concentration in a fixative and the optimal pH of the solution may depend on the biomolecule of interest, especially in the case of immunohistochemical analysis. Practice is not standardized, and these measures are not always recorded in pathology reports and thus represent important unknowns in research. In the past, the use of such fixatives as Bouins solution (which contained picric and glacial acetic acid with formaldehyde) or special hematopathologic fixatives that contained metals, such as B5 zinc or B5 mercuric chloride, was common, and the fixative type was sometimes not recorded as a part of the pathologic record. Many of those fixatives are incompatible with modern molecular-analysis platforms. When specimens for research are accrued from multiple institutions that use different stabilization and preservation practices, data from molecular analyses may be neither reliable nor comparable or institution-specific batch effects may be seen.

Important variation in pathologic processing also occurs before stabilization. For example, the length of time that elapses between specimen removal from a patient and specimen fixation ("time to fixation" or "cold ischemia time") and the conditions to which the specimen is exposed during this period, such as desiccation or various room temperatures (as opposed to refrigeration), may seriously alter both the molecular quality and the molecular content of the specimen and thus create artifacts that may be misinterpreted as reflecting disease biology. In some cases, the variations may even compromise histologic quality. Highly labile biomolecules may

be lost altogether as time to fixation increases. Those factors are neither controlled nor recorded in common clinical practice. Rapid stabilization of tissue with cryopreservation of various kinds (for example, immersion in liquid nitrogen, freezing in the vapor phase of liquid nitrogen before immersion, immersion in dry ice–isopentane slush, embedding in a freezing medium based on polyethylene glycol–sucrose,[3] and placement in a –80°C freezer or a cryostat) may be used in exceptional circumstances but are not the standard of care for all tissues. Thus, if frozen (unfixed) tissue is needed for research, this requirement often cannot be met pathologic tissue. If viable cells or tissues are required for research, pathologic samples cannot fulfill this requirement unless viable aliquots are preserved appropriately at the moment of acquisition of the specimen and not used as a part of a retrospective pathologic sample set.

Sample aliquot content might be unknown to the investigator, and too little of the lesion of research interest might remain in the residual tissue after clinical workup.

Each paraffin tissue block processed for a case is thinly sliced (at 5-µm intervals) with a microtome to produce sections that are placed on glass microscope slides and stained for histopathologic analysis under a light microscope. As previously noted, the standard histopathologic stain is hematoxylin and eosin, but a wide variety of stains may be used on adjacent tissue sections to reveal special features as a part of the pathologic workup. Unstained sections also are often cut and set aside for or used for immunohistochemical analyses of various types required for pathologic diagnosis and characterization. In many cases, small amounts of tissue may remain in a block after complete workup, and this can result in inadequate residual amounts for research. Inadequacy of residual tissue for research is particularly problematic if the original specimen from the patient is very small or the lesion of interest is small, focal, or both and thus not of sufficient quality (or, indeed, at present all) in the residual tissue in a block. The lack of quality control of pathologic tissue blocks made available for research, to verify the nature and content of the remaining tissue, can detract from their usefulness for research. It can also skew data from investigational studies if the residual blocks are assumed to be representative of the overall diagnosis but are depleted of diagnostic tissue.

The original pathologic diagnosis might be unconfirmed or incorrect.

Unconfirmed or incorrect diagnosis of pathologic material is uncommon (Lind et al., 1995; Ramsey and Gallagher, 1992; Renshaw et al., 2003a,b; Safrin and Bark, 1993; Wakely et al., 1998), but in cases of rare diseases or

[3]Also known as optimal cutting temperature (OCT) compound.

diseases that have a documented, notoriously high degree of interobserver variation in diagnostic interpretation, it can be an important issue for both patient management and research. In such cases, it is considered standard of care to seek a second, specialty pathologic opinion, such as the consultative opinions produced for specimens submitted to the JPC repository and its predecessors. Verification of diagnosis by obtaining a new pathologic analysis in every case used for research is recommended.

However, it may also be problematic for research if the diagnosis that accompanies the case is outdated and no longer appropriately classifies the disease. Outdated diagnostic terminology (correct diagnosis but arcane language) or outdated diagnostic criteria for identification (classification according to a schema that is no longer in use) may cause considerable difficulty in mapping a historical case to a current diagnostic category accurately. Over the span of decades that the JPC repository has existed, pathologic classification of disease has evolved substantially. In some disease categories, such a hematopathologic malignancies, entire disease classifications have changed repeatedly because knowledge of pathogenesis has grown. Modern diagnosis of lymphoma and leukemia may require delineation of specific molecular features that were never tested for in older cases. Depending on the specific preanalytic variation associated with a historical case, it may not even be possible to test accurately for the molecular features required for diagnostic classification.

The more common problem in all disease categories is the lack of standardization in diagnostic terminology that was widespread in pathology for many years. That has been exemplified both by the use of a given diagnostic term for different disease entities and by the use of multiple diagnostic terms for a given disease entity (Cooper, 2006). A researcher using a historical case may not have the requisite expertise to interpret the existing diagnostic terminology accurately and map it to the current diagnostic terminology standard correctly. Failure to reclassify cases correctly according to current diagnostic standards and current diagnostic terminology for any of the above reasons may skew research data.

Preanalytic variations related to preoperative or intraoperative factors may create molecular artifacts.

Many drugs used in preoerative and intraoperative periods and such surgical events as devascularization or arterial ligation with cessation of blood supply during resection (called *warm* ischemia time) may cause changes in the molecular profiles of resected tumor and normal tissues and preclude use of specimens for research. Shifts in molecular profiles due to iatrogenic interventions may not be recognized as artifacts and may be mistakenly interpreted as disease signatures. Some drugs used in perioperative and interoperative periods have powerful molecular effects and are, in fact,

used specifically for these effects (Juhl, 2010), although little research has been published on this topic. In addition, the type of surgical procedure, the individual surgeon performing the procedure, and the use of robotic instruments are variables that affect the duration of the resection and the resulting tissue ischemia in the resection specimen. Although some information related to the number and types of drugs given before and during an operation may be available in clinical records, such as the anesthesia report, it is uncommon to have these data available to a biorepository. The committee does not know whether or how many specimens in the JPC repository are annotated with data related to perioperative variables that may be pertinent to molecular research on the molecular profiles of tissue samples.

Perhaps the most common preanalytic variable with an important effect on results of analytic tests, such as immunohistochemical staining, is the time that elapses after surgical removal of tissue until it is stabilized with fixation or freezing (*cold* ischemia time). The process of structural and biochemical tissue degradation occurring during this time is termed autolysis. The amount of time can be substantial, ranging from minutes to hours, and is rarely recorded in the pathology report. It may cause gain or loss of signal on molecular analysis, depending on the molecular entity in question. An analysis done without knowledge of the duration of the time to fixation and without an intrinsic control within the same specimen that can serve as a reference (for example, surrounding normal tissue that is known to express or not to express the molecule constitutively) may be misleading or even completely incorrect (Spruessel et al., 2004).

Storage conditions or duration may compromise specimen quality.

Oxidation occurs in both blocks and cut sections, but it is much greater on cut surfaces exposed to room air. Thus, tissue blocks stored at temperatures below the melting point of paraffin yield cut sections that show little deterioration of immunohistochemical signal compared with freshly embedded controls for as little as 2 years or as long as 25 years (Engel and Moore, 2011). RNAases are active even in FFPE tissues. For many antigens, immunoreactivity has been shown to deteriorate more rapidly if specimens are stored as cut sections rather than whole blocks; both the time line and the magnitude of the effect are antigen-dependent.

On a crude level, paraffin blocks that have been stored under conditions that do not include climate control may lead to melting of paraffin blocks in warm weather or destruction from other causes. Gross specimens, albeit formalin-fixed, may undergo dehydration, fungal contamination, and putrefying deterioration when stored under conditions that expose them to environmental extremes. All those issues have affected specimens held by the JPC at some point over the course of the repository's history (Asterand, 2008).

Case-matched normal control samples from a tumor patient might be unavailable.

A normal specimen is needed as a source of a reference genome in tumor patients in for correct identification of tumor-specific mutations. Depending on the disease, the diagnostic or therapeutic procedure that produced the specimen, or the tissue remaining in a case after diagnostic analysis, it may not be possible to meet this requirement.

The clinical data associated with specimens may be inadequate, inaccurate, or nonstandardized.

Even if biospecimens are of sufficient quantity and quality for a particular molecular analysis, their value for translational research may be severely limited by the amount, type, and quality of clinical data that are available for an individual case and by the consistency of the data on the many cases that may be required for a study. Clinical data provide the essential functional or biologic behavioral correlations that define the medical relevance of the molecular data. The lack of relevant clinical data elements limits the value of the molecular analysis data for prediction and the conclusions that can be drawn.

The type and amount of clinical data provided by the physician requesting consultation was not prescribed in a standardized fashion by the JPC repository. Furthermore, it did not require that any clinical data submitted adhere to a standardized format.[4] Thus, clinical data associated with cases varies widely in quality, quantity, and consistency, which may create important limitations in the utility of the JPC biospecimens for research studies.

In some cases, it may be possible to acquire missing clinical data from the medical record in the institution in which the referred case originated. For some institutions, such as those within the Department of Veterans Affairs health system or the Department of Defense and many private institutions, the acquisition of additional data elements for a case may be technically facilitated by using an electronic medical record (EMR). Nevertheless, additional technical hurdles—such as the difficulty in combining data from an EMR with the JPC's information technology and the unreliability or unavailability of identifiers that would allow data from disparate sources to be combined—may limit the ease with which the data can be transferred or may preclude electronic transfer altogether. Acquiring or transferring additional data by nonelectronic means is labor-intensive, is expensive, and adds a risk of introducing errors. However, given the number of hospital mergers and closings in recent years, it may not be easy to trace a patient

[4]The Contributor's Consultation Request Form used in recent years does require that some standardized information be submitted. The most recent version of the form is reproduced in Appendix B.

record through the original submitting institution. The ability to acquire additional data may also be constrained by ethical and legal restrictions, such as privacy laws, as noted briefly below.

Consent from the source might be inadequate for use, permission to re-contact might be lacking, or recontact might be prohibitively expensive.

Although the acquisition of additional clinical data for a case may be technically possible, there may be circumstances where it would be prohibited or restricted by ethical or legal issues related to recontact or privacy laws, including the federal Health Insurance Portability and Accountability Act of 1996 (PL 104-191, 110 Stat. 1936, and accompanying regulations). In other situations—especially where a number of years have passed since the data or specimen were collected—it may require extensive research to locate the source individual. Those issues may render specific cases unusable for some types of research. Chapter 3 addresses consent and other ethical, legal, and regulatory aspects of use of the JPC materials for consultative, educational, and research purposes.

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3

Ethical, Legal, and Regulatory Considerations

This chapter focuses on ethical, legal, and regulatory considerations underlying the committee's approach to responding to the questions posed by the Department of Defense (DoD). It begins with a general discussion of those considerations and previous scholarly work concerning them and then addresses considerations regarding the source of specimens. The chapter finishes with an examination of the federal laws and regulations, DoD directives and instructions, and Armed Forces Institute of Pathology and Joint Pathology Center (JPC) regulations regarding research on biospecimens and their associated data.

THE CHANGING ETHICAL, LEGAL, AND REGULATORY LANDSCAPE OF BIOREPOSITORIES

Identifying Changes, Trends, and Gaps

The scientific and technologic developments of the last 20 years in genomics and informatics have greatly increased the potential value of biorepositories for understanding diseases and developing diagnostic, prognostic, therapeutic, and preventive modalities. They have also brought about substantial changes in the ethical, legal, and regulatory landscape of tissue repositories. These changes have been propelled by increased informatics capacity and other technologies that allow for larger-scale research; the mounting commercialization of research; public anxieties about possible uses and misuses of genetic information, particularly with ever larger data-sharing networks; expanded conceptions of patients' and research partici-

pants' rights; and heightened concerns about legal liability on the part of organizations that hold or study human genetic material and health records (Cambon-Thomsen et al., 2007; Hoeyer, 2008).

The changes have also been driven by a series of events that have captured the attention of the public and prompted examination by various professional and government bodies. Dramatic and troubling cases tend to galvanize public attitudes, thereby altering the social and cultural context of research. Much as the notorious U.S. Public Health Service syphilis study at Tuskegee, the Jewish Chronic Disease Hospital case, the Willowbrook hepatitis study, and other such events in the United States from the 1930s to the 1970s transformed approaches to research involving human subjects (Katz, 1972), recent attention to problematic uses of human biologic materials in research have altered the ethical, legal, and regulatory landscape of biorepositories. Some examples are the Havasupai tribe's lawsuit against the Arizona Board of Regents for unapproved secondary uses of tribal members' biologic samples (Harmon, 2010); the legal actions against Texas A&M University's use of bloodspots from newborn screening in genetic research and the Texas Department of Health exchange of such material for money and services, all without parental knowledge or consent (*Beleno v. Texas Department of Health Services*[1]; *Higgins v. Lakey*[2]); the derivation of the HeLa cell line, a highly important research resource, from tissue clinically removed from a patient without notice to or consent from the patient for research use (Skloot, 2010), and the dispute between a researcher and his institution over ownership of a cell repository (*Washington University v. Catalona*[3]). Those cases have focused attention and debate on the adequacy of the federal regulations on human-subjects research (principally the Common Rule, at 45 CFR Part 46) to address the use of archived biospecimens, especially because—under some circumstances—research use of such specimens is not considered research on human subjects under the regulations.

One essential task for the committee has been to identify and assess the crucial changes in this landscape to make it possible to offer recommendations for JPC governance of, policies for, and practices at its repository. This section maps the challenges posed by the changing landscape, identifies important normative trends for biobanking, and examines some specific decisions facing the JPC to lay the groundwork for responding to the questions that the committee has been asked to address. The committee's task is complicated by a lack of broad public consensus on the meaning of

[1]SA-09-CA-188-FB (W.S. Tex., September 17, 2009).

[2]SA-10-CV-990-XR (W.D. Tex., July 7, 2011).

[3]437 F. Supp. 2d 985 (E.D. Mo. 2006), aff'd, 490 F.3d 667 (8th Cir 2007), cert. denied, 128 S. Ct. 1122 (2008).

key terms, as well as by the changing—and sometimes conflicting—ethical, legal, and regulatory standards.

Characterizing Biorepositories and Their Norms

Different terms are used to describe collections of the type held by the JPC, including *tissue repository*, *biorepository*, and *biobank*. Each term has a variety of meanings and somewhat different ethical, legal, and regulatory implications (Cambon-Thomsen et al., 2007; Tutton, 2010; With et al., 2011; Wolf et al., 2012, Appendix). Consider the term *tissue repository*, which has been used to describe collections of human biologic specimens of the sort that were accumulated over 150 years by what is now the JPC. The term seems accurate enough in suggesting that the JPC is archiving material of potential value. But by placing emphasis on the biologic material, *tissue* repository fails to signal the presence of associated data in the JPC collections, such as medical records and pathology reports, or of the digital slide collection. The same could be said of the more modern term *biorepository*, which suggests a place to hold *bio*logic materials and hints at their use for *bio*medical research.[4] However, many biorepositories also include data on the persons whose specimens are in the repositories, which led in the 1990s to coinage of the term *biobank*, defined as "organized biological sample collections with associated personal and clinical data" (Cambon-Thomsen et al., 2007). But the latter term and the related *biobanking* are still not fully settled with clear and definite boundaries, though the use of the term "bank" rather than "repository" implies a place where not merely deposits but also withdrawals are regularly made. Biobanks have various designs and sizes and include national biobanks set up in a number of countries where people voluntarily place genetic samples and allow the ongoing collection of medical, occupational, and other personal data that are necessary for longitudinal study of potential associations between environmental exposures, genetic variants, and health-related outcomes (Austin et al., 2003). Finally, *database* and *genetic database* sometimes also encompass both biologic specimens and associated data; this emphasizes their potential for genomic, epigenomic, proteomic, and related molecular studies (Tutton, 2010).

In line with much of the current literature, the present report uses *biorepository* and *repository* interchangeably to refer to the organized collections of biological samples with associated personal and clinical data now held by the JPC for consultative, educational, and research purposes. Another complexity for the committee's analysis stems from the fact that,

[4]For instance, the International Society for Biological and Environmental Repositories (ISBER) defines a biorepository as "an entity that receives, stores, processes and/or disseminates specimens as needed" (ISBER, 2008).

unlike a modern biobank created for research purposes, the different collections under the JPC's auspices were acquired over a long period in varied ways from military and civilian pathologists primarily in the course of clinical care, and they consist of materials that are domestic and international, contemporary and historical.

Whatever their label, collections of human biologic specimens with related data, including those held by the JPC, have been used for research and education for well over a century. Some of the collections are held by individual pathologists or academic pathology departments. Others are held by hospitals or other medical-care facilities. The JPC collections are unusual because they were started in the middle of the 19th century and have accumulated millions of specimens. Scale aside, the accumulation of specimens and associated data for consultation, education, and research is a long-established practice.

Until fairly recently, these activities continued in the United States with little scrutiny. Only in the recent past have the traditional practices of pathologists and their institutions regarding the use of stored specimens for research and educational purposes and the liberal sharing of such material with medical colleagues come under scrutiny. In 1999, when the National Bioethics Advisory Commission issued a report with recommendations on the ethical use of stored human tissue, it was reflecting a new sensitivity to the ethical, legal, and regulatory issues raised by collecting, storing, and using those specimens and associated data. A substantial literature has since arisen analyzing the ethical and legal issues raised by such collections of human material (Eiseman et al., 2003; Weir and Olick, 2004).

Even as pathologists and their institutions have begun to grapple with the implications of performing research on material from source individuals[5] who have rights and interests, the rise of prospective, population-based, and research-oriented biobanks has raised questions about the feasibility of meaningful contact with sources when the scale of the biobank is large. Collections, such as the JPC's, with data and specimens obtained from pathologists involved in clinical care, are faced with the practicability of communicating about future research uses of sources' data and specimens when those sources typically have little to no knowledge that their specimens are stored and the specimens may have been collected long ago.

As the JPC seeks to capitalize on the research potential of its collections and to accumulate new specimens in an era of ever more sophisticated and

[5]The term source individual (sometimes abbreviated to source) is used in this report to refer to the individual from whom biospecimens and data were obtained. Unlike the term donor, it does not imply that the person necessarily made a decision about the storage and use of the materials; such an implication would be mistaken in the case of almost all the materials held in the JPC repository.

powerful research methods, it must confront the changing ethical, legal, and regulatory standards for biorepositories. A central issue is what sort of recontact or consent, if any, is needed from a source individual for the JPC to permit his or her specimens and data to be used in various ways, including in research. To address that question, the following section discusses the surrounding ethical and legal landscape and the current challenges posed as the standards evolve.

Traditional Ethical Principles and the Need for a Contemporary Approach

Three and a half decades have passed since the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research issued its landmark *Belmont Report* in response to its mandate from Congress "to identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research" (National Research Act, PL 93-348; July 12, 1974). During that time, the three principles that it articulated—respect for persons, beneficence, and justice—have come to provide a foundational means of evaluating the ethics not only of research with human subjects but of patient care. Not surprisingly, those principles carry great weight in the present committee's analysis of the JPC's ethical obligations in managing and using its biorepository.

For at least five reasons, however, the committee believes that it must go beyond the original applications of the *Belmont* principles, especially "respect for persons." In articulating what is meant by respect for persons the National Commission attempted to yoke together "at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection" (National Commission, 1978). The latter is relevant to the ethics of a biorepository constructed from specimens and related data obtained during clinical procedures inasmuch as some of the specimens will have come from patients who had diminished capacity to consent, either generally (for example, children and mentally disabled persons) or temporarily (for example, as a result of injury or disease). Some (perhaps most) of the sources whose material is contained in the JPC repository cannot now be contacted because they are deceased, so whatever their ability to exercise autonomous choice when their material was collected, that ability is now not merely "diminished" but nonexistent as to potential research with the material.

The second reason why it is not possible in the JPC context simply to apply the *Belmont* principle of respecting autonomous choice is that autonomy is usually regarded as requiring—for example, by the Common Rule[6]—"legally effective informed consent," which involves the disclosure

[6]The Common Rule is addressed in greater detail later in the chapter.

of a long list of "basic" and "additional" information (45 CFR § 46.116[a] & [b]). As a historical matter, such disclosure and agreement did not accompany the gathering of the material that now resides in the JPC collections; it seems unlikely that an elaborate form of consent addressing future clinical, educational, and research uses will be obtained regarding the material routinely referred to the JPC in the future for pathologic examination. That raises the question of whether it is possible, as an ethical matter, to respect the principle of autonomy by a process of informed decision-making that differs from the consent ordinarily expected before people may be enrolled in a clinical trial.

A third reason for the apparently limited applicability of "respect for persons" to biorepositories is that specimens separated from the person have traditionally not been regarded as "persons" requiring respect. In the *Moore* case, the California Supreme Court refused to recognize that John Moore, whose excised tissue had been used in research without his informed consent to generate a profitable cell line, had a claim based on conversion of his property (*Moore v. Regents of the University of California*[7]). Guidance issued by the Office for Human Research Protections (OHRP), which allows research without consent on de-identified samples that were not originally collected for research, continues this approach by determining that de-identified specimens are not considered "human subjects" at all (OHRP, 2008a). However, recent analyses have appealed to a broader notion of respect for persons to justify attention to the beliefs, values, and preferences of source individuals in the use of their materials in research (Trinidad, 2011). Even in the *Moore* case, the California Supreme Court indicated that physicians had a fiduciary duty to Moore to disclose the use of his tissue in research. The principle of respect for persons has important implications for the use of persons' specimens in research without entailing that specimens are persons or even the property of persons.

A fourth reason to question the simple application of "respect for persons" lies in the difference between research scandals of the sort that propelled the creation of the National Commission (Beecher, 1966; Katz, 1972) and research that involves material from biorepositories. The ethical framework recommended by the National Commission was designed to protect subjects in their dyadic relationship with investigators by imposing obligations on the latter and subjecting their decisions to independent review by an institutional review board (IRB) before the start of research. However, biorepository research involves not a relatively small number of subjects who interact directly with an investigator but usually a large number of people who have no direct involvement with investigators in the context of research which may or may not be reviewed by an IRB.

[7]793 P. 3d 479 (Cal. 1990).

The nonclinical focus of some types of research on populations, such as studies that use the records and biologic material held in repositories, generates the fifth reason why *Belmont* cannot be taken as a complete statement of the relevant ethical principles for this analysis. Not only is *Belmont* built on the investigator–subject dyad but it focuses on protecting subjects as discrete individuals. In recent years, many ethicists have recognized the importance of thinking of research in terms of groups as well as individuals (Goldenberg et al., 2011). That does not mean simply substituting "community" for "individual autonomy" as a main guiding value but rather recognizing that some interests that need protection belong to a group rather than solely to individuals and that a means is needed to allow the welfare of the group to be represented in decisions about whether to go forward with some research.

Although issues of that sort were not in the foreground when the *Belmont* principles were set forth, the desire not to foreclose all research for which obtaining individual informed consent would be difficult or impossible was certainly on the minds of the authors of the federal regulations on human-subjects research, now stated in the Common Rule. Influenced in particular by large-scale studies that involved data that were either publicly accessible or anonymous or that involved the use of dead bodies or material obtained from them (as was an accepted part of hospital autopsies and medical-school education), the rule drafters either excluded from IRB oversight any research that involved such material or data or permitted institutions to waive consent requirements. That kind of research did not expose anyone to a risk of physical harm or of serious harm to other interests (given the nature of the data, such as public records or information from telephone directories), so the lack of IRB review of it did not seem problematic. Today, however, the extent and types of information that can be generated by analyzing the biologic specimens and data in biorepositories—including genetic and genomic analysis—far exceed what could have been produced when the *Belmont Report* was written. Thus, just as the literal application of the *Belmont Report*'s autonomy principle could unduly constrain the potential of biorepositories as important components in the modern system of research, reliance on the exclusions and exemptions of the Common Rule could remove such repositories from appropriate oversight.

The solution adopted by the committee was to revisit the mission that guided the National Commission and, rather than focus on the particular instantiation of the principles in the *Belmont Report*, to concentrate on the foundations of the principles that are "generally accepted in our cultural tradition" (National Commission, 1978). In addition, the committee carefully considered more recent statements of the ethical and legal standards that should govern biorepositories, along with evolving practices. It was

then able both to modify the particular manifestations of the *Belmont* principles in current use and to use the principles to develop a framework for biorepository governance, especially if they are understood more broadly and less individualistically than has sometimes been the case (Childress et al., 2006; Weir and Olick, 2004). Later sections of this chapter and the next chapter address the need to specify and balance those and other principles (Beauchamp and Childress, 2009) in the process of developing concrete recommendations for the governance, policies, and practices of the JPC biorepository.

Governance refers to organizational structures and processes of decision-making and accountability (Gottweis and Petersen, 2008; Kaye et al., 2012b). In the world of biobanks, governance often includes an organization's policies regarding acquisition, storage, access, and the like, as well as specifying the persons or institutions that set and apply those policies. Some proponents of governance view it as a way to move beyond or provide a substitute for informed consent in light of practical and regulatory limitations on consent in large-scale contexts (Hoeyer, 2008; Prainsack and Buyx, 2011). Because an obligation to demonstrate respect for persons does not diminish even with good governance, others have proposed using consent to a process, or governance structure, to overcome problems with seeking consent at one point in time for a range of future research uses (Caulfield et al., 2008; Kaye et al., 2012a).

Proposals for biobank governance often reflect one or more guiding metaphors, mainly drawn from ownership or from stewardship, custodianship, and trusteeship (Jeffers, 2001; O'Brien, 2009; Yassin et al., 2010). The latter metaphors recognize the role of the biobank as protector of interests other than its own and stress responsibility *for the materials* and their uses. It is also important to recognize, where appropriate and possible, responsibility *to the individual sources* of biological specimens and data—sometimes called participants—even if the research does not qualify as research on human subjects under the Common Rule. Because of the historical nature of the JPC collection, it makes more sense to adopt a governance framework that captures the fiduciary obligations of the collection holders (such as stewardship over the specimens and data) rather than one that relies on active, engaged partnership with participants. However, there are ways to express the principle of respect for persons and other ethical principles even in these circumstances.

Implementing Broader and Richer Conceptions of Respect for Persons and Other Ethical Principles

U.S. and European biobank policies tend to differ in important ways regarding the use of biologic specimens and data in research. There is an in-

creasing acceptance of broad or general prior consent in European biobanks (Noiville et al., 2011). A person who gives broad or general consent does not surrender the right (within limits) to withdraw biologic materials and data later. Such consent also presupposes that an appropriate ethics committee will review the future research (Elger and Caplan, 2006; Tutton, 2010).

In the United States, in contrast, requirements for informed consent to research on biologic specimens have generally been closely connected with risks to privacy and confidentiality, considered the major risks posed by research uses of excised tissue and associated data (Elger and Caplan, 2006; Tutton, 2010). If the samples used in research are not identifiable and the risks to the sources are considered to be minor, the samples may be used without informed consent. According to that view, adequate protection of the sources' personal identities through deidentification obviates the need for informed consent to research uses. Proponents of this approach stress that it provides adequate protection for the privacy interests of source individuals while costing the organization less.

The approach is not unproblematic. First, the definitions of and boundaries between identifiable and nonidentifiable samples are debatable. Those terms are used in varied and inconsistent ways. Moreover, as a result of scientific and technologic developments, OHRP and others have suggested that in principle all biologic specimens should be viewed as potentially identifiable (HHS, 2011; McGuire and Gibbs, 2006; Schadt et al., 2012). Third, breaches of privacy and confidentiality remain possible, however slightly, and their probabilities are magnified by research networks and wide sharing of data. It is thus important to recognize, but not exaggerate, this risk (Malin et al., 2011).

Additional arguments focus on the losses to scientific research and to sources themselves from reliance on deidentification or anonymization. If deidentification is irreversible (that is, a key code for reidentifying individuals is not retained or is not accessible), researchers cannot gain access to some information that would be useful in their research and sources cannot receive potentially valuable individual information from the research (Wolf et al., 2012). Regarding the latter, studies indicate that sources attach high value to the disclosure of potentially valuable results and incidental findings (Hoeyer, 2008). To be clear, though, it is possible to perform valuable research on deidentified data (Clayton et al., 2010).

Obtaining informed consent for biorepository research is not only a possible way to protect sources from harm but serves the purposes of manifesting respect for persons and allowing sources' values and preferences to shape research. As this report has suggested, biorepositories can and should develop ways to respect persons who are sources of biospecimens as participants in research on archived materials even when informed consent to research uses may not be required or may be impossible (Prainsack

and Buyx, 2011). Studies suggest that sources want more control, even though they do not necessarily insist on exercising specific informed consent to particular research protocols (Hoeyer, 2008; Wendler and Emanuel, 2002). Of course, caution is required in interpreting surveys and qualitative studies of the perspectives of sources of biospecimens; responses vary for an array of reasons (Hoeyer, 2008). Nevertheless, the preferences for more participation in the research process and for being informed about research results that are particularly relevant to them appear to be widespread and strong views among people who could be the source of biospecimens,[8] and new ways are being developed to enable participants to engage in the research process through the use of such tools as interactive information technologies (Kaye et al., 2012a).

Several analysts of the changing normative landscape of biorepositories contend that repositories should focus less on informed consent alone and more on becoming institutions that can generate and maintain trust (O'Doherty et al., 2011). One commentator concludes that "it is time to move the debates beyond informed consent and to critically assess what can be done to make biobanks into trustworthy institutions of long-term social durability" (Hoeyer, 2008). Trust is essential for biorepositories (Dabrock et al., 2010; Hansson, 2009; Hawkins and O'Doherty, 2010; Manson and O'Neill, 2007; O'Neill, 2002) because they depend on voluntary participation and without trust cannot succeed. In seeking to generate and maintain trust, it is crucial for biorepositories to develop and display trustworthiness through their governance, policies, and practices (Yarborough et al., 2009). Those points have long been recognized with respect to organ transplantation: the public's trust in the process of organ donation and allocation is crucial to its willingness to donate organs.

Studies of industries that have lost public trust and worked to regain it have identified proactive attention to relationships (engagement and communication) and accountability as essential in building trustworthy practices (Yarborough et al., 2009). Other trust conditions often include faithfulness in keeping promises, meeting legitimate explicit or implicit expectations, and truthfulness (Hoeyer, 2008; Prainsack and Buyx, 2011). Transparency also appears on most lists of conditions (O'Doherty et al., 2011). However, some commentators worry that transparency will actually reduce trust (Cambon-Thomsen et al., 2007). When biorepositories' policies and practices are publicly justifiable, transparency can help to generate and maintain trust. Justification should be preceded by engagement with the relevant stakeholders. Exactly what kind of engagement and with whom is both desirable and feasible can be debated and depends upon many factors.

[8]Hoeyer (2008) has summarized the empirical research, and others have also addressed the topic (Chen et al., 2005; Trinidad et al., 2011; Wendler and Emanuel, 2002).

The materials in the JPC repository were collected largely from military personnel and their families, with some additional materials from difficult civilian cases submitted for consultation. The JPC may be able to engage military personnel and their families in ways that can inform its governance. Such engagement may increase the likelihood that its policies and practices will be consistent with the values of that community, address group concerns, and reduce the risk of harm to the group and its members (McCarty et al., 2008; Newman et al., 2011). Practices vary widely, depending on the needs of the repository and the community it is serving, from community representatives on data-access committees participating in every data-release decision to community advisory boards (CABs) that consult on policy and general directions for the repository rather than on day-to-day decisions (O'Doherty et al., 2011).

Those contemporary approaches to biobank governance also draw on the other traditional principles that guide research ethics: beneficence and justice. The principle of beneficence has generally been specified through two complementary general rules: to do no harm and to maximize possible benefits and minimize possible harms (National Commission, 1978). Those rules have obvious application to biorepositories in that the realization of their potential benefits for scientific and technologic progress is more likely if their governance is responsive and adaptive. Specifically, the principle of beneficence requires minimizing harms, costs, and other burdens on research participants and balancing any that remain against the potential benefits of the research. Governance mechanisms, such as data-access committees and CABs, and traditional oversight mechanisms, such as IRBs, can go a long way toward assessing whether a proposed use of specimens in the collection will minimize harm and maximize benefits. Input from the specimen sources can, for example, help ensure that the evaluation of benefit expresses the perspectives of the source population as much as possible, rather than merely reflecting scientific perspectives. Figure 3-1 provides an example of a governance mechanism that uses a scientific review committee, a committee on data and material access, a CAB, and an IRB.

The third principle articulated in *Belmont* (along with respect for persons and beneficence)—justice or fairness in the distribution of the benefits and burdens of research—likewise has several implications for biorepository governance. An obvious one concerns fair access to biologic specimens and data for research, education, and consultation, especially in the case of rare and unique materials. This is an important issue for the JPC's governance. The taxpayer funding of the repository appears to support the broadest possible access subject to appropriate priorities and limits. Reasonable priority setting could, for example, include meeting the needs of the military and of military personnel and veterans first; defensible limits could include protection of national security. Ensuring the sustainability of the collections

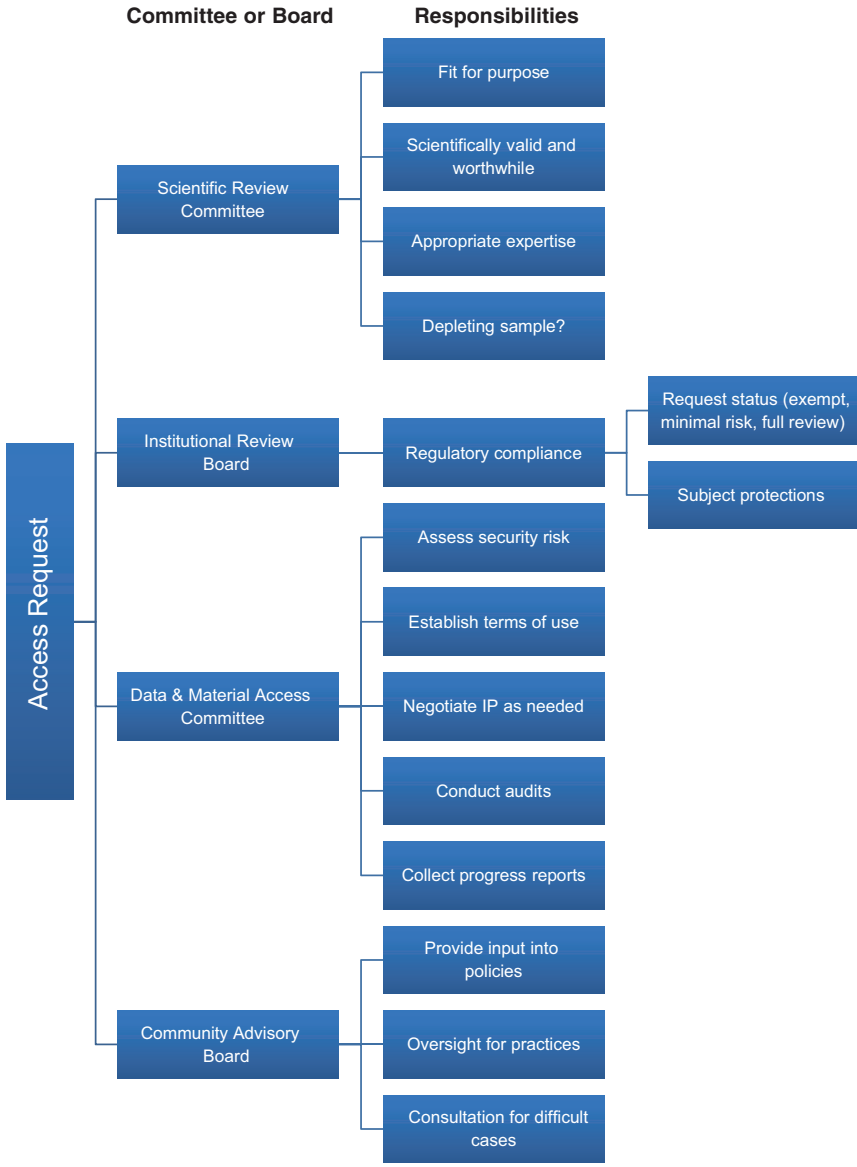

FIGURE 3-1 A biorepository governance mechanism that uses a scientific review committee, an institutional review board, a data and material access committee, and a community advisory board.
NOTE: IP = intellectual property.

may also affect the extent to which rare and unique biospecimens may be distributed and the costs passed on to users of the materials for research, education, and consultation. And it will be important to ensure that no one group of specimen sources bears undue burden or risk of exposure.

Another sense of justice has become important over the years: participatory justice. Justice in this sense encompasses fair participation in the biorepository's process of setting policies and priorities, for instance, regarding uses of biologic specimens and data. Fair participation is particularly important in the partnership model of biorepository governance, but it is also relevant to models of custodianship, trusteeship, or stewardship. It is not easy to specify fair participation in terms of the stakeholders to be included or the mode of participation to be extended. Nevertheless, such participation is important not only as a matter of justice but also because of its potential contribution to trust in the biorepository.

Conflicts Within and Between Ethics, Law, and Regulations

Ethics, law, and regulation both overlap and conflict in the normative guidance that they offer for biorepositories. Law and regulation often embody ethical considerations and set minimum standards of ethical conduct. However, there are diverse views about the relevant ethical norms (Capron et al., 2009; Häyry et al., 2007), and some ethical norms go beyond or even contradict operative laws and regulations. At other times, laws or regulations may set a higher standard than current ethical norms require. In either case, there can be what commentators have termed a "growing gulf" with regard to research using human biologic materials and associated data between the current legal and regulatory frameworks and practice, on the one hand, and ethical and cultural perspectives and participant preferences, on the other hand (Trinidad et al., 2011).

Conflicts may also arise among particular laws and regulations, making it difficult to determine which is determinative in a particular decision or case, especially with respect to the myriad laws and regulations—federal, military, and state—that may apply to the JPC's activities. One example—addressed later in the chapter—is the tension between the Common Rule (as interpreted by OHRP), which allows general consent for research uses of donated tissue, and HIPAA, which requires authorization by a patient for the use of his or her protected health information (PHI) in a specific research proposal (With et al., 2011). Moreover, the standards adopted by other countries and by international organizations become relevant and important when research crosses national boundaries.

The remainder of this chapter will examine several issues raised by the JPC's new structure and mission in light of the above and other ethical, legal, and regulatory frameworks and principles. Most of the questions

posed to the committee center on research uses, and the text concentrates on these uses. Attention is also paid to the ethical, legal, and regulatory issues that arise when repository materials are used in clinical consultation and education because all three uses may involve purposes beyond direct benefit to the individual sources of the biospecimens and data. At the end of the chapter, the committee offers some concluding reflections on consent and custodianship of biological materials and associated data.

CONSIDERATIONS REGARDING THE SOURCE OF SPECIMENS

The DoD, noting that the JPC repository contains consultation material from both military facilities and civilian providers, asked the committee to offer comments on whether materials from civilian providers could be used in the future in the same manner as those from military facilities. This section addresses some considerations surrounding that issue. It approaches the discussion from the viewpoint of what the committee believes to be the salient distinction: whether a sample is derived from a civilian or from a current or former member of the U.S. military.

There are several reasons why military personnel might be viewed differently from civilians. They generally cannot resign their position; they are obliged to follow lawful orders, including orders that may result in their physical harm; the rules under which they agree to serve may be changed without their consent; and they may under some circumstances be recalled into service after they have left it (Weedn, 2011). With relation to health matters, they are required to be physically and mentally fit; they cannot refuse treatment, immunizations, or prophylactic drugs; and they may be compelled to provide biologic specimens (Baker personal communication, 2011; Henricks, 2004; Rushenberg, 2007). Protected health information in their records may in some circumstances be provided to "military command authorities" without their authorization or without an opportunity to object (Rushenberg, 2007). In addition, "military expediency" is recognized as a justification for waiving informed consent (Executive Order 13139; September 30, 1999).

As noted in Chapter 1, specimens in the JPC collection come from a number of sources. Clinicians in military health facilities in the United States and abroad submitted samples for clinical consultation. Diagnostic material and data from military health facilities that were shut down under the Base Realignment and Closure (BRAC) process were transferred to the JPC to satisfy accreditation requirements for specimen retention. Registries of samples collected from military personnel who served in a particular conflict or shared a particular exposure are housed there. And pathologists from around the world who were seeking second opinions from the expert specialists at the repository provided case materials.

The answer to the question of whether different rules apply to specimens derived from the different sources—military patients, civilian patients (most often, military dependents or retirees) under the care of military physicians, and civilian patients receiving care at nonmilitary facilities around the world—depends principally on what policy is proposed regarding future use of the samples generally. If their use is limited to applications that directly benefit the patients from whom the specimens were derived (for example, a clinical consultation) or to research studies for which the patients gave explicit informed consent, there is no reason to differentiate between military-derived and civilian-derived specimens. But if uses beyond those two are contemplated, the legal and ethical reasoning in support of such broader access may require differentiating between military and civilian patients. The primary categories of future use—diagnostic uses or other uses to benefit persons other than those from whom the samples were derived and research uses beyond those explicitly agreed to by the persons from whom the samples were derived (or their legal representatives)—can be examined separately.

Two principal groups of persons could benefit from allowing medical professionals access to a patient's stored specimen: members of the patient's family and members of a group with whom the patient shared a life experience that was possibly relevant to his or her medical condition. For this type of use, the specimen and related medical records would, of course, need to be personally identifiable. If the patient is known to still be alive, ethical considerations suggest that a person seeking access to the specimen and any related data would provide evidence of the patient's consent for the release. In the case of a patient known or reasonably believed to be deceased, the patient's personal representative[9] would control release whether the material came from a civilian or military source. Under certain circumstances, there may further allowance to fulfill a close relative's legitimate medical need.

In responding to requests for access, custodians of the JPC collection would have no reason to differentiate between specimens and records of military and civilian origin. In ordinary circumstances, it may be assumed that any close relative[10] would have an equal, personal right to access a stored specimen when doing so is necessary to meet a medical need that his or her physician attests cannot be met with equal ease and utility by another available means. If an objection were lodged by another relative—because, for example, the information obtained from the material held by the JPC would not be used solely to benefit the person seeking it but might

[9]In brief, "[t]he personal representative stands in the shoes of the individual and has the ability to act for the individual and exercise the individual's rights" (HHS, 2003a). Rules regarding personal representatives under the HIPAA Privacy Rule are explicated in 45 CFR 164.502(g).

[10]Such as a parent, sibling, child, grandchild, niece, nephew, aunt, uncle, or first cousin.

be imposed on others, such as relatives who do not want it—the JPC would have to consider whether some safeguard could be found to avoid or at least minimize the potential harm and second to balance any remaining unavoidable harm against the good that disclosure would serve.

Ordinarily, in the absence of a judicial order, nonrelatives would not be entitled to have access to identifiable samples and associated data held in a pathology laboratory. Consequently, persons other than close relatives seeking access to civilian-derived material in the JPC collection would be referred to the pathology service that sent the material to the repository, and the pathology service could make its own determination, on the basis of its understanding of applicable rules and its ability, if any, to contact persons who may speak on behalf of the deceased patient.

There are good reasons for potentially taking a different view concerning access to specimens sought by persons who have a military connection with the deceased, such as having served in the same unit or same theater of operations. If the material is sought for what amounts to an epidemiologic study—an examination of specimens derived from a number of patients who shared common experiences and possible exposures, for example—it could be provided on a deidentified basis with the requirement that those receiving it make no effort to break the anonymity or to contact any persons, or relatives of those persons, whose materials have been provided. And, given the allegiance of military personnel to the men and women with whom they have served, it may be more reasonable to suppose that the armed forces members whose samples and data are held in the JPC would, if it were possible to consult them, approve the use of their samples (with appropriate protections for personal information) when they are needed by a fellow service member for diagnostic or treatment purposes. It may be appropriate to explore with service-member organizations whether the latter presumption seems reasonable and whether they would support the conclusion that deidentified samples and information should be provided when requested by a present or former service member (or a representative of such a person's family) who has a service-related connection with the persons whose samples and information are being sought.

Potential research use of the various parts of the JPC collection raises two connected issues: first, the conversion of some of or all the parts into an accessible biobank that would be made available (under appropriate rules and procedures) to researchers and research institutions; and second, access to particular specimens, and sometimes related data, for particular research projects. The two differ in that a presumption of relatively easy access to specimens seems to accompany the creation of a biobank, whereas a case-by-case decision process admits of the possibility, but not necessarily the probability, that researchers will be able to make use of material in the JPC collection for research purposes.

There are three potentially differentiating issues for civilian-derived vs. military-derived specimens. First, it can be argued that presumed consent to research may make more sense for military-derived specimens in cases in which release might otherwise be contested, if the JPC has received approval for the research from the DoD, by analogy to the special rules for research on service members without consent.[11] Second, it is possible to turn to groups of service members, veterans, and their families to act roughly as surrogates for military patients whose materials are in the collection and review proposed research uses of samples and data from the collection that raise particularly sensitive issues, whereas there is no natural surrogate group for the highly heterogeneous populations from which the civilian-derived specimens were obtained. Third, it is arguable that current and former military members and perhaps their family members would have more inherent trust in and see themselves as having an indirect relationship with a military facility, such as the JPC, whereas it is unlikely that civilian patients whose materials are held at the JPC are even aware of—or have any sense of having consented to—the presence of their materials in the JPC collection.

CONSIDERATIONS REGARDING RESEARCH ON DIAGNOSTIC SPECIMENS AND ASSOCIATED DATA

The committee was asked to offer advice on whether tissue collected for clinical use may be used for research, including cases in which the tissue came from patients who did not specifically consent to its use in research. As noted above, this is a complex question of law, ethics, and policy. Indeed, controversy has surrounded the question of under what circumstances clinically obtained tissue may be used for research[12] and, in July 2011, the Department of Health and Human Services issued an advance notice of proposed rule making (HHS, 2011). The discussion that follows references law and guidelines that were in place when the committee completed its substantive work in the middle of 2012 but notes pending proposals that have the potential to affect the answer to the question.

[11]DoDI 3216.02 (Enclosure 3, § 9(c); November 8, 2011) indicates that the Assistant Secretary of Defense for Research and Engineering may waive the requirement for informed consent for certain types of research when all of the following are met: (1) the research is necessary to advance the development of a medical product for the military services; (2) the research may directly benefit the individual experimental subject; and (3) the research is conducted in compliance with all other applicable laws and regulations.

[12]*Moore v. Regents of the University of California* (51 Cal. 3d 120; 271 Cal. Rptr. 146; 793 P.2d 479), discussed, for example, by Skloot (2010).

Background

As detailed in the first chapter, the JPC repository holdings were collected over a period of more than 100 years at a wide range of both military and civilian facilities in the United States and abroad. Consent, if any, to use of the materials was not obtained by the repository itself but by the clinicians or clinical centers where the specimens were removed from patients. In recent years (since at least 1995, the earliest date found by the committee or the JPC), a physician or other medical professional submitting material to the repository has been required to include a signed Contributor's Consultation Request Form. The form requests detailed information on the patient and case and notifies the contributor of the repository's retention policy, which states that the facility generally retains slides permanently and formalin-fixed, paraffin-embedded blocks for at least 10 years. The policy further states that "other pathological material, X-rays, CT scans, MRI scans, echograms, angiograms, photographs, and similar diagnostic studies *may be retained for education and research* or discarded" (JPC, 2011a; emphasis added). The form also mentions possible research use in a section titled "Privacy Act Statement": "medical information received is considered during the consultative process and is used to form a database for education and research in pathology" (JPC, 2011a).

It is unclear whether patients were notified of or asked to consent to having their material sent to the repository's staff for consultation; it is unlikely that they were notified of or asked to consent to retention of their specimens and data for future use by the repository, with the possible exception of materials gathered for some of the war or cohort registries.[13] The committee was informed that the individual sources generally were not notified or asked to consent by either repository investigators or parties outside the repository (Baker personal communication, 2011).

In any case—again, with a few possible exceptions—the JPC does not have copies of any consent forms used in obtaining the material in its collection (Baker personal communication, 2011). In light of the variety of the possible consents, including no consent, the committee broadened the question before it to address whether tissue collected for clinical use may be used for research in the full array of circumstances represented in the JPC collection. That included the acceptability of research not only on tissue but on the associated material (such as X-ray images and computed tomography scans) and clinical data (such as patient information provided by the contributing physician up to and including patient medical records) and research on archived material and data in the absence of a tissue specimen.

[13]These registries are described in Chapter 1. Consent for future research use may have been obtained for materials gathered for the war or cohort registries, but JPC has no documentation regarding this (Baker personal communication, 2011).

Almost all tissue specimens in the repository are archived with at least some associated data.[14] The Contributor's Consultation Request Form (JPC, 2011a) asks for patient information, including name, date of birth, Social Security number, race, ethnicity, contributor's working diagnosis, and clinical history. The form states that "pathology consultation records contain individually identifiable health information." Although it notes that the contributor's providing patient information on the form is voluntary, it also says that "if the information is not furnished, a consultation may not be possible." Thus, research on specimens might include research on associated data. Furthermore, a portion of the repository's BRAC Collection consists of only records with no associated biospecimens. Consequently, JPC repository biospecimens and associated data—and records in the absence of tissue—could all be sought for research.

As discussed below, some of the persons whose specimens and data are archived in the JPC collections may qualify as research subjects or participants, and others may not even if their tissue, material, and data are used in research. There is no consensus term for research that does not constitute research on human subjects, although Brothers and Clayton (2010) have suggested "human non-subjects research." There is also no consensus on a term to use for the individuals from whom these materials are obtained; the literature variously calls them participants, donors, contributors, and sources (the last is the term used in this report). Most specimens and data were submitted to the repository for clinical consultation although BRAC materials are an exception in that they were simply transferred to the repository for retention and storage when the military facilities that housed them were closed, and some of the war and cohort registry materials were collected specifically for documentation or research purposes.

Veterans' Attitudes Regarding Research Use of Biorepository Materials

A small literature exists on veterans' opinions regarding research use of their biological material. Kaufman and colleagues (2009) surveyed veterans receiving health care through the Department of Veterans Affairs (VA) system on their attitudes regarding the establishment and operation of a repository of genetic material and related clinical information. The biobank, VA's Genomic Medicine Program (GMP), is to be made available for health-related research. Eighty-three percent of the participants in the study (n = 931) indicated support for the GMP and 71 percent said they

[14] A small number of cases in the Central Collection have only medical records because the associated slides or biomaterials were returned to the contributor or otherwise lost or destroyed (Baker personal communication, 2011).

would participate in it. Approval was consistently high in all demographic and age groupings, although black non-Hispanics and veterans who first served during or after the Gulf War were less likely to back the program. Altruistic motivation was commonly cited as a reason for support, with about 80 percent of respondents indicating that participation would make them feel like they were helping other veterans. A follow-up paper by the investigators examined veterans' views on opt-in and opt-out enrollment options in research studies (Kaufman et al., 2012). It reported that just over three-quarters of those sampled felt it was a "good idea" to use leftover biological materials for research applications, although almost half were not aware of their materials being used in research at all. Support for both opt-in and opt-out enrollment models was found; however, more women and minorities significantly preferred the opt-in approach.

Federal Regulations Regarding Research on Biospecimens and Associated Data

A comprehensive analysis of applicable law (statutes, regulations, and governmental guidance) would consider both federal law, including any specialized military requirements, and state law.[15] Two domains of law are particularly relevant here: law on research involving human beings and derived tissues, material, and data and law on protecting the privacy of individuals. The goal of the present analysis is to determine what duties and limitations the law places on the JPC's use or dissemination of specimens, associated material and data from the repository, for research purposes when the source has not given consent beyond that needed for the collection of specimens in the course of clinical care. Further, when such use is permitted, the goal is to articulate the various considerations and conditions surrounding research use.

Generally speaking, research on biospecimens and associated data in the United States is subject to two[16] primary sets of federal rules related to the protection of study subjects and their health information: those promulgated under HIPAA and the implementing regulations at 45 CFR Part 164, and the so-called Common Rule, the regulations for protection of human subjects in research adopted by federal departments and agencies that conduct and sponsor such research (including the DoD and the Department of Veterans Affairs) and administered by the OHRP in the Department of Health and

[15]This report does not address state statutes and regulations, which may apply to some uses of biospecimens and data but do not materially affect overall policy planning in the JPC as a federal entity.

[16]Human-subjects research under Food and Drug Administration (FDA) purview is subject to FDA's rules at 21 CFR Parts 50 and 56. These are similar to but not identical with the Common Rule.

Human Services (HHS).[17] This section briefly summarizes salient sections of the current rules and guidance statements. Far more detailed and complete discussions of some of these rules are available in the 2009 Institute of Medicine report *Beyond the HIPAA Privacy Rule: Enhancing Privacy, Improving Health Through Research*, from which much of the material in this section is excerpted or derived. Additional human-subjects research and privacy rules applied by the U.S. military are addressed in the next section.

The Health Insurance Portability and Accountability Act of 1996

The primary goals of the U.S. Congress in passing HIPAA in 1996 were to make health care delivery more efficient and to increase the number of Americans with health insurance coverage. In furtherance of these goals, the statute mandated what is now known as the HIPAA Privacy Rule, which regulates the uses and disclosures of "protected health information" (PHI) that health care professionals and institutions are permitted to make. PHI is defined as "individually identifiable health information" that is held or transmitted by a "covered entity."[18] Although the HIPAA Privacy Rule applies to information uses and transactions necessary for the provision of health care, it is also applicable to a great deal of information used in health research. When obtaining PHI from a covered entity to use in their research, researchers are required to follow the Privacy Rule's provisions. The Privacy Rule permits a covered entity to use and disclose PHI for research purposes without an individual's authorization if the covered entity obtains either of the following (45 CFR § 164.512(1)):

- Documentation that an alteration or waiver of the individual's authorization for the use or disclosure of the information has been approved by an IRB or privacy board.
- Specified representations from the researchers that the PHI is being used or disclosed solely for purposes preparatory to research or for research using only the PHI of decedents.

A covered entity may also use or disclose PHI without an individual's authorization if the PHI is contained as part of a "limited dataset" from which specified direct identifiers have been removed and the researcher enters into a data-use agreement with the covered entity (45 CFR § 164.514(e)). And data may be publically shared under HIPAA's so-called "safe harbor"

[17]The HHS version is at 45 CFR Part 46, and the DoD version is at 32 CFR Part 219.

[18]Covered entities are individuals and organizations that transmit information in electronic form in connection with a transaction for which HHS has developed a standard under HIPAA (45 CFR § 160.103). AFIP was and the JPC is a covered entity.

provisions if 18 categories of information comprising "explicit identifiers (e.g., names), 'quasi-identifiers' (e.g., dates, geocodes), and traceable elements (e.g., medical record numbers)" (Malin et al., 2011) are stripped from them. The categories are listed in Table 3-1.

In crafting the Privacy Rule, HHS acknowledged that it is not always possible to obtain authorization for using or disclosing PHI for research, particularly in circumstances in which thousands of records may be in-

TABLE 3-1 Individual Identifiers Under the Privacy Rule

The following 18 identifiers of a person or of relatives, employers, or household members of a person must be removed, and the covered entity must not have actual knowledge that the information could be used alone or in combination with other information to identify the individual for the information to be considered deidentified and not protected health information.

- Names
- All geographic subdivisions smaller than a state, including county, city, street address, precinct, ZIP code (first 3 digits OK if geographic unit contains over 20,000 persons), and their equivalent geocodes.
- All elements of dates (except year) directly related to an individual; all ages over 89 years and all elements of dates (including year) indicative of such age (except for an aggregate into a single category of age over 90 years)
- Telephone numbers
- Fax numbers
- Electronic mail addresses
- Social Security numbers
- Medical-record numbers
- Health-plan beneficiary numbers
- Account numbers
- Certificate and license numbers
- Vehicle identifiers and serial numbers, including license-plate numbers
- Medical-device identifiers and serial numbers
- Internet universal resource locators (URLs)
- Internet protocol (IP) addresses
- Biometric identifiers, including fingerprints and voiceprints
- Full-face photographic images and any comparable images
- Any other unique identifying number, characteristic, or code, except that covered identities may, under certain circumstances, assign a code or other means of record identification that allows deidentified information to be reidentified

SOURCE: MMWR, 2003; 45 CFR § 164.514(b)(2)(i).

volved (Pritts, 2008). In such circumstances, the Privacy Rule permits a covered entity to use and disclose PHI for research purposes without obtaining authorization from each patient if an IRB reviews a research proposal and determines that it is appropriate to grant a waiver of authorization (45 CFR § 164.512(i)(1)(i)).

The HIPAA Privacy Rule does not cover such materials as biospecimens themselves, but it does cover the PHI associated with them. Biospecimens in the JPC repository generally do have data associated with them that would qualify as PHI.

The Common Rule

The Common Rule grew out of HHS regulations to protect human subjects in research that were first published in 1974 (45 CFR Part 46) in response to the revelation of serious breaches of respect for and protection of participants in research, including cases noted earlier in this chapter. In 1991, the central portion of those regulations (45 CFR Part 46, Subpart A) was adopted by many federal agencies, including the DoD, in response to an initiative to achieve uniformity of federal regulations on human-subjects protection, eliminate unnecessary regulations, and promote increased understanding by institutions that conduct federally supported or regulated research—this is the Common Rule.[19] It governs most federally funded research conducted on human beings and aims to ensure that the rights of human subjects are protected during the course of a research project. The Common Rule stresses the importance of individual autonomy and consent, requires independent review of research by an IRB, and seeks to minimize physical and mental harm. Privacy and confidentiality protections are included as important protections against some kinds of risk in research. The framework for achieving the goal of protecting human subjects is based on two foundational requirements: the informed consent of the research participant and the review of proposed research by an IRB.

In general, the Common Rule applies only to research on human subjects that is supported or conducted by the federal government or performed by an institution (such as a university) that commits to conducting non-federally supported research in compliance with human-subjects research regulations via a Federalwide Assurance (45 CFR § 46.101).[20] Research is defined as "a systematic investigation, including research

[19]To the extent that an agency needed to modify the general version because of the types of research it sponsors or special features of the research population, it could do so through a short separate rule.

[20]The Food and Drug Administration (FDA) human-subjects protection regulations apply to research in development of all products that require FDA approval.

development, testing, and evaluation, designed to develop or contribute to generalizable knowledge" (45 CFR § 46.102(d)). Under the Common Rule, a "human subject" is defined as "a living individual about whom an investigator . . . conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information" (45 CFR § 46.102(f)).

Data are considered personally identifiable if the identity of a subject is or may be readily ascertained by the investigator or associated with the information accessed by the researcher (45 CFR § 46.102(f); OHRP, 2008b). However, the Common Rule exempts from its requirements (45 CFR § 46.101(b)(4)) research that involves solely

> the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources 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.

Some research on human biospecimens and associated data does not constitute research on human subjects as defined by the Common Rule. OHRP has issued guidance on ethical approaches to such research on human materials (2008a,b), sometimes called "human nonsubjects research" (Brothers and Clayton, 2010). In 2011, HHS issued an ANPRM to elicit comments on possible changes to the Common Rule that would affect both human-subjects research and some human nonsubjects research (HHS, 2011). That rule making was still in progress when the present report was completed (the middle of 2012).

Under OHRP guidance, the research use of specimens or data not originally collected for that research is not considered research on human subjects under the Common Rule if the investigators cannot readily identify the source individuals (OHRP, 2008b). That suggests that under current rules, if a repository removes identifiers linked to individual sources from the clinically derived specimens and data it makes available to researchers, such that the sources cannot individually be readily identified by the researchers, research conducted using these specimens or data would not constitute human subjects research under the Common Rule (OHRP, 2008a; Wolf et al., 2012). Data that are otherwise identifiable may be deidentified for purposes of the Common Rule if they are coded and some other conditions are met (HHS, 2004). Under guidance issued by OHRP (2008a), information is "coded" if data (such as name or Social Security number) that would enable the investigator to readily 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 (the code) and there is a

key for deciphering the code and enabling linkage of the identifying information to the private information or specimen.

Differences Between the Health Insurance Portability and Accountability Act and the Common Rule

Table 3-2 presents in schematic form some of the major provisions of HIPAA and the Common Rule and how the two differ. These differences are explicated below.

Both the Common Rule and HIPAA allow waivers or alterations of the requirement for informed consent if certain criteria are met. The Common Rule allows a waiver (45 CFR § 46.116(d)) provided the IRB finds and documents that

(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.

A waiver of HIPAA authorization is similar to (but not identical with) a waiver of consent requirements under the Common Rule. A waiver of authorization is permitted (NIH, 2012) when

(1) Use or disclosure involves no more than minimal risk to the privacy of individuals because of the presence of at least the following elements:
    (a) An adequate plan to protect health information identifiers from improper use or disclosure,
    (b) an adequate plan to destroy identifiers at the earliest opportunity absent a health or research justification or legal requirement to retain them, and
    (c) adequate written assurances that the PHI will not be used or disclosed to a third party except as required by law, for authorized oversight of the research study, or for other research uses and disclosures permitted by the Privacy Rule;
(2) research could not practicably be conducted without the waiver or alteration; and
(3) research could not practicably be conducted without access to and use of PHI.

TABLE 3-2 HIPAA and Common Rule Human-Subjects Protection Regulations

Category of Distinction	HIPAA Privacy Rule: Title 45 CFR Part 164	HHS Protection of Human Subjects Regulations: Title 45 CFR Part 46 (Common Rule)
Overall objective	To ensure that individuals' health information is properly protected while allowing the flow of health information needed to provide and promote high-quality health care.	To protect the rights and welfare of human subjects involved in research conducted or supported by any federal department or agency.
Applicability or scope	Applies to health plans, health care clearinghouses, and any health care provider that transmits health information in electronic form.	Applies to all research involving human subjects conducted, supported, or otherwise subject to regulation by any federal department or agency subscribing to the Common Rule.
Definition of research or clinical investigations	Defined as a systematic investigation—including research development, testing, and evaluation—designed to develop or contribute to generalized knowledge.	Defined as a systematic investigation—including research development, testing, and evaluation—designed to develop or contribute to generalized knowledge.
Definition of human subjects	Defined as the individual (or the individual's personal representative) who is the subject of the health information being used or disclosed.	Defined as a living person about whom an investigator conducting research obtains data through intervention or interaction with the person or identifiable private information.
IRB or privacy board requirement	Required for projects involving requests to alter or waive the individuals' authorization for the use or disclosure of their protected health information for research purposes.	Required for all projects involving human subjects supported, conducted, or regulated by a federal department or agency.
IRB or privacy board responsibilities	To review all requests to alter or waive the individuals' authorization for the use or disclosure of their protected health information for research purposes; not required to review or approve authorizations.	To ensure that informed consent will be sought from and documented for each prospective subject or the subject's legally authorized representative in accordance with and to the extent required by HHS regulations; to ensure that adequate provisions are taken to protect the privacy of subjects and to maintain the confidentiality of data. (Other conditions not specific to biorepositories apply.)

TABLE 3-2 Continued

Category of Distinction	HIPAA Privacy Rule: Title 45 CFR Part 164	HHS Protection of Human Subjects Regulations: Title 45 CFR Part 46 (Common Rule)
IRB or privacy board exemptions	Research involving personal health information if it is deidentified by the "Safe Harbor Method,"[a] if validation is obtained from a statistician that the risk that the information could be used by the anticipated recipient to identify the subject of the information is very small, or if only a "limited dataset"[b] is used or disclosed.	Research involving the collection or study of existing data, documents, records, pathologic specimens, or diagnostic specimens; and research involving only coded private information or specimens so that the subject's identity cannot be readily ascertained if the research does not qualify as human-subjects research. (Other conditions not specific to biorepositories apply.)
Permissions for research or use of private information	Authorization.	Informed consent.
What qualifies as identifiable information?	All "individually identifiable health information" held or transmitted by a covered entity or its business associate in any form or medium, whether electronic, paper, or oral.	Any form or medium in which the identity of the subject is or may readily be ascertained, directly or through identifiers linked to the subjects, by the investigator or person associated with the information.
Qualifications for a waiver of authorization or informed consent	If use or disclosure involves no more than minimal risk[c] to the privacy of individuals, research could not practicably be conducted without the waiver or alteration, and research could not practicably be conducted without access to and use of protected health information.	If the research involves no more than minimal risk to the subjects, the waiver or alteration will not adversely affect the rights and welfare of the subjects, the research could not practicably be carried out without the waiver or alteration, and, when appropriate, the subjects will be provided with additional pertinent information after participation. (Other conditions not specific for biorepositories apply.)

SOURCE: Adapted from HHS, 2003b.

[a]The "Safe Harbor Method" states that 18 identifiers of the individual or of relatives, employers, or household members of the individual must be removed. These identifiers are listed in Table 3-1.

[b]A limited dataset may include such information as dates and locations. It may be used or disclosed only for public-health, research, or healthcare operations purposes, and it is subject to other requirements (45 CFR 164.514(e)).

[c]In order to qualify as minimal risk there must be an adequate plan to protect health-information identifiers from improper use or disclosure, an adequate plan to destroy identifiers at the earliest opportunity in the absence of a health or research justification or legal requirement to retain them, and adequate written assurances that personal-health information will not be used or disclosed to a third party except as required by law, for authorized oversight of the research study, or for other research uses and disclosures permitted by the Privacy Rule.

Because both the Common Rule (and OHRP guidance) and HIPAA rules refer to deidentification as a condition for a waiver, it is important to recognize that HIPAA defines this level of deidentification differently from the Common Rule. The HIPAA Privacy Rule generally defines deidentified PHI as information that "does not identify an individual and with respect to which there is no reasonable basis to believe that the information can be used to identify an individual" (164.514(a)). It does not require there to be no risk of reidentification but instead that "the risk [be] *very small* that the information could be used, alone or in combination with other reasonably available information, *by an anticipated recipient* to identify an individual who is a subject of the information" (*emphasis added*) (164.514(b)(1)(i)). To meet that standard of deidentification, the 18 specific identifiers listed in Table 3-1 must be removed or a statistical certification must be made that states that the risk of reidentification is very small. In addition, "the covered entity does not have actual knowledge that the information could be used alone or in combination with other information to identify an individual who is a subject of the information" (164.514(b)(2)(ii)).

Another conflict between the Common Rule and HIPAA is in coverage of deceased individuals. Although the Common Rule restricts its definition of "human subjects" to living individuals, HIPAA applies to both the living and the deceased. HIPAA requires assurance from researchers who seek to use or disclose PHI from deceased persons that With and colleagues (2011) summarize as follows:

(1) that the use and disclosure of PHI is solely for research,
(2) that the PHI is necessary for the research, and
(3) that documentation of death . . . be provided, if requested by the covered entity.

HIPAA authorization applies to a specific research protocol, not to a general intent to use the PHI in research in the future. Current HIPAA regulations do not permit broad consent to future research without waiver of the authorization requirements (Clayton, 2005). In response to public comments on HIPAA, the Office of Civil Rights (which administers HIPAA) noted that "the Department disagrees with broadening the required 'description of the purpose of the use or disclosure' because of the concern that patients would lack necessary information to make an informed decision" (67 Fed. Reg. 53,226). Authorization to use PHI, it asserted, must be "specific and meaningful," and general descriptions are inadequate (HHS, 2011; Wendler, 2006).

Potential Changes in the Common Rule Under the 2011 Department of Health and Human Services Advance Notice of Proposed Rule Making

The federal rules governing research on samples collected for clinical purposes were in flux when the present committee completed its work in the middle of 2012. As already noted, HHS issued an ANPRM in July 2011 requesting comments on possible regulatory changes that would alter required consent for research. Consent is currently required unless research falls under the deidentification exceptions, including waivers, contained in the Common Rule and the HIPAA Privacy Rule. Much of the justification for not requiring consent rests on the idea that as long as participants remain unidentifiable, potential harm is so limited that it makes consent unnecessary. The ANPRM, however, noted growing recognition that identifiability is a fluid concept that advances with technology and that what was formerly considered deidentified could be identifiable with advances in technology and increased information flow. Thus, current justifications for foregoing consent or HIPAA authorization were not necessarily sustainable.

The ANPRM therefore proposed that written consent for possible future use in research be required for "any biospecimens collected for clinical purposes after the effective date of the new rules." That would include all specimens taken in the course of clinical care for use in research even if later deidentified. However, the consent required would be broad, "would allow for waiver of consent under specified circumstances" and would "generally permit future research." That differs from policy in place in 2012 that generally disfavors broad consent and broad authorization for future research and does not require consent for research on specimens collected in clinical care that can be deidentified (HHS, 2011). The fate and scope of any actual change in regulatory language based on the ANPRM remained uncertain when this report was finished.

Military Rules Addressing Human-Subjects Research and Privacy

Although the military is subject to civilian control, it has its own internal governance structure. The pinnacle of the military's internal governance system is the DoD, which issues regulations, directives, instructions, memoranda, and manuals that may be binding on any department[21] or entity of the military named in the issuance. Each department also promulgates regulations, policies, and orders covering the parts of its own service. These regulations and other issuances may not contradict or be inconsistent with federal statutes.

[21]The departments under the secretary of defense are the Departments of the Army, Air Force, and Navy (which includes the Marine Corps). Some military regulations refer to "components," a broader term that also refers to operational units of the DoD.

The Federal Privacy Act (5 U.S.C. § 552a) was enacted in 1974 to govern what medical and other information the Executive Branch of the federal government (including the DoD) may collect about individuals, what uses may be made of that information, and what consent is required. DoD Directive 5400.11-R (2007) provides guidance on the Act and establishes procedures for implementing it.

The DoD was one of the first organizations in this country to adopt policies explicitly addressing the protection of human research participants; however, its original pronouncement on the subject was a top-secret memorandum that had little effect on researchers' actual practices (Lederer, 2003; NBAC, 2001). The DoD's codification of the Common Rule can be found at 32 CFR Part 219. It formally announced its compliance with HIPAA in April 2003 (DoD, 2003a). The DoD Human Research Protection Program is housed in the office of the deputy assistant secretary of defense for force health protection and readiness (Miner, 2011). The program has responsibility for supervising DoD IRBs, conducting education and training regarding human-participant protections, conducting quality-improvement and quality-assurance activities, and developing policy.

In 2002, the DoD issued Directive 3216.02 on the Protection of Human Subjects and Adherence to Ethical Standards in DoD Supported Research (DoD, 2002). Directives "establish policy, assign responsibility, and delegate authority to DoD components" (DoD, 2010). Directive 3216.02 makes the principles of respect for persons, beneficence, and justice official policy in military research. In addition to applying the Common Rule, Directive 3216.02 requires the appointment of an independent medical monitor for research involving more than minimal risk to participants, requires auditing for research misconduct, requires training in research ethics for personnel involved in research with human participants, and includes a variety of other substantive and procedural requirements beyond those in the Common Rule.

In November 2011, the DoD issued Instruction (DoDI) 3216.02, which reissued Directive 3216.02 with a few modifications, additional requirements, and procedures (DoD, 2011). DODI 3216.02 expands substantive protections for human research participants beyond those described in Directive 3216.02 and adds or clarifies some review procedures. It also expands on the Common Rule's guidance for assessing risk in research.

Box 3-1 lists some of the DoD and service-specific regulations related to research on materials in biorepositories. Appendix C reproduces the version of DoDI 3216.02 dated November 8, 2011, the most current available when this report was completed.

BOX 3-1
Military Rules and Regulations Related to Research on Biorepository Materials and Associated Data

Department of Defense
- 32 CFR Part 219 (1991) – Protection of Human Subjects
- DoD 5400.11-R (14 May 2007) – Department of Defense Privacy Program
- DoD 6025.18-R (24 Jan 2003) – DoD Health Information Privacy Regulation
- DoD 8580.02-R (12 July 2007) – Health Information Security Regulation
- Instruction 3210.1 (16 Sep 2005) – Administration and Support of Basic Research by the Department of Defense
- Instruction 3216.01 (13 Sep 2010) – Use of Animals in DoD Programs
- Instruction 3216.02 (8 Nov 2011) – Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research [reproduced as Appendix C]
- Instruction 6000.08 (3 Dec 2007) – Funding and Administration of Clinical Investigation Programs

Air Force
- Instruction 40-402 (5 May 2005) – Protection of Human Subjects in Biomedical and Behavioral Research

Army
- Regulation 40-33 (16 Feb 2005) – The Care and Use of Laboratory Animals in DoD Programs
- Regulation 40-38 (1 Sep 1989) – Clinical Investigation Program
- Regulation 70-25 (25 Jan 1990) – Use of Volunteers as Subjects of Research

Marine Corps
- Order 3900.18 (21 Jan 2011) – Human Research Protection Program

Navy
- SECNAV Instruction 3900.39D (6 Nov 2006) – Human Research Protection Program

SOURCE: Adapted from With et al. (2011) and expanded.

Armed Forces Institute of Pathology and Joint Pathology Center Rules Addressing Human-Subjects Research and Privacy

A number of AFIP[22] and JPC regulations articulate their compliance with civilian and military human-subjects research and privacy rules. The

[22]JPC, which became fully operational in September 2011, is still in the process of establishing its own regulations and policies. In the interim, it is applying AFIP regulations and policies.

overall policy, which mirrors that of other DoD health entities, states (AFIP, 2005) that the organization is committed to

- protecting patient confidentiality and maintaining integrity and security during the collection, creation, analysis, storage, and destruction of protected health information.
- establishing systems and mechanisms to safeguard patient privacy without disrupting the provision or quality of health care.
- enforcing the rights of patients with respect to health information privacy.
- designating appropriate representatives to carry out privacy functions in accordance with applicable federal and state laws and regulations.
- incorporating parameters to monitor and improve compliance with health information privacy standards in the design of the organizational compliance program.

AFIP Regulation 40-1, *Retention, Loan, and Disposition of Accessioned Case Materials* (2009)—which the committee understands is still in force for the JPC—includes a section "Privacy Act Guidelines When Conducting Research Using Medical Records" that states

a. Medical information and associated materials are protected by the Privacy Act, 5 U.S.C. 552a. Qualified individuals may have access to medical information and associated materials covered by this Act for research and study when approved by the AFIP Research Committee and the AFIP IRB as applicable in accordance with AFIP Regulation 70-1.[23]
b. Information abstracted from AFIP records will be treated as confidential, and the identities of the patients, photographs, or other identifying information will not be used in any publication or released without the consent of the patient or authorized legal representative.
c. All identifying information will be removed from abstracts or reproduced records to be used in studies conducted outside the AFIP except when there is a valid patient/legal representative's authorization. No original records may be removed from the AFIP. All material being loaned that is not part of an approved AFIP protocol or does not have proper patient/legal representative authorization, must be

[23] AFIP Regulation 70-1 *Research and Investigation Program* (2006) defines the responsibilities of the repository's research committee and IRB and the review and approval process for research studies.

> anonymized to include removing the AFIP accession number since it could eventually be linked to the patient by the recipient. The Associate Chair, Department of Repository Services, can assign a control number to anonymized specimens for release as necessary.

The JPC *Contributor's Manual* states that "all pathology consultation records maintained by the JPC are protected by the Privacy Act and by the regulations implementing the Health Insurance Portability and Accountability Act" and that "JPC falls under the DoD Notice of Privacy Practices" (JPC, 2011b). The Notice of Privacy Practices specifies (DoD, 2003b) that

> we may disclose your protected health information to researchers when authorized by law, for example, if their research has been approved by an institutional review board that has reviewed the research proposal and established protocols to ensure the privacy of your protected health information.

And, as noted in Chapter 1, the JPC *Contributor's Consultation Request Form* (2011a)—which medical professionals use to submit materials to the repository—includes the DoD's Privacy Act statement.

Regulation 40-16, *Health Information Privacy* (AFIP, 2005) lays out how compliance with the rules is maintained. It requires yearly staff training in health-information privacy standards and describes the duties of a privacy officer, a HIPAA training officer, and a HIPAA compliance committee.

Concluding Considerations Regarding Consent and Custodianship

Even though the various laws and regulations embody ethical considerations, they do not fully address or resolve all the ethical issues. Controversy over the research use of clinically obtained tissue specimens without informed consent, or with only incidental and cursory general consent, is long-standing. Several problematic cases, referred to early in this chapter, provide some of the background of this controversy.

In 1999, the National Bioethics Advisory Commission (NBAC), appointed by President Clinton to study and make recommendations on a range of bioethics issues, published a report on research using stored human biological material. This report is part of a significant and still-growing literature on ethical research use of stored tissue as it relates to the ethical responsibilities of biorepositories and large-scale collections of tissue, material, and data. The NBAC advised that research on identified samples is indeed human-subjects research under the Common Rule and so "requires consent of the source, unless the criteria for a consent waiver have been satisfied" (NBAC, 1999). The commission recommended (p. 64) that

> whether obtaining consent to the research use of human biological materials in a research or clinical setting, and whether the consent is new or renewed, efforts should be made to be as explicit as possible about the uses to which the material might be put and whether it is possible that the research might be conducted in such a way that the individual could be identified. . . . The current debate about the appropriate use of millions of stored specimens endures because of the uncertain nature of past consents. Investigators and others who collected and stored human biological materials now have the opportunity to correct past inadequacies by obtaining more specific and clearly understood informed consent.

It also specifically addressed research use of pre-existing samples—those obtained before the implementation of its recommendations—urging (p. 64) that

> *general releases for research given in conjunction with a clinical or surgical procedure must not be presumed to cover all types of research over an indefinite period of time.* Investigators and IRBs should review existing consent documents to determine whether the subjects anticipated and agreed to participate in the type of research proposed. *If the existing documents are inadequate and consent cannot be waived, the investigator must obtain informed consent from the subjects for the current research or in appropriate circumstances have the identifiers stripped* so that samples are unlinked. [emphasis added]

The NBAC noted that research on identified samples is human-subjects research and ordinarily requires consent and that "seeking this consent demonstrates respect for the person's right to choose whether to cooperate with the scientific enterprise, and it permits individuals to protect themselves against unwanted or risky invasions of privacy" (p. 66). The NBAC's reasoning suggests that unless consent to research use is waived under applicable regulations, ethical research use of tissue, materials, and data that carry identifiers requires either informed consent for the contemplated work or deidentification.

A substantial literature over the last decade argues for recognizing a biorepository duty of responsible custodianship, a concept introduced earlier in this chapter. The National Cancer Institute, for example, in its 2011 *Best Practices for Biospecimen Resources* (updating its 2007 *Best Practices*) stresses that "responsible custodianship requires careful planning and transparent policies to ensure the long-term physical quality of the biospecimens, the privacy of human research participants, the confidentiality of associated data, and the appropriate use of biospecimens and data" (NCI, 2011, p. 31). The best practices formulated by the International Society for Biological and Environmental Repositories (ISBER, 2008) maintain that

biobanks need to provide responsible "custodianship" of the tissues and data that they collect, maintain, and share. Biobanks—private and public—commonly have a variety of committees and governance structures to address operational and ethical issues, including access to data and samples by secondary researchers (Eiseman et al., 2003; ISBER, 2008; NCI, 2011). Core issues addressed in discussions of biobank ethics include consent and withdrawal of consent, as well as protection of privacy and confidentiality.

Several well-recognized challenges regarding informed consent to research involve archival biospecimens. Even when recontact and consent or reconsent are possible because the individual sources are still alive, requesting consent for already archived materials can be prohibitively expensive; further, the act of contacting a source for consent can itself be regarded as an invasion of the privacy or, at the least an unwelcome intrusion, especially for persons who were unaware that their or their family's tissue was used for research (Bathe and McGuire, 2009). When comprehensive collections of material have been assembled—such as specimens from all patients with a particular diagnosis or a common exposure—having to obtain consent for research use may introduce a selection bias if some of those contacted decline to consent. The use of archival tissues requires a balance between the possibility of suboptimal consent and the use of valuable resources. Figure 3-2 illustrates Bathe and McGuire's suggested framework for using archived tissue samples derived from clinical care.

Bathe and McGuire suggest reconsent if research presents greater than minimal risk; even if the research presents only minimal risk, they call for reconsent if it is practicable. Only if research presents minimal risk and reconsent is impracticable do they indicate that research should be allowed with a waiver of consent. They go on (Bathe and McGuire, 2009, pp. 714–715) to identify a set of guiding principles for making such decisions, including the following:

- The primary objective of the ethics committee is to balance benefits of research against risks of harm.
- Privacy risks need to be assessed; but if risks are minimal and reconsent is impracticable, informed consent may be waived.
- Risks are minimal if samples or data are in databases restricted to "bona fide researchers," data-access requests are reviewed for merit and ethics standards, the proposed research is consistent with any existing consent, and the research is not "stigmatizing or sensitive."
- Impracticability of recontact should be judged by such factors as availability of contact information, probability of the subject's being alive, harm in recontact, and time or expense of recontact.
- If privacy risks are greater than minimal, reconsent should be required.

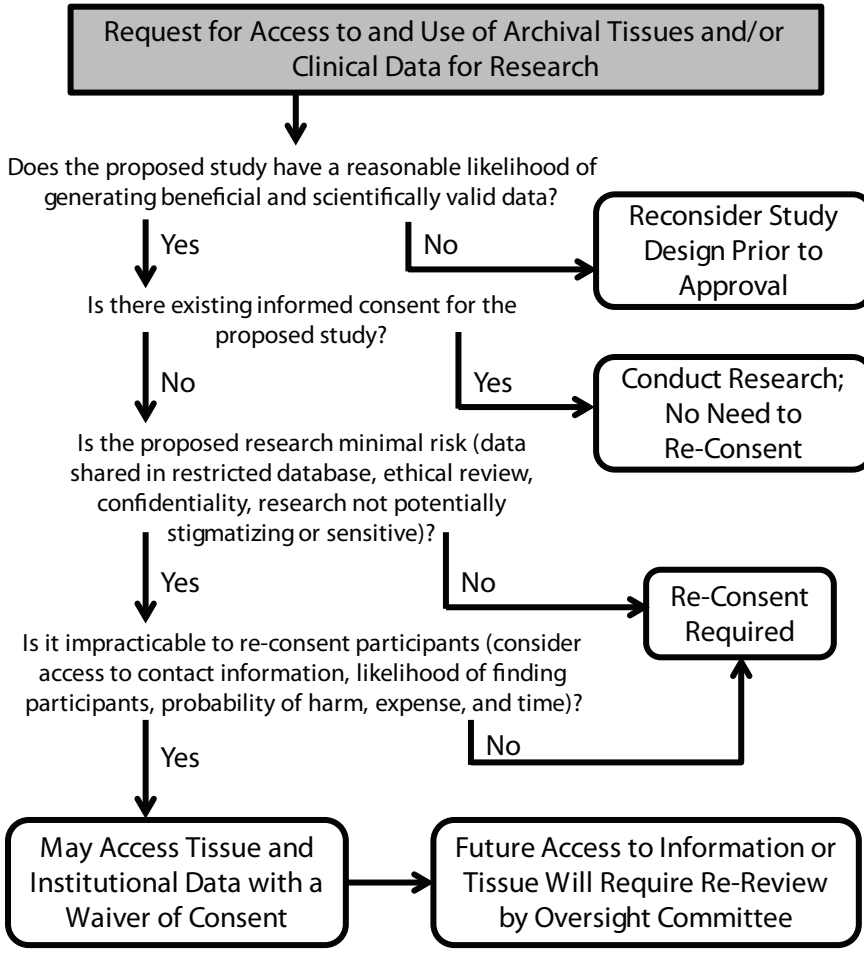

FIGURE 3-2 A framework for accessing archival tissues and clinical data for research. Reprinted by permission from Macmillan Publishers Ltd: *Genetics in Medicine* (Bathe and McGuire, 2009). Copyright 2009.

- Preventive consent should be considered if risks to privacy and stigmatization cannot be accurately predicted.
- "Data derived from unconsented patients should never be shared in a publicly accessible database. It may be permissible to share data in a database with controlled access. However, any future access to information or tissue from such a database mandates review by an ethics or data access committee."

- Security procedures "should be commensurate with the sensitivity of the information recorded."

Helgesson and colleagues (2007) suggest a similar framework that seeks to balance individual risks against the value of research. To weigh the risks and benefits, the authors suggest use of an ethics review board. If no previous consent or refusal exists and the study "is not particularly sensitive . . . genetic analyses of identifiable samples should be permitted without [new] consent" provided that there is strict coding, secrecy laws apply, and "vital research interests are at stake" (p. 975).

If the JPC continues to collect biospecimens and associated data, it will need to determine what kind of consent is appropriate for the research use of the newly acquired materials and the extent (if any) to which it can suggest or even prescribe language regarding consent to use materials submitted to it in subsequent research. A schematic presentation of the arguments for and against different types of consent is presented in Table 3-3.

TABLE 3-3 Ethical Considerations Regarding Different Source Consent Options to Provide Access to Data and Specimens for Research Purposes

Option	No Consent from Source (Exemptions or Waivers)	Notification to Source and Opt-Out	Opt-In by Source (Broad Consent)	Opt-In by Source (Reconsent)
Arguments for	• IRB responsible for ensuring acceptable (minimal) risk vs. benefits gained • Respects negative right of privacy through requiring minimal risk of reidentification • Other governance mechanisms (oversight, data-use review) can provide protections for sources • Recontact uses resources otherwise needed for research • Research is advancing the "common good" and, as an act of altruism or solidarity, individuals should release control of their specimens or data	• Respects persons by informing them about sample use • Meaningful choice is possible without overburdening source or institution with consent processes • Accountability obligations are enacted through transparency regarding intentions • Permits diverse participant preferences • Provides lower bar (than opting in) for remaining in the collection • Increased health and science literacy through transparency	• Respect for autonomous choice: person assesses risk–benefit tradeoff • Issues at stake for individuals other than risk of reidentification (anonymization is not the only concern) • Positive right to privacy: ability to control who sees my data or specimens • Repository managers are custodians of samples but not "owners" (individuals retain control)	• Emerging technology is permitting dynamic consent, which permits diverse participant preferences and facilitates recontact • HIPAA requires purpose-specific information for consent • Enhanced control may encourage diverse participation from historically mistreated populations • Positive right to privacy: ability to control who sees my data or specimens • Repository managers are custodians of samples but not "owners" (individuals retain control)

Arguments against	• Removes sources' right to know or control what is happening to their samples • Genetic material is inherently unique (even if not "readily" identifiable) • Misses an important public education opportunity	• Can be resource-intensive • Existing oversight and protections should be sufficient • Supererogatory (exceeds current regulatory requirements) • Can be difficult to identify all data and specimens for removal correctly • Can be difficult to ensure that notification has been read and understood • Can be disruptive to the research collection	• Resource-intensive • Broad or blanket consent does not achieve the goal of informed choice (therefore, requiring broad opt-in does not meet autonomy obligations while creating undue burdens) • Can be difficult to ensure consent has been read or, given the broad nature of consent, understood	• Resource-intensive • Exceedingly difficult to keep track of participants to update current contact information • Risks sample bias due to nonresponders • Can be difficult to ensure that notification has been read and understood
Special considerations	• Current standard of practice in most settings • Useful for routine projects and minimal risk or high-public-benefit projects (such as public-health concerns)	• Preventive approach to liability risk • Public websites and materials can serve multiple purposes (such as marketing, outreach)	• Historically traumatized populations may need additional choice options to build trust • Proposed changes to the Common Rule require consent for specimen use (even deidentified)	• As technology improves our ability to manage individual preferences, these dynamic consent options should become more useful • Maintaining current contact information is a responsibility of the source, as well as the repository manager
References	Shickle, 2006	Brothers and Clayton, 2009 Pulley et al., 2010	Emanuel and Menikoff, 2011 Lunshof et al., 2008	Kaye et al., 2012a Ludman et al., 2010 Saha and Hurlbut, 2012 Trinidad et al., 2010, 2011

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4

Findings, Conclusions, and Recommendations

This chapter builds on the foundation laid in Chapters 1–3 to draw out the overarching themes of the report and present the committee's findings, conclusions, and recommendations related to its statement of task.

OPENING OBSERVATIONS AND GENERAL RECOMMENDATIONS

The Joint Pathology Center (JPC) faces major challenges as it transforms into a modern biorepository that provides clinical consultation, education, and research services. Many of these arise from the way in which much of the existing collection of biospecimens and associated clinical data were obtained. The challenges include determining the utility of the collection—which consists of materials collected, handled, and stored under a variety of conditions—and establishing appropriate ethical and legal standards for using the materials, especially in research, inasmuch as they were generally collected without sources' consent for use in research.

The threshold issue that the JPC must confront in facilitating use of the repository is the uncertainty regarding the utility of its collection of biospecimens. Experience with other biorepositories that, like the JPC, are composed of samples collected in the absence of a purposefully designed protocol indicates that their value may be severely limited by the state of specimens and their associated documentation (Compton et al., 2009). Variations in the preanalytic handling of specimens, in specimen preparation and fixation, in postfixation handling and storage, and in accompanying documentation greatly affect their suitability for some forms of analysis. That is not to say that such specimens lack value—almost all have utility

in at least some applications—but it indicates that the operators of such a repository must be circumspect in their expectations and representations. Advances in technology will undoubtedly change the criteria for determining whether particular specimens are fit for purpose in ways that may make fewer or more of them useful.

The committee recommends that the JPC, as part of its plan for improving the use of repository materials in research, evaluate the strengths and limitations of the collection to the extent permitted by its resources and current science and technology, consider how to enhance the repository's value given the JPC's organizational and budgetary constraints, and formulate its retention policy and dissemination management and marketing strategies accordingly. In this regard, the committee believes that it is crucial for the JPC to find ways to engage the relevant professional community in discussion concerning future use of the repository so that it can understand better the potential demand for collection materials and how to facilitate their use.

The committee believes that the JPC will increase its appeal to researchers as an important source of biological materials if the repository undertakes a more thorough documentation of its holdings and makes this information more easily accessible to medical professionals and scientists so they can better determine whether the JPC has specimens that meet their needs. Harvard's Pathology Specimen Locator (PSL) Core, for example, provides a searchable database of pathology samples left over from diagnostic procedures performed in five university-associated facilities (NCI, 2009). These samples are made available for research study with their accompanying clinical data. The PSL Core uses a number of privacy safeguards for its database: it may be accessed only via a password provided to qualified investigators, data transmissions are encrypted, all data are deidentified and coded with link-backs to repository specimens and data held on a separate fire-wall-protected system, users are limited in how much information they can access on specific specimen sources, and data access is further limited if a query returns only a small number of source individuals who meet the search criteria (Drake et al., 2007).

The JPC may wish to consider whether the utility of a subset of biorepository samples could be enhanced via limited, focused audits of existing materials (both specimens and data) in response to requests for access to those materials. For example, following a request for samples of a particular disease, repository staff or an honest broker might abstract annotations from the database for archived cases or perform a specific screen on archived samples as an add-on service to assess the accuracy of the recorded diagnosis, viability of the tumor, or quality of the specimen.[1] Thus, the

[1]Such information would be appended to existing records to enhance their future value.

biorepository might offer two tiers of samples: unscreened—where the recipient would take on the burden of reviewing sample quality—and prequalified samples that pass a JPC lab screen. Presumably the cost of such an audit would be borne by the requesting party. The ability to provide such services would of course be dependent on the availability of the requisite expertise and any organizational and budgetary constraints.

The JPC may also wish to consider means such as the "honest broker" model for providing specimens and data to researchers while protecting the interests of specimen sources in privacy and confidentiality. An honest broker is an individual, organization, or system that serves as neutral intermediary between a provider of materials (a source individual or biorepository, for example) and researchers, collating pertinent specimens and data, replacing identifying information with a code, and releasing only coded information to the researchers (Eiseman et al., 2003; NCI, 2011). The code may be maintained consistently for a specific specimen and study or generated anew for each study (or investigator) to lessen the chance of unsanctioned linkage of records between investigations. Information on subjects may be from one source or several.[2]

The notion of an honest broker has not only been adopted by some biorepositories (Amin et al., 2008; Boyd et al., 2009; Dhir et al., 2008; Drake et al., 2007) but also has been applied more generally in facilitating the dissemination of materials to life-science researchers (Boyd et al., 2006). It is critical that the organization managing the brokering process define appropriate policies for exchange of information between the repository and the researcher as well as train and certify its personnel on how to execute those policies.[3] Honest brokers may either be entities that are outside and independent of a biorepository or be situated within the organization, provided that they are disassociated both from the research projects in which the data and specimens are being employed and from the management of the specimens and data within the repository.

The JPC indicated to the committee that it would like to make repository materials available for research on a cost-neutral basis (Baker, 2011). Because the federal government is in general prohibited from charging nongovernment entities for such services,[4] **the committee recommends that the JPC immediately determine whether it has the statutory ability to recover**

[2]For example, depending on the study, the Department of Defense, the Department of Veterans Affairs, the Centers for Medicare and Medicaid Services, private insurers, and the Centers for Disease Control and Prevention (through the National Death Index) might have relevant data on a particular subject.

[3]An example of such practices is described by the University of Pittsburgh Medical Center (UPMC, 2008).

[4]Federal organizations can recover such costs from other parts of the federal government through interagency transfers (31 U.S.C. § 1535).

the costs of providing specimens and data for approved research projects. If it does not, the JPC should work with Department of Defense (DoD) leadership to determine the best way to establish such an ability. The committee notes that other government agencies have used such mechanisms as partnering with nonprofit organizations (which may accept nongovernment funds) to provide services that they cannot charge for or to receive funds from outside parties.[5]

Another major set of challenges arises from the application of current legal and ethical standards to the repository. The nature of these challenges depends on whether the focus is on previously collected biologic materials and medical information already held by the biorepository or on biologic materials and medical information to be collected and accessioned in the future. There is no documentation of the nature and extent of the consents by source individuals for future use associated with the JPC's existing biospecimens, associated data, and medical records. The challenge is to determine under what conditions previously archived materials may now be used for research and to devise policies and practices that reflect that determination and to govern future collection of biospecimens and medical information in a way that complies with relevant and evolving legal and ethical standards.

In the sections below, the committee elaborates on its recommendations regarding those and other issues raised by the DoD in the committee's statement of task. The DoD's questions[6] are organized in two major categories: those related to the retention and maintenance of biospecimens and those related to the future use of biospecimens and associated data and medical records in clinical care, education, and research. Issues of future use are further divided into ethical and legal considerations and scientific considerations.

RETENTION AND MAINTENANCE OF BIOSPECIMENS

General Retention and Maintenance Issues

The Tissue Repository currently contains paraffin-embedded tissue, glass slides, wet (formalin-fixed tissue) and frozen tissue; some of it is not usable for consultation, education, and research given current technology. Should material not deemed currently usable for consultation, education, and research be stored indefinitely or should the JPC develop a plan for disposal of unusable or non-viable specimens and are there any legal considerations with disposal of said specimens?

[5]For example, the CDC Foundation (CDC Foundation, 2012).

[6]The questions posed by DoD appear in *italics* at the start of each subsection below.

The JPC's current retention policy is set forth in two documents that spell out how the repository obtains material by retaining specimens and other material submitted to it for consultative and research purposes. Section 4-1 of the *Contributor's*[7] *Manual* (2012) provides this general information:

a. Slides submitted with each case are retained at the JPC. If blocks are also submitted, representative slides prepared at the JPC may be sent to the contributor as enclosures to the consultation report. Exceptions to this slide retention policy are normally approved by the senior pathologist of the service that would review the case. If the return of original slides is approved, digital images of the slides will be made for retention in the case folder.
b. Paraffin blocks and wet tissue specimens may be returned to the original contributor upon request. The return of blocks should be requested at the time of submission on the JPC *Contributor's Consultation Request Form* or later by separate correspondence.
c. Clinical and gross photographs will be copied for retention at the JPC and the originals returned if their return is requested at the time of submission. X-ray films will also be copied for retention and returned.

The JPC's *Contributor's Consultation Request Form* (JPC, 2011) supplies further detail:

1. MICROSCOPIC SLIDES SUBMITTED WITH EACH CASE ARE RETAINED PERMANENTLY. Under certain circumstances original slides may be returned to the Contributor if requested by the Contributor and approved by the JPC. If slides are returned, then each slide will be digitized at the expense of the Contributor.
2. [Tissue] blocks are retained for a minimum of ten (10) years, unless return is requested by the Contributor at the time the case is submitted. Contributors may request return or loan of blocks at some later time. If blocks are returned, then JPC will retain representative diagnostic material.
3. Other pathologic material, X-rays, CT scans, MRI scans, echograms, angiograms, photographs, and similar diagnostic studies may be retained for education and research or discarded.

The committee did not identify any ethical considerations that would call for routine retention of specimens beyond the limits specified in the

[7]In JPC's nomenclature, the "contributor" is the pathologist, other medical professional, or institution that sends a specimen to the repository. It does not refer to the specimen source.

CAP guidelines, DoD regulations, or other legal requirements. Once the JPC makes a decision to retain rather than return materials, a policy is needed regarding how long the repository should hold onto them. Any retention policy adopted should continue, at a minimum, to follow the guidelines and requirements set forth in the College of American Pathologists (CAP) Laboratory Accreditation Program[8] in addition to the DoD's Clinical Laboratory Improvement Program (CLIP) standards. CLIP standards conform to the Centers for Medicare and Medicaid Services Clinical Laboratory Improvement Amendments (CLIA) certification requirements except where they "may be required to meet unique aspects of DoD missions, training, and preparations during peace, contingency, and war time operations which preclude compliance" (DoD, 1994; § 4.3). Table 4-1 summarizes the guidelines and requirements.

As the committee noted above, some of the biological materials being held by the JPC cannot be reliably or productively interrogated using current methods. Since advances in tissue-analysis technology continue to be made, no one can confidently predict the potential future scientific value of particular repository specimens. That prospect depends not only on the refinement or development of technologies but on whether the materials held by the JPC turn out to be worth examining in comparison with those held by other sources, such as more modern biorepositories and hospital or university pathology departments. Several existing and emerging technologies in morphology, RNA, DNA, and bioinformatics—detailed in Chapter 2—hold the potential for making JPC repository materials more useful than they are now by permitting specimens previously considered unusable to be analyzed or by allowing more information to be extracted from specimens. However, technologic advances could clarify that the collection, processing, and storage conditions of some JPC specimens have rendered them undesirable or unsuitable for future use. A good policy will thus include a process for periodically assessing how new analytic technologies relate to the material held in the JPC collection and be updated regularly to reflect technological advances.

The possibility that some currently unusable material might become useful does not mean that all of the material that the JPC holds must be stored indefinitely to safeguard against losing something of possible prospective value. **The committee recommends that the JPC develop protocols for determining when to retain potentially useful materials and when to dispose of specimens that have no special research or educational value and are past the point of required retention for clinical use.**

[8]The JPC held full CAP accreditation at the time that this committee completed its work in the middle of 2012.

TABLE 4-1 Specimen Retention Policy, Guidelines, and Requirements for the Joint Pathology Center (JPC), Clinical Laboratory Improvement Program–Clinical Laboratory Improvements Amendments (CLIP–CLIA), and College of American Pathologist (CAP) Laboratory Accreditation Program as of 2012

Medium	JPC (JPC, 2011)	CLIP–CLIA (42 CFR § 493.1105; AFIP, 2007)	CAP (CAP, 2010)
Slides	Permanently	Cytology: 5 years Histology: 10 years	Permanently stained slides—microbiology: 7 days Cytogenetics—permanently stained: 3 years Cytology: 5 years Surgical pathology: 10 years Fine-needle aspiration: 10 years Nonforensic autopsy: 10 years Forensic autopsy: permanently Cytogenetics fluorochrome-stained: discretion of laboratory director
Paraffin blocks	10 years; representative samples of returned specimens are retained	2 years	Surgical pathology: 10 years Nonforensic autopsy: 10 years Forensic autopsy: permanently
Wet tissue	10 years	Until diagnosis is obtained	Surgical pathology: 2 weeks after final report Nonforensic autopsy: 3 months after final report Forensic autopsy: 1 year Cytogenetics: until adequate metaphase cells are obtained
Other pathology materials	Discarded or retained at the JPC's discretion	Clinical and gross radiographic diagnostic materials: 2 years	Urine: 24 hours Serum–heparinized or EDTA plasma–cerebrospinal fluid–body fluids: 48 hours Peripheral blood smears–body-fluid smears: 7 days Cytogenetics fixed-cell pellet: 2 weeks after final report Body fluids–tissues for toxicology: 1 year Patient test records: 2 years Cytogenetics diagnostic images: 20 years Accession log: permanently Gross photographs/negatives: permanently Representative tissue suitable for DNA analysis: permanently
Pathology reports	Permanently	No specific requirements	Surgical pathology: 10 years Cytology: 10 years Nonforensic autopsy: 10 years Cytogenetics: 20 years Forensic autopsy: permanently

Among the considerations in such protocols is the condition of a specimen and its accompanying data. **The committee recommends that the criteria for determining when specimens should be disposed of** include whether the specimens fall into any of these categories:

- Wet tissue specimens and slides that have been obviously contaminated, desiccated, or otherwise damaged.
- Tissue blocks that have been contaminated, exhausted, dried out, or have otherwise deteriorated.
- Frozen specimens that show evidence of freezer burn or of having been melted and refrozen.
- Specimens of any type that cannot be associated with a data record in the system.

Specimens in those categories should be disposed of unless they meet the standards for retention discussed in "Use of Rare and Unique Materials" below. It should be noted that although visual inspection yields some information on sample quality, specimens that have no apparent damage may still have degraded biomolecular integrity and may thus be unsuitable for some research applications.[9]

Auditing the vast holdings of the JPC repository to determine the condition of specimens would be a long and expensive undertaking. **The committee recommends that as long as it is less expensive to retain specimens than it is to assess their condition comprehensively, specimens be evaluated only when they are retrieved for clinical, education, or research purposes. If a specimen is found to satisfy the disposal criteria, it should be removed from the collection. If and when the cost of retaining specimens exceeds the estimated cost of auditing the collection, a procedure for setting priorities for review and systematically removing specimens that are not usable for clinical, education, or research purposes from the collection should be implemented.**

Two types of specimens merit particular attention in any review of materials for possible removal from the collection and disposal.

1. Information developed for the Asterand report (2008) suggests that almost all wet tissue specimens are in poor condition: a survey of materials found that more than 99 percent of such specimens accessioned in 1917–1969 and more than 72 percent of those in 1970–2002 were completely desiccated. The committee suggests that the JPC prioritize the review of wet tissue specimens in any audit of the holdings that it conducts and that it consider conduct-

[9]Such specimens may still be useful for light microscopy.

ing a focused audit of wet tissue materials to remove contaminated and desiccated specimens.

2. Frozen tissue is especially vulnerable to melting and deterioration, and freezers are expensive to maintain and monitor properly. The committee suggests that the JPC prioritize the review of frozen tissue specimens in any audit of the holdings that it conducts and that it consider conducting a focused audit of frozen materials to remove specimens that show evidence of past melting or freezer burn. If the audit of specimen quality suggests that the frozen tissue resources are potentially useful, the JPC should ensure that the freezers are being maintained according to current laboratory practice guidelines (ISBER, 2012; NCI, 2011), including the use of continuous temperature monitoring and recording, alarms, emergency power supply, and the like.

The materials contained in the Base Realignment and Closure (BRAC) Collection come from a variety of sources and are likely to vary greatly in their quality and in the documentation associated with them. The committee believes that other biorepositories are likely to have readily available alternatives for such materials that are more suitable for future research because they have been collected under more modern, more uniform, or better documented circumstances. An exception might be specimens that could be used as reference materials,[10] although it is unclear whether auditing the BRAC Collection would be the most cost-effective way of obtaining suitable samples. The committee offers further comments on the BRAC Collection materials below.

Material contained in some of the war and cohort registries may be subject to additional retention requirements that were part of the agreement made by the repository to serve as custodian. Any retention requirements agreed to in setting up such a registry will need to be honored. If specimens are no longer fit for registry or other purposes, the JPC will need to consult with the government entity that provided them when making decisions about their future disposition. Advice from the DoD Office of the General Counsel may be needed.

Statutory requirements for retention change, and **the committee recommends that the JPC seek the advice of the DoD Office of the General Counsel regarding the procedures it should have in place to conform to the laws in force when implementing disposal policies.**

[10]A reference material is, in this context, a specimen that is an exemplar of a particular medical condition or tissue characteristic. Reference materials are typically used for educational purposes or as an aid in diagnosis.

The BRAC Collection

Should the BRAC Collection of materials be maintained indefinitely?

BRAC Collection materials were moved to the JPC repository when the medical facilities that held them were closed. They are subject to CLIP and other requirements for retention for possible further clinical reference. The information available to the committee suggests that the BRAC Collection of materials has no greater value for education or research purposes than the collections of pathology materials found in hospitals comparable with the facilities that transferred them. The several reasons for this determination include the relationship of the BRAC Collection to other collections, the provenance associated with it, and the methodologic challenges associated with its use in a research setting.

First, the specimens and data in the BRAC Collection appear no different from ones that can be obtained from other sources, such as hospital and university pathology departments and currently open military healthcare facilities. To the extent that rare disorders were identified by pathologists in the facilities that contained the materials that became the BRAC Collection, it is expected that the specimens would have been sent to the Armed Forces Institute of Pathology (AFIP) for consultation and hence become part of the Central Collection or one of the special registries. Furthermore, the material in the BRAC Collection is not classified in such a manner as to make it easy to identify any particular rare specimen that does not already reside in the Central Collection. On the basis of that observation, the committee believes that the materials in the BRAC Collection as a whole are not rare or unique and offer no special opportunities for education or research.

Second, the documentation associated with the BRAC Collection and the storage protocols for the specimens are varied and some specimens do not have any accompanying documentation. Having information on how specimens were prepared and managed before transfer to the repository and data on the persons from whom the specimens were derived greatly enhances their utility for research purposes. Although data are associated with specimens in the BRAC Collection, the collection's heterogeneous nature makes use of samples problematic for research and perhaps for education. In contrast, specimens and data can be obtained from other sources that provide better and more consistent documentation. Furthermore, for research that requires data beyond what is contained in pathology department records, it will typically be easier to use material obtained from medical facilities—which will possess accompanying medical records linked to the specimens—than materials from the BRAC Collection, for which the medical records may not be held by the JPC.

Finally, the one characteristic that is sometimes mentioned as a reason

why the BRAC Collection would be attractive to researchers—its considerable size—actually provides little advantage, because it is not expected that the collection will be analyzed as a single source. Indeed, for many types of research, it would be a mistake to do so given the unknown (and unknowable) variations in clinical and pathologic practices among the contributing sources. In hypothesis-driven research, treating specimens or data from disparate sources as though they came from a single source would introduce potential errors into analyses and, for most types of studies, would confound analysis. It is possible to deal with such potential biases by treating each source as a variable in the analysis or by analyzing specimens from each source and composing the results with statistical techniques, such as meta-analysis. However, if the components of the BRAC Collection are treated separately, they are no more attractive than other collections of specimens and data and, for the reasons already mentioned, are actually less useful for research than materials with better documentation.

Therefore, **the committee recommends that the JPC retain materials in the BRAC Collection for potential clinical consultation only for as long as required by CAP or CLIP–CLIA guidelines and requirements, whichever specifies the longer period.** For the sake of simplicity, the date of each BRAC facility collection's accession into the JPC repository could be treated as the starting date for calculating how long the material should be retained. Thereafter, no scientific reason exists for the JPC to retain the BRAC Collection, other than any of its component parts that—notwithstanding the committee's doubts on this score—have proven attractive to researchers or educators.

USE OF BIOSPECIMENS IN CLINICAL CARE, EDUCATION, AND RESEARCH

Ethical and Legal Considerations

Use in Clinical Care and Education

What are the ethical and legal considerations regarding utilization of the Tissue Repository in support of clinical care and education?

The ethical and legal considerations regarding use of the repository in the support of clinical care and education depend on the circumstances of the proposed use.

The use of the stored biospecimens and other clinical data in the JPC repository for clinical care of the person from whom they were obtained is subject to the same considerations as arise in the management of any clini-

cal pathology collection. First, as previously described, the materials must be retained in compliance with legal and professional requirements and accreditation guidelines. Second, sufficient information must exist about the specimens to allow them to be used in a clinically useful and responsible fashion (that is, they are "fit for purpose").

As discussed in Chapter 3, use of repository materials for the medical care of other persons—notably, genetically related persons and persons who have a life experience (such as an exposure or service in a military unit) in common with the source—constitutes a special case that requires careful consideration of the relevant ethical and legal issues as well as the circumstances of the request. **The committee recommends that the JPC develop a policy for evaluating such requests and, when it is appropriate, fulfill them in a manner that protects the privacy of persons from whom the specimens were obtained. The policy should include consideration of whether the material can be provided in a deidentified manner, whether access is necessary to address a medical need that cannot be equally well met by another available means, and applicable legal constraints.**

JPC's predecessor, AFIP, had a distinguished history of educational use of specimens and data; the best known example is its *AFIP Fascicles* series of reference texts. Generally speaking, educational use of repository materials that have been stripped of all information that would allow sources to be identified poses no ethical or legal issues and should continue to be facilitated by the JPC. But it should be noted that the DNA identifiability concerns that apply to research applications are also relevant to educational uses: DNA in otherwise anonymized biologic material is uniquely identifying if sequenced and matched to a separate source (or reference sample) that includes personal information. **The committee recommends that dissemination of biospecimens by the JPC for educational purposes should be subject to strict compliance with rules and procedures to protect source identity.** Those requirements should be developed and updated to ensure that reidentification of source individuals cannot readily be accomplished. In addition, material-transfer agreements[11] and other documents offered to individuals and institutions seeking access to JPC repository materials (whether for education or other purposes) should explicitly forbid reidentification efforts.

Use in Research

Can tissue collected for clinical use be used for research (i.e. from patients not specifically consented for use of tissue in research)?

[11]Material-transfer agreements are also addressed below in the section "Access to Repository Materials."

What are the ethical considerations regarding use of tissues originally submitted for clinical use for research and can this be accomplished within current accepted guidelines for clinical research?

As Chapter 3 notes, the policy landscape governing research on clinically collected specimens that are assembled in a biorepository and then made available for research use is in transition. The Department of Health and Human Services (HHS) Office for Human Research Protections has determined that deidentified specimens and data collected for clinical care can be used for research without patient consent because such work is not considered research on human subjects (HHS, 2008). Furthermore, the Common Rule has exempted studies using "existing data, documents, records, 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."[12] When research is undertaken on clinically derived materials after the death of the source individual, it is not research on a "human subject" (who under the Common Rule must be a living person) and so does not require consent although Health Insurance Portability and Accountability Act (HIPAA) privacy rules, Federal Privacy Act (5 U.S.C. § 552a), and some state-specific restrictions still apply in such circumstances.[13] Should a study using stored specimens be subject to the Common Rule, the institutional review board (IRB) reviewing the proposal may waive the requirement of informed consent if it finds that the research poses minimal risk to the source individuals and that it would be impracticable to recontact them for permission to use their stored specimens or data in research (Miller and Emanuel, 2008; Rhodes et al., 2011).

This approach to research on stored specimens and data, however, is being reconsidered by policy makers. Increasing capabilities for reidentification of genetic material (Homer et al., 2008; McGuire and Gibbs, 2006) have raised concerns about the adequacy of deidentification measures. Emerging public opinion also suggests that research to which a source did not consent can be a source of concern even when material is deidentified (Hull et al., 2008; Kaufman et al., 2009; Lemke et al., 2010; Trinidad et al., 2011). Legal challenges to research use of clinically derived material

[12]The usual citation for the Common Rule is to the version published by the Department of Health and Human Services (HHS) because the Office for Human Research Protections (OHRP) in HHS is the lead agency for the Common Rule. The quoted exemption appears at 45 CFR § 46.101(b)(4) in the HHS regulations; the same provision appears in the Department of Defense (DoD) regulations at 32 CFR § 219.101(b)(4).

[13]Washington State, for example, defines deceased persons as human subjects (RCW 70.02.140; 1991).

(such as newborn blood spots, as in *Bearder v. State of Minnesota*[14]) further indicate growing concern over research use without consent. A 2011 Advance Notice of Proposed Rulemaking from HHS invited comment on possible changes in the regulations governing human-subjects research, including a proposed change that would seek at least general consent from individuals at the time that they receive clinical care, asking permission for future research use of specimens and data (HHS, 2011).

Against that backdrop, the committee believes that it is important to consider which approaches for using archived clinical data and specimens in research and which approaches for accessioning new data and specimens accomplish the goals of protecting and respecting source individuals, meeting public expectations, and supporting the efficient functioning of the repository. It offers guidance based on both current (middle of 2012) and emerging legal, regulatory, and ethical standards.

The committee recommends that the JPC adopt a policy regarding research use of tissues originally submitted for clinical consultation that places transparency and respect for source individuals and populations at its core. The procedures adopted should remain flexible enough to adapt to the changing legal, regulatory, and ethics landscape. The policy should include the elements listed below:

- Establishment of a Data Access Committee (DAC) that would examine requests to use repository materials (both specimens and data) and that would operate in addition to the Research Review Committee and IRB that the JPC already uses.[15] It would be composed of persons in and outside the JPC who have expertise in research ethics, military research, and research on biospecimens. The DAC's responsibilities should comprise
  - — evaluating whether proposed research meets the JPC's goals for the use of its materials.
  - — determining whether the researcher's credentials and specimen- and data-handling protocols satisfy the JPC, DoD, and current legal and regulatory requirements.
  - — reviewing and providing guidance on the proper management of any ethical issues raised by the proposed research.
  - — ensuring that data use and material transfer agreements made with researchers protect the privacy of source individuals and

[14]A10-101 (Minnesota Supreme Court, November 16, 2011).

[15]The most current repository protocol regarding review of research proposals available at the time of this report was contained in AFIP Regulation 70-1, *AFIP Research Program*, dated June 7, 2005. The protocol called for review of proposals by a research committee and an IRB and specified the composition and function of these bodies. The committee understands that this regulation is being followed by the JPC.

obligate the researchers to keep information secure, to avoid efforts to identify data or specimen sources, and to otherwise protect the interests of specimen sources and the DoD.

- Solicitation of input from the community of people—in particular, active-duty military, veterans, and their family members—whose specimens are held by the repository through, for example, representation on the DAC or creation of a community advisory board. DACs are in use by other repositories to address such issues, which lie beyond considerations related to the scientific merit of a proposed research initiative (Broad Institute, undated; NCBI, undated; NCI, 2012a).
- Notification through public means—for example, posting on its website, in newsletters, and in other media that reach the military community and the general public—of the JPC's intention to allow repository materials to be used for research purposes, including
  - examples of the kinds of research that have been done with repository specimens in the past.
  - a description of the oversight and review mechanisms governing access to the materials that can be easily understood by the general public.
  - a clear statement that no access will be allowed without the review and approval of an IRB.
  - user-friendly means by which people may ask questions or request that a good-faith effort be made to determine whether the repository holds specimens from them, with the option to request that any specimens be withheld from research use (through, for example, a Web form, e-mail address, or telephone number for inquiries).[16] The committee notes that given the state of the records and the manner in which subject information is coded, it may not be feasible to make such a determination in all cases; this limitation should be made clear to persons who make inquiries, and they should be assured that personally identifiable information will be protected in all circumstances.
- Posting, in a forum such as the JPC website, of the active research projects that are using repository materials. This will promote accountability to specimen sources and citizens regarding how repository materials are being used; it will also help to inform the

[16]Procedures for withdrawing data and materials from research use are in place in other repositories of military biospecimens, including the collection maintained as part of the Department of Veterans Affairs Million Veteran Program (http://www.research.va.gov/resdev/mvp/veterans.cfm).

research community about the repository's collection and potential research uses.

- Regular review of JPC forms, protocols, and procedures to ensure that they meet evolving legal and regulatory requirements and reflect best practices for biorepository operations and management, as defined by, for example, the National Cancer Institute (NCI, 2011) and the International Society for Biological and Environmental Repositories (ISBER, 2012).

Protocols and procedures regarding research use of materials should be public documents and should be regularly updated on the JPC website.

One way that many modern biorepositories manage the difficult issues involved in the ethical use of their materials is to educate specimen sources on the possible use of their materials in research and to seek their consent for such uses. The JPC has no direct control over the mechanisms used to obtain consent from sources whose specimens are sent to its repository. However, it can—in consultation with legal and ethics experts in and outside the military—develop recommended language to be added to existing consent forms and devise accompanying educational materials (such as brochures) that allow substantive choice regarding the research use of specimens obtained for clinical consultation. The JPC can also suggest that physicians who seek consultations with the JPC use consent forms that include this language and can ask the contributing physician for information about research consent from the source individual as part of the Contributor's Consultation Request Form and code that information in the JPC database for future use. Several model educational materials (NCI, 2012b) and consent forms (Beskow et al., 2011; Hansson et al., 2006; Hofmann, 2009) could serve as a starting point for developing recommended materials for source individuals to consider.

More broadly, the committee believes that the DoD should consider changing patient education materials and consent requests and forms in the manner outlined above to facilitate future use of pathologic materials in research.

The JPC's IRB may be able to consider many research-use requests under the provisions for exemption or waivers of consent under the Common Rule and waivers or alterations of the authorization to use protected health information (PHI) under HIPAA regulations. Current exemptions[17] from human-subjects regulations include studies that use deidentified data

[17]Changes to the Common Rule that would require that clinical materials used in research be obtained from individuals who had been informed of their potential use in research and afforded the opportunity to give (or withhold) permission for such use of their specimens and data were under debate in mid-2012 (Emanuel and Menikoff, 2011; HHS, 2011).

and specimens not originally collected for the research (HHS, 2008). Regulatory requirements for waiver of consent under the Common Rule are set forth in 45 CFR 46.116(d) and are as follows[18]:

(1) the research involves no more than minimal risk to the subjects;
(2) the waiver or alteration of consent 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.

HIPAA (HHS, 2007) allows waiver or alteration of the requirement of authorization for the use of PHI in research when an IRB or privacy board determines that

1. The use or disclosure of the PHI involves no more than minimal risk to the privacy of individuals based on, at least, the presence of the following elements:
   a. An adequate plan to protect health information identifiers from improper use and disclosure.
   b. An adequate plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a health or research justification for retaining them or a legal requirement to do so).
   c. Adequate written assurances that the PHI will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.
2. The research could not practicably be conducted without the waiver or alteration.
3. The research could not practicably be conducted without access to and use of the PHI.

Some study protocols may require recontact and reconsent of sources. The determination of whether and under what conditions this is necessary should be made by the JPC's IRB based on factors including the level of identifiers requested and the sensitivity of the research question being asked.

Acceptable uses of materials for research may be broader when consent is documented. The terms of the consent, if available, must be carefully

[18]As of early 2012.

considered. Some specimens in the war and cohort registries may have been provided under consents that included research use, but the JPC has no documentation of such consents (Baker personal communication, 2011).

Given the changing legal, regulatory, and ethics landscape, this guidance should be reviewed in light of further developments before implementation.[19]

Use of Consultation Materials from Federal Facilities and Civilian Providers

The Tissue Repository currently contains consult material from both federal facilities as well as that submitted for consultation by civilian providers. Can tissue within the repository from civilian providers be utilized in the same manner as that from federal facilities?

Access by researchers to human materials that entered the JPC repository from federal facilities and from civilian providers[20] is generally governed by the same legal requirements and ethical standards. The JPC has an ethical obligation to ensure *all* materials (as well as data) in its repository are utilized in a manner that respects the privacy of the specimen sources, prevents misuse by researchers who obtain access to them, and protects the security and other interests of the government. Additional protections regarding research on human subjects, especially requirements regarding informed consent, do apply to U.S. military service members,[21] and these impose additional review and procedural responsibilities on the JPC.

As noted above, materials contained in some of the war and cohort registries may be subject to additional or different handling requirements that were part of the agreement made by the repository to serve as custodian. The JPC will need to conform to such requirements when making policies for the materials.

Scientific Considerations

Current and Emerging Technologies

What existing or emerging technologies (either as an intrinsic function or through partnership) should be considered in developing a plan for utiliza-

[19]The Advance Notice of Proposed Rulemaking issued by HHS in 2011, for example, may lead to changes in the Common Rule that could affect the recommendations offered here.

[20]The *providers* are the physicians who and medical facilities that submitted materials for consultation or educational purposes, not the persons from whom the samples were derived. When the provider is a medical professional, this person is also a *contributor* as defined above.

[21]These are spelled out in DoD Instruction 3216.02 (November 8, 2011), *Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research*.

tion of the Tissue Repository in research and how would they potentially affect the mission of the JPC?

Several existing and emerging technologies in protein and gene-expression profiling and advances in DNA, elemental, and chemical studies—detailed in Chapter 2—hold the potential for making the JPC repository materials more useful by permitting specimens previously considered unusable to be analyzed or by allowing more information to be extracted from specimens.

For example, advances in proteomics allow the identification of proteolyzed protein fragments and their association with the protein from which they are derived. That allows one to circumvent, in part, any protein degradation that has occurred during specimen transport, handling, and fixation. In theory, posttranslational modifications of proteins can also be detected in the proteolyzed fragments, and this allows insight into cell signaling events. DNA analysis has become quicker, and the ability to detect pathogens responsible for past epidemics and disease clusters can be of value in understanding virulence in future outbreaks. Although mRNA is quite unstable unless specimens are handled very carefully, mRNA analyses can still be useful under some conditions. Small non-coding RNAs, such as micro RNA (miRNA), are very stable and are of increasing importance in certain scientific studies.

However, although the technical ability to extract and analyze biomolecules from archived specimens has improved and is likely to increase, the many unknown types and degrees of preanalytic variation to which the specimens have been subjected before stabilization will affect the validity of analytic results and may limit many types of research studies. This shortcoming is not limited to JPC materials but is endemic in older collections of biomaterials and collections that were assembled for purposes other than research (Carlson, 2010; Khleif et al., 2010). The committee is thus uncertain whether these research methods can successfully be applied broadly to the JPC repository collection and whether the collection will be the best source for investigators seeking to exploit the new technologies.

If the JPC is to fulfill its stated mission to provide "world class" research services, it will need to establish procedures that minimize the adverse consequences of inconsistent preanalytic handling of new specimens it acquires. **The committee therefore recommends that the JPC adopt a set of best practices for the collection, processing, and storage of all incoming specimens, either by developing its own standards or by using one developed by another entity—for example, NCI's *Best Practices for Biospecimen Resources* (NCI, 2011).** The best practices should be posted on line, contributors should be encouraged to follow them, a means should be established for identifying specimens that have been handled in accordance with the best practices (check-off boxes on the *Contributor's Consultation*

Form, for example), and compliance should be recorded on a specimen's record. Even if those handling procedures are not optimal for a particular type of analysis, having specimens that are subject to well-defined, uniform handling rules will allow investigators to factor the specimens' condition in their studies. The best practices should be revisited regularly and updated as necessary.

Technologies that present solutions to biobanking challenges of quality control, quality management, specimen tracking, retrieval or aliquoting, inventory control, or other issues could also be of great benefit to the repository (Frey, 2010). Devices that allow high-throughput generation of molecular quality-control data, for example, may be of use in selecting cases when certain quality thresholds are required (Patel et al., 2006). The extent to which such technologies should be adopted, however, depends on the extent to which the JPC envisions streamlining repository management, making the repository available to external researchers, and conducting research in its own right.

As the JPC takes steps to enhance its laboratory information management system by improving basic search and analytic functionality, its system should, at a minimum, include fields that detail how specimens were collected and handled before accessioning in the repository, quality-control data, and what record there is of consent to future research use.

If the JPC contemplates moving beyond basic management of the repository to support clinical, educational, and research use toward more active involvement in research or enhancement of its collection by adding new data generated by researchers, the committee suggests that it consider investing in high-performance computing technologies to assist in processing the volumes of data that will be produced. This class of technologies is not necessary to maintain the repository, but it may enable greater use by merging biologic and computational proficiencies.

The committee notes that implementation of such systems requires outlays for equipment and training that may not be feasible in the current funding environment. The JPC will need to consider whether its current budget allows such investments and, if so, which have highest priority.

Digitization of slides, which has already been performed on some of the collection, preserves visual information in a form that may be more easily deidentified and disseminated for research and educational purposes. However, it is a time-consuming process: digitizing a slide at 400× magnification with three Z-axis planes, for example, takes a minimum of 5 minutes per slide with current (2012) technology. Unless the slide illustrates a rare condition or is to be used as part of a teaching or reference collection, it is questionable whether that is worth the effort. Moreover, digitizing slides that lack associated clinical data is likely to be of little value in research. Association of specimens with clinical data is highly desirable

from a research perspective,[22] but raises issues of consent and privacy that are discussed elsewhere in this report. Nonetheless, the committee believes that there may be merit in digitizing all new cases coming to the repository and suggests that the JPC consider whether it is feasible given economic and logistical circumstances.

Finally, the committee believes that the JPC would derive value from pursuing research partnerships with the Department of Veterans Affairs (VA). Specimens held by the repository and data on long-term health outcomes possessed by VA can be productively combined to examine questions regarding the health consequences of military service and the determinants of disease and wellness. The JPC may wish to consider using the unique resources of the DoD to advance the state of the art in pathology through, for example, partnering with the DoD's cutting-edge research entities to explore how technologies developed for other purposes might be used in pathology applications. It should also consider partnering with DoD medical or information-technology investigators to examine how JPC materials and data may be combined with other DoD or federal databases to facilitate medical research.

Use of Rare and Unique Materials

What considerations should be given to utilization for research of unique, one-of-a-kind, material within the central collection of the Tissue Repository?

Rare and unique materials in the Central Collection of the repository are a resource for the JPC, the country, and the global scientific community. As the experience with genetic analysis of the 1918 influenza virus illustrates, such materials may play a vital role in today's health research. The question of what constitutes rare and unique material is complex, however, and depends on several factors: even relatively common diseases have rare subtypes, for example. Moreover, particular collections of specimens may be "unique" in the aggregate, although until a particular set of desired material characteristics is defined it may not be possible to determine whether or not other similar collections are available elsewhere or whether the number of representative samples in the collection is small or unusual enough to merit special handling. It is also difficult to predict what may prove to be valuable at some future time or under particular circumstances.

[22]Moreover, in circumstances in which research using personally identifiable information is permissible, data-matching techniques may allow content from diverse military and civilian databases to be merged and married to specimens, thus expanding the array of studies that can performed on them and enhancing their value.

Eiseman et al. (2003) note that "[i]n most cases, the procedure for prioritizing requests for rare or precious tissue is the same as that used for easily available tissue" but that some repositories have "specific policies for regulating the distribution of the last sample of a particular specimen" and that such policies are considered best practice (pp. 102–103). However, there are no generally-recognized protocols for evaluating whether and when to exhaust a specimen.

The committee recommends that the following considerations be taken in account in evaluating whether *any* given specimen should be made available for research:

- The age of the specimen.
- The disease state that it represents.
- The specimen's medical, scientific, and historical[23] significance.
- The condition of the specimen and its fitness for the proposed use.
- Whether a proposed use would exhaust the research potential of the specimen.
- Whether the same research need might be met by another, less rare specimen or another source of specimens.
- The importance of the public-health or military need the proposed use aims to meet.

The JPC should also develop criteria for determining when a collection of specimens—rather than an individual sample—is unique or has special medical, scientific, or historic value, and for managing access to such collections.

The JPC does not have any specific policy regarding how the depletion of a repository specimen should be factored into decisions regarding access to it, beyond ensuring that all applicable CAP and CLIA–CLIP retention requirement are met (Baker personal communication, 2011). The committee believes that the JPC needs such a policy to ensure that the repository remains a resource for otherwise unobtainable material. **The committee recommends that the JPC establish criteria for deciding whether to deplete a specimen to exhaustion. The criteria should be determined in close consultation with pathology subspecialty experts in and outside the JPC.** Detailed recommendations are beyond the scope of the present committee's task but the criteria may include such considerations as the following:

- Retaining a set percentage of the tissue-containing portion of a tissue block unless a designated repository officer authorizes its use.

[23]The National Museum of Health and Medicine (http://www.medicalmuseum.mil) houses military pathology specimens with historical value and would be the authority on this question.

- Retaining a set number of stained or unstained tissue sections from a specimen.
- Not permitting any specimens collected before a given date to be used for research without specific review of whether the need justifies depletion of the resource and without explicit authorization by a designated repository officer.
- Not disposing of any specimen collected before a given date, no matter its condition.

More broadly, the JPC should consider whether the goal of sustaining and enhancing the research potential of its collection could be advanced by requiring researchers who receive specimens to return analysis results to the repository for integration into the specimens' documentation. Such a requirement would need to be predicated on the JPC's developing the infrastructure to manage such returns.

Access to Repository Materials

Given the defined mission and vision of the Joint Pathology Center, should access to repository materials be limited to the federal government or open to a larger pool of potential users? What advantages and disadvantages should be considered in defining the potential users of the repository in research?

Permitting wide access to the JPC repository materials promotes the public good through the advancement of medical and scientific knowledge. It also benefits the DoD by fostering the development of information on the determinants of disease and good health in service members and veterans.

The JPC's mission and vision are focused on service to the DoD and the rest of the federal government but do not preclude working with other entities. The committee does not believe that there are any intrinsic advantages or disadvantages to any particular set of potential users of the repository's resources. **The committee recommends that there be no a priori restrictions on which applicants may apply for access to the repository's specimens and data.**

When data or specimens are disseminated to outside investigators, the JPC must be especially attentive to employing mechanisms to manage privacy and security issues properly. **The committee recommends that the JPC condition its provision of repository materials to researchers outside of the federal government on**

- **Approval of a Data Access Committee that develops and applies criteria for determining whether the interests of specimen and data sources,[24] the repository, and the federal government are being met.**
- **Participation of a DoD-affiliated monitor trained in and assigned the responsibility of ensuring the appropriate use of repository specimens and data and safeguarding the interests of its sources, the repository, and the federal government.** The monitor would also facilitate research by helping outside investigators to identify and gain access to the most appropriate JPC resources for a particular project.
- **Implementation of data-use agreements and material-transfer agreements, as appropriate, to help to protect the identified interests.** A data-use agreement (DUA) is, in brief, a contract between a data provider (here, the JPC) and a user (such as a researcher) that explicates how the data may be used, who may have access to them, how they must be stored and secured, and how they must be handled after the authorized research is completed. A material-transfer agreement (MTA) serves the same purpose for such items as biospecimens. DUAs and MTAs were used by AFIP and are widely used by other research biorepositories and by the federal government to inform investigators of their responsibilities and to gain their agreement to abide by a set of requirements.

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[24]Including privacy interests.

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Appendix A

Public Meeting Agendas

PUBLIC MEETING

April 21, 2011
Keck Center of the National Academies
500 Fifth Street, NW, Washington, DC

1:00 p.m.
Conduct of the Open Session and Introduction of Participants
James Childress, PhD
Professor, Director of Practical Ethics and Public Life, University of Virginia
Committee Chair

1:05 p.m.
Charge to the Committee/Background on the AFIP and the JPC
Thomas P. Baker, MD, COL, MC
Interim Director, Joint Pathology Center; and Chief, Integrated Department of Pathology, Walter Reed Army Medical Center and National Naval Medical Center

2:30 p.m.
Open Session Adjourns; Break

2:45 p.m.
Committee Departs Keck Center for the JPC Repository

3:15 p.m.
Open Session Reconvenes at the JPC Repository
Tour conducted by Dr. Baker and JPC staff

4:45 p.m.
Open Session Ends; Committee Returns to Keck Center

WORKSHOP

July 11, 2011
Keck Center of the National Academies
500 Fifth Street, NW, Washington, DC

12:30 p.m.
Welcome; Conduct of the Open Session and Introduction of Participants
James Childress, PhD
Professor, Director of Practical Ethics and Public Life, University of Virginia
Committee Chair

12:35 p.m.
The State of the AFIP Repository in 2008
Victoria Blanc, PhD
Vice President, Strategic Planning and Government Affairs, Asterand, Inc.

1:05 p.m.
Legal and Ethical Issues Related to the Management of the Repository
Catherine M. With, MA, JD, LLM, LLM
Major, Judge Advocate, U.S. Army; Legal Counsel, Armed Forces Institute of Pathology

1:35 p.m.
Special Considerations in the Use and Management of Military Biorepositories
Victor W. Weedn, MD, JD
Maryland State Office of the Medical Examiner

2:05 p.m.
Management of the Department of Veterans Affairs Biorepository Assets
Marianna Bledsoe, MA
Senior Program Manager for Biorepository and Biobanking, U.S. Department of Veterans Affairs

2:35 p.m.
Roundtable Discussion 1
James Childress, PhD, moderator

3:05 p.m.
Break

3:15 p.m
Recommendations of the 2005 AFIP Tissue Repository Consensus Conference
David Korn, MD
Vice Provost for Research, Harvard University; Professor of Pathology, Harvard Medical School

3:45 p.m.
Property and Intellectual Property Issues Regarding Biorepository Assets
David E. Winickoff, MA, JD
Associate Professor, Bioethics and Society, University of California, Berkeley

4:15 p.m.
A Perspective on Stakeholder Interests in the Use of Biorepository Assets
Simone Sommer, MD
Founder, the Chordoma Foundation

4:45 p.m.
Roundtable Discussion 2
James Childress, PhD, moderator

5:15 p.m.
Workshop and Open Session End

PUBLIC MEETING

September 8, 2011
J. Eric Jonsson Center of The National Academies
Woods Hole, MA

1:00 p.m.
Conduct of the Open Session and Introduction of Participants
James Childress, PhD
Professor, Director of Practical Ethics and Public Life, University of Virginia
Committee Chair

1:05 p.m.
Proposed Changes to the Common Rule
Jerry Alan Menikoff, MD, JD [participating via conference call]
Director, Office for Human Research Protections, Office of the Secretary, Department of Health and Human Services

1:30 p.m.
Roundtable Discussion—Committee, Speaker, and Observers
James Childress, PhD, moderator

2:00 p.m.
Open Session Ends

Appendix B

Contributor's Consultation Request Form Joint Pathology Center

As noted in the report text, the Joint Pathology Center uses a standardized form for obtaining clinical data associated with the specimens submitted to it for consultation. What follows is a reproduction of the version of this form posted to the JPC website (www.jpc.capmed.mil/docs/consultation_request_form.pdf) when the committee completed its work in mid-2012. The form is dated 03/30/2011.

CONTRIBUTOR'S CONSULTATION REQUEST FORM
ARMED FORCES INSTITUTE OF PATHOLOGY

ATTN: Armed Forces Institute of Pathology
CMAD
6825 16th Street NW
Bldg 54, Room G071
Washington DC 20306-6000

PATIENT INFORMATION (Required)

AFIP Accession No. (previous if known):

LAST NAME	FIRST	MIDDLE INITIAL

DATE OF BIRTH	AGE	SOCIAL SECURITY NO.
Month: Day: Year:	**SEX:** ❑ Male ❑ Female	

RACE
❑ American Indian or Alaskan Native
❑ Asian or Pacific Islander
❑ Black ❑ White ❑ Unknown

ETHNICITY
❑ Hispanic ❑ Not of Hispanic Origin

MATERIALS FORWARDED
❑ Clinical Information (req'd)
❑ Formalin Fixed (Wet Tissue)
❑ Frozen Tissue _____
❑ Surgical Path Report (req'd)
❑ Autopsy Protocol
❑ X-rays _____
❑ Slides (req'd)_____
❑ Rpt of Investigation (AFME)
❑ Photos _____
❑ Blocks _____
❑ Rpt of Toxicologic Studies (AFME)
❑ Other _____

CASE IDENTIFICATION
Specific Biopsy Site or Organ (Required)

SPECIMEN IDENTIFICATION
Specimen Containers must be labeled with two identifiers.

Contributor's Accession No.(s)

Requested Department

_____

FIXATIVE (Required)
❑ Formalin
❑ B5
❑ Glyo-Fixx
❑ Alcohol (eg: Omnifx* Safe-Fix*, Histochoice*) (*TM)
❑ Frozen
❑ Immunoflouresence
❑ EM
❑ Other
_____ Zenkers, Bouins, etc.

REGISTRIES/SERS
❑ SERS
❑ POW
❑ Kuwait/Persian Gulf
❑ Iraqi Freedom
❑ Enduring Freedom (Afghanistan)
❑ Agent Orange
❑ Depleted Uranium
❑ Leishmaniasis
❑ Embedded Metal Fragments
❑ Chemical Agent (nerve)
❑ Other

CONTRIBUTOR'S WORKING DIAGNOSIS: (Differential diagnosis and questions should be entered in "Comments and Requests" Section)

CLINICAL HISTORY: Include: Location, Size, Symptoms, Duration, Physical and Laboratory Findings, Type and Date of Operation(s) and/or other Treatment.

(Continue in "Comment and Requests" section)

CONTRIBUTOR'S INFORMATION

CONTRIBUTOR'S NAME _____

NAME OF FACILITY _____

BUSINESS ADDRESS _____

_____

CITY _____ STATE _____ ZIP CODE _____

COUNTRY _____

TELEPHONE _____ FAX _____

EMAIL _____

This form may be reproduced by the contributor or requested from AFIP.

AFIP Form 288-R (October 2010)

IMPORTANT

Have you enclosed a legible summary of the clinical findings, laboratory data, operative findings or report, and specific treatment? Cases selected for inclusion in specific registries often require additional information. Clinical or gross photos, pertinent X-rays, CT scans, MRI scans, echograms, angiograms, and similar diagnostic studies add substantially to the education value of the case. They are highly desired by some departments and required by others.

COMMENTS AND REQUESTS:

AFIP RETENTION POLICY

1. MICROSCOPIC SLIDES SUBMITTED WITH EACH CASE ARE RETAINED PERMANENTLY. Under certain circumstances original slides may be returned to the Contributor if requested by the Contributor and approved by the Chair of the Department that would review the case. If slides are returned, then each slide will be digitized at the expense of the Contributor.
2. Blocks are retained for a minimum of ten (10) years, unless return is requested by the Contributor at the time the case is submitted. Contributors may request return or loan of blocks at some later time. If blocks are returned, then AFIP will retain representative diagnostic material.
3. Other pathologic material, X-rays, CT scans, MRI scans, echograms, angiograms, photographs, and similar diagnostic studies may be retained for education and research or discarded.

SIGNATURE OF CONTRIBUTOR	DATE REQUEST FORWARDED (YYYYMMDD)

PRIVACY ACT STATEMENT

1. AUTHORITY: 5 U.S.C. 301 and 10 U.S.C 176, 5 U.S.C. 552a, 10 U.S.C 1079b.
2. PRINCIPAL PURPOSES: Medical information received is considered during the consultative process and is used to form a database for education and research in pathology. Other patient information is used for filing and retrieval of consultation records. Information concerning the contributor is used to maintain contributor mailing lists.
3. ROUTINE USES:
   a. In addition to those disclosures generally permitted under 5 U.S.C. 552a(b) of the Privacy Act, these records or information contained therein may specifically be disclosed outside the DoD as a routine use as follows.
   b. Pathology consultation records are tracked in the Pathology Information Management System database for filing and retrieval of records, medical research, and statistical purposes. Individual consultation records may be released to the contributing medical care provider (physician, veterinarian), when required by law or as otherwise permitted by 45 C.F.R. 164.
   c. The DoD 'Blanket Routine Uses' set forth at the beginning of the Army's compilation of systems of records notices also apply to this system.
   d. Pathology consultation records contain individually identifiable health information. The DoD Health Information Privacy Regulation (DoD 6025.18-R) issued pursuant to the Health Insurance Portability and Accountability Act of 1996, applies to most such health information. DoD 6025.18-R may place additional procedural requirements on the uses and disclosures of such information beyond those found in the Privacy Act of 1974 or mentioned in this Privacy Act Notice.
4. PROVISION OF INFORMATION: The provision of patient information requested on this form is voluntary. However, if the information is not furnished, a consultation may not be possible. If so, the material submitted may be returned at the discretion of the AFIP without a consultation.

Appendix C

DoD Instruction 3216.02 Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research

DoD Instruction 3216.02 "establish[es] policy and assign[s] responsibilities for the protection of human subjects in DoD-supported programs to implement . . . 'the Common Rule.'" The text below reproduced the version of the document dated November 8, 2011, the most current available when this report was completed.

Chapter 3 of the report discusses this and other military rules addressing human subjects research and privacy.

Department of Defense
INSTRUCTION

NUMBER 3216.02
November 8, 2011
USD(AT&L)

SUBJECT: Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research

References: See Enclosure 1

1. PURPOSE. This Instruction reissues DoD Directive (DoDD) 3216.02 (Reference (a)) as a DoD Instruction in accordance with the authority in DoDD 5134.01 (Reference (b)) to establish policy and assign responsibilities for the protection of human subjects in DoD-supported programs to implement part 219 of title 32, Code of Federal Regulations (CFR) (also known and hereinafter referred to as "the Common Rule" (Reference (c)).

2. APPLICABILITY

   a. This Instruction applies to:

      (1) OSD, the Military Departments, the Office of the Chairman of the Joint Chiefs of Staff and the Joint Staff, the Combatant Commands, the Office of the Inspector General of the Department of Defense, the Defense Agencies, the DoD Field Activities, and all other organizational entities within the Department of Defense (hereinafter referred to collectively as the "DoD Components").

      (2) All DoD-conducted or -supported research involving human subjects as defined in the Glossary. All such activities must include both systematic investigation designed to develop or contribute to generalizable knowledge AND involve a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or about whom identifiable private information is obtained. All activities meeting both of these conditions will hereinafter be referred to as "research involving human subjects" in this Instruction.

      (3) Activities such as research, development, testing, and evaluation (RDT&E) that meet the definition of research involving human subjects (as defined in the Glossary), as well as clinical investigations or medical activities regulated by the Food and Drug Administration (FDA) in parts 50, 56, 312, 600, and 812 of title 21, CFR (Reference (d)). DoDI 3216.02, November 8, 2011

   b. Applicability is not dependent upon the budget activities funding the research, the mission of the DoD organization conducting or supporting the research, the security classification of the research, the location of the research in the United States or a foreign country, or whether the research is conducted or supported under a program that is not considered research for other purposes.

3. DEFINITIONS. See Glossary.

4. POLICY. It is DoD policy that:
    a. All research involving human subjects that is conducted or supported by the Department of Defense shall comply with part 219 of Reference (c), which incorporates the ethical principles of respect for persons, beneficence, and justice, as codified in page 23192 of the Federal Register (also known as "The Belmont Report" (Reference (e)).
    b. Certain categories of human subjects in research are recognized as vulnerable populations, groups, or individuals and are afforded additional protections as specified in section 7 of Enclosure 3 of this Instruction.
    c. Research involving human subjects for testing of chemical or biological warfare agents is generally prohibited by section 1520a of title 50, United States Code (U.S.C.) (Reference (f)), subject to possible exceptions for research for prophylactic, protective, or other peaceful purposes.
    d. DoD-appropriated funds shall not be used to support research involving a human being as an experimental subject, as defined in this Instruction, without the prior informed consent of the experimental subject or in accordance with section 980 of title 10, U.S.C. (Reference (g)) and this Instruction (see section 9 of Enclosure 3 of this Instruction for details). The definitions of research involving a human being as an experimental subject and research involving human subjects are different; see the Glossary for an explanation.
    e. Research involving human subjects covered under this Instruction shall also comply with applicable Federal and State laws and regulations. When the research is conducted outside of the United States, it must also comply with applicable requirements of the foreign country and its national laws and requirements. In the event of an unresolved conflict between this Instruction, including its references, and other applicable laws and requirements such that compliance with both is impossible, the requirements most protective of the human subjects shall be followed. When there is an unresolved conflict, DoD Components shall consult with legal counsel and seek guidance from the Assistant Secretary of Defense for Research and Engineering (ASD(R&E)).
5. RESPONSIBILITIES. See Enclosure 2.
6. PROCEDURES. See Enclosure 3.
7. RELEASABILITY. UNLIMITED. This Instruction is approved for public release and is available on the Internet from the DoD Issuances Website at http://www.dtic.mil/whs/directives.
8. EFFECTIVE DATE. This Instruction is effective upon its publication to the DoD Issuances Website.

Frank Kendall
Acting Under Secretary of Defense
for Acquisition, Technology, and Logistics

Enclosures
1. References
2. Responsibilities
3. Procedures
Glossary

ENCLOSURE 1

REFERENCES

(a) DoD Directive 3216.02, "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research," March 25, 2002 (hereby cancelled)

(b) DoD Directive 5134.01, "Under Secretary of Defense for Acquisition, Technology and Logistics (USD(AT&L))," December 9, 2005

(c) Parts 22 (Appendix B), 37 (Appendix D), 108 and 219[1] of title 32, Code of Federal Regulations

(d) Parts 50, 56, 312, 600, and 812 of title 21, Code of Federal Regulations

(e) Page 23192 of Volume 44, Federal Register, April 18, 1979 (also known as "The Belmont Report")[2]

(f) Section 1520a of title 50, United States Code

(g) Sections 139(a)(2)(A), 980, 1074f , and 1102 of title 10, United States Code

(h) Part 46, subparts A-D of title 45, Code of Federal Regulations

(i) Memorandum of Understanding between the Food and Drug Administration and the Department of Defense, "Concerning Investigational Use of Drugs, Antibiotics, Biologics, and Medical Devices by the Department of Defense," May 21, 1987

(j) Sections 241(d) and 289g–289g-2 of title 42, United States Code

(k) Public Law 107-347, "Confidential Information Protection and Statistical Efficiency Act of 2002 (CIPSEA)," December 17, 2002

(l) Pages 33362-33377 of Volume 72, Federal Register, June 15, 2007

(m) Sections 2105, 3109, 3371-3376,[3] and 5536 of title 5, United States Code

(n) Sections 2.101 and 252.235-7004 of title 48, Code of Federal Regulations

(o) Section 252 of Public Law 103-160, "National Defense Authorization Act for Fiscal Year 1994," November 30, 1993

(p) DoD Directive 2310.01E, "The Department of Defense Detainee Program," September 5, 2006

(q) Section 30 of title 24, United States Code

(r) Executive Order 13526, "Classified National Security Information," December 29, 2009

(s) DoD 6025.18-R, "DoD Health Information Privacy," January 24, 2003

(t) Executive Order 12333, "United States Intelligence Activities," as amended, August 18, 2010

(u) DoD 5400.11-R, "Department of Defense Privacy Program," May 14, 2007

(v) DoDI 6000.08, "Funding and Administration of Clinical Investigation Programs," December 3, 2007

(w) DoD Instruction 5025.01, "DoD Directives Program," October 28, 2007

[1] Also known as "the Common Rule"

[2] Available on the Internet at http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm. The Belmont Report's 2-volume appendix is available from the Government Printing Office as DHEW Publication Nos. (OS) 78-0013 and (OS) 78-0014

[3] Also known as "The Intergovernmental Personnel Act of 1970, as amended"

(x) DoD Instruction 6200.02, "Application of Food and Drug Administration (FDA) Rules to Department of Defense Force Health Protection Program," February 27, 2008

(y) DoD Instruction 6025.13, "Medical Quality Assurance (MQA) and Clinical Quality Management in the Military Health System (MHS)," February 17, 2011

(z) DoD Directive 5240.01, "DoD Intelligence Activities," August 27, 2007 DoDI 3216.02, November 8, 2011

ENCLOSURE 2

RESPONSIBILITIES

1. ASD(R&E). The ASD(R&E), under the authority, direction, and control of the Under Secretary of Defense for Acquisition, Technology, and Logistics, shall:
    a. Be the single DoD point of contact for all matters related to DoD compliance with this Instruction and shall act as the principal DoD liaison with organizations outside the Department of Defense on matters pertaining to research involving human subjects.
    b. Provide guidance and procedures necessary to implement this Instruction. The ASD(R&E) will consult with the Assistant Secretary of Defense for Health Affairs (ASD(HA)) for matters affecting medical research involving human subjects.
    c. Exercise the authorities of the Head of the Department identified in part 219 of Reference (c), the Secretary as identified in subparts B-D of part 46 of title 45, CFR (Reference (h)) for research described in section 7 of Enclosure 3 of this Instruction, and the Secretary of Defense identified in section 980 of Reference (g).
    d. Grant exceptions to any procedures or requirements in this Instruction based upon an appropriate justification from the Head of an OSD or DoD Component and consistent with law.
    e. Establish a process to oversee the DoD Components' implementation of their respective Component human research protection program (HRPP) management plan and compliance with this Instruction.
    f. Establish a framework for educational training requirements for DoD personnel in key HRPP roles commensurate with their duties and responsibilities.
    g. Work with the DoD Components supporting international research involving human subjects to resolve conflicts between this Instruction, including its references, and other applicable foreign laws and requirements.
    h. Maintain a list of foreign country and international standards that are at least equivalent to those in part 219 of Reference (c).
    i. Designate DoD representatives to Federal committees, such as the Human Subject Research Subcommittee of the National Science and Technology Council's Committee on Science or other committees established by the White House.
    j. Designate a DoD representative to the Secretary's Advisory Committee on Human Research Protection established by the Secretary of Health and Human Services (HHS) and successor entities established by the Secretary of HHS.
    k. Establish the DoD Coordinating Committee for Human Research Protection Programs (CCHRPP) to act as the central advisory committee to the ASD(R&E) on all matters regarding the ethical involvement of human subjects in research. Membership shall be appointed as described in section 18 of Enclosure 3 of this Instruction.
2. ASD(HA). The ASD(HA), under the authority, direction, and control of the Under Secretary of Defense for Personnel and Readiness (USD(P&R)), shall:
    a. Advise the ASD(R&E) on matters related to the participation of human subjects in research, especially regarding medical safety, bioethics, and standards of professional health care and conduct.

b. Represent the Department of Defense on matters relating to implementation of FDA regulatory requirements in Reference (d) and the Memorandum of Understanding between the FDA and the Department of Defense (Reference (i)).

3. HEADS OF THE OSD AND DoD COMPONENTS. The Heads of the OSD and DoD Components that conduct or support research involving human subjects covered by this Instruction shall:

a. Develop, issue, and monitor a Component HRPP management plan (see section 1 of Enclosure 3 of this Instruction for details).

b. Establish and oversee DoD Component policies and procedures that ensure compliance with this Instruction and any other supplementing or implementing issuances (see section 1 of Enclosure 3 for details).

c. Exercise the authority as outlined in this Instruction.

d. Oversee each institutional official's (IO) (see Glossary) implementation of their organization's HRPP.

e. Provide members to intra- and interagency committees and to the CCHRPP when requested by the ASD(R&E) consistent with section 18 of Enclosure 3.

f. Provide in a timely manner to the ASD(R&E) the following:

(1) A copy of all reports provided to the appropriate Congressional Committees in accordance with Reference (f) for any research involving human subjects for testing of chemical or biological warfare agents. DoD Components shall also send a copy to the Assistant Secretary of Defense for Nuclear, Chemical, and Biological Defense Programs.

(2) Copies of any waivers from requirements that have been granted in accordance with this Instruction.

(3) Copies of any approved fetal research covered under sections 289g–289g-2 of title 42, U.S.C. (Reference (j)).

(4) Copies of any research involving human subjects conducted consistent with section 512 of Public Law 107-347 (Reference (k)). DoD Components shall also send a copy to the Office of Management and Budget (OMB), as required by Reference (k) and pages 33362-33377 of Volume 72, Federal Register (Reference (l)).

(5) Any allegation of serious or continuing noncompliance related to research involving human subjects that has been substantiated by inquiry or investigation and any subsequent actions taken based on the findings consistent with section 16 of Enclosure 3. The DoD Component may send an initial notification of potential serious or continuing noncompliance to ASD(R&E) based on the gravity or magnitude of the initial allegation.

(6) Any notifications to a DoD Component by another Federal agency or by an appropriate State agency or foreign government that an institution of the Component is under investigation for cause or for noncompliance with the applicable laws and regulations, including the Common Rule.

(7) Any substantiated unanticipated problems involving risks to human subjects or others (UPIRTSO).

g. Maintain all records identified in this Instruction or required by a reference in this Instruction as described in section 15 of Enclosure 3.

4. IOs OF DoD INSTITUTIONS. Each IO, under the authority, direction, and control of the Heads of the OSD and DoD Components shall:

a. Establish and maintain an HRPP to ensure the institution's compliance with this Instruction.

b. Provide the resources needed to ensure compliance with this Instruction.

c. Establish and maintain a DoD assurance and other appropriate Federal assurances, if the institution is engaged in non-exempt research involving human subjects (see Glossary).

d. Evaluate and improve the institution's HRPP.

ENCLOSURE 3

PROCEDURES

1. DoD COMPONENT HRPP MANAGEMENT PLAN

   a. The DoD Component HRPP management plan shall include, by reference, DoD Component policies to implement the procedures set forth in this enclosure and identify the responsible DoD Component office(s) for actions identified in this Instruction. DoD Component policies may be more restrictive than the requirements in this Instruction, but they may not be less restrictive. They may also impose additional requirements needed to implement this Instruction.

   b. The plan shall identify a single, senior official having the authority and responsibility for implementing the DoD Component HRPP management plan. This authority shall not be delegated lower than the general or flag officer (GO/FO), Senior Executive Service (SES), or equivalent level. All authorities delegated by the Head of the OSD or DoD Component must be identified in the management plan.

   c. The plan shall reference DoD Component policies and procedures that:

      (1) Direct each institution within the DoD Component conducting or supporting research involving human subjects to establish an HRPP that is compliant with this Instruction and the DoD Component's HRPP management plan.

      (2) Describe DoD Component oversight of each institution's HRPP.

      (3) Describe DoD Component administrative review of DoD-conducted and -supported research involving human subjects (see sections 3 and 4 of this enclosure for details).

      (4) Delineate institutional responsibilities when performing research involving human subjects in collaboration with another DoD Component. These responsibilities shall include establishing written agreements for tasks such as minimizing the number of institutional review boards (IRBs) and DoD Components that review and approve the research (see sections 3 and 4 of this enclosure for details). DoD Component policies and procedures shall include a requirement to justify the duplication of reviews of protocols (for example, IRB and Component Headquarters reviews).

      (5) Outline education and training for implementation, management, and oversight of this Instruction (see paragraph 1.f. of Enclosure 2 and section 5 of this enclosure for details).

      (6) Address the management of allegations and findings of noncompliance concerning DoD-conducted and -supported research involving human subjects (see section 16 of this enclosure for details).

      (7) Identify and manage conflicts of interest, not limited to financial, for DoD personnel involved in the HRPP.

      (8) Require a process to evaluate and improve the DoD Component's implementation of its HRPP management plan down to the level of the institutional HRPP.

d. A DoD Component may rely on another DoD Component for implementation of elements of the management plan except for designation of the single, senior official responsible for the management plan identified in paragraph 1.b. of this enclosure. Any such reliance must be reflected in the DoD Component's HRPP management plan.

2. REQUIREMENTS FOR A FEDERAL ASSURANCE

a. Activities for Which an Institution is Required to Have a Federal Assurance. Any institution engaged in non-exempt research involving human subjects that is conducted or supported by the Department of Defense shall have a Federal assurance consistent with section 219.103 of Reference (c) and acceptable to the funding agency.

(1) A DoD institution engaged in non-exempt research involving human subjects shall have a DoD assurance of compliance. Additionally, a DoD institution shall have an HHS assurance when engaged in non-exempt research involving human subjects funded by HHS (unless HHS will accept a DoD assurance). When conducting HHS-funded research involving human subjects, the DoD institution must follow this Instruction and any additional HHS requirements.

(2) In complying with the requirements of section 219.103 of Reference (c), a non-DoD institution that is engaged in DoD-supported non-exempt research involving human subjects:

(a) Need not have a DoD assurance if it has an existing Federal assurance appropriate for the research being conducted. If the institution does not have a Federal assurance, the institution must provide either a DoD assurance to the DoD Component supporting the research or a Federal wide assurance to HHS, Office for Human Research Protections. Alternatively, if the institution does not have a Federal assurance, the researcher may use an Individual Investigator Agreement to associate with an institution having a Federal assurance and thus fulfill the requirement of conducting non-exempt research involving human subjects under an approved Federal assurance. In summary, all researchers conducting non-exempt research involving human subjects must be covered either directly under their institution's Federal assurance or indirectly using an Individual Investigator Agreement.

(b) Shall comply with the terms of its Federal assurance, applicable sections of this Instruction, and relevant policies of the supporting DoD Component.

(3) All institutions providing a DoD assurance to a designated DoD Component office shall include the items identified in section 219.103(b) of Reference (c).

(a) All institutions shall identify at least one IRB on their DoD assurance. DoD institutions shall identify all IRBs that are internal to the institution on their DoD assurance.

(b) When any institution relies upon another institution's IRB, there must be a written agreement defining the responsibilities and

authorities of each organization in complying with the terms of each institution's Federal assurance and this Instruction (e.g., an Institutional Agreement for IRB Review). The existence of a DoD Institutional Agreement for IRB Review or a similar agreement will satisfy the Federal assurance requirements at sections 219.103(b)(2)-(5) of Reference (c).

b. Activities for Which an Institution is not Required to Have a Federal Assurance

(1) An institution is not required to have a Federal assurance if its personnel only conduct research that does not involve human subjects or the research involving human subjects meets at least one of the exemption criteria in section 219.101(b) of Reference (c).

(2) An institution that is only providing resources to support research involving human subjects (see Glossary definition of DoD-supported research involving human subjects) is not required to have a Federal assurance unless its involvement also meets the definition of being engaged in non-exempt research involving human subjects. When a DoD institution passes resources to another institution that will not be engaged in research, but will only transfer the resources to a third institution that will engage in research involving human subjects, the pass through institution is not required to have a Federal assurance. The institution engaged in non-exempt research involving human subjects must have a Federal assurance.

(3) An institution is not required to have a Federal assurance if it is collaborating in a research protocol that is non-exempt research involving human subjects and the institution's role in the collaborative research is limited to any of the following:

(a) Specific tasks that do not involve research involving human subjects; or

(b) Specific tasks that do not include the collection or handling of identifiable data or specimens. Research in which the human subjects' data or specimens are coded and the institution is prevented from having access to the code are considered non-identifiable for the purpose of this subparagraph.

(4) A DoD institution that does not meet the criteria for requiring a Federal assurance but conducts only exempt research involving human subjects or supports research involving human subjects must have an HRPP approved by its DoD Component that includes relevant policies and procedures to ensure compliance with this Instruction.

3. DoD-CONDUCTED RESEARCH INVOLVING HUMAN SUBJECTS

a. DoD Institutional Approval and Oversight

(1) DoD institutions conducting intramural research as defined in the Glossary involving human subjects shall have procedures to ensure appropriate regulatory determinations for activities that constitute research, activities that constitute research involving human subjects, or activities that are research involving human subjects but that meet the exemption criteria in section 219.101(b) of Reference (c). Such procedures shall include the designation, oversight, and appropriate training of DoD personnel.

(2) The DoD institution shall have policies and procedures to require scientific review of non-exempt research involving human subjects and to ensure this review is considered during the IRB review process.

(3) IRBs may use expedited review procedures under section 219.110(a) of Reference (c) to review minimal risk, non-exempt research involving human subjects using materials (e.g., data, documents, records, or specimens) that have previously been collected for any purpose, provided the materials were not collected for the currently proposed research.

(4) When the research is being conducted in a foreign country whose laws and regulations are applicable to that research, the DoD institution shall confirm that all applicable national laws and requirements of the foreign country have been met in addition to the requirements in this Instruction. The IRB shall also consider the cultural sensitivities in the setting where the research will take place.

(5) The DoD institution shall have policies and procedures to ensure the research involving human subjects has been approved by all required organizations before human subjects are recruited or any other research activities with human subjects begin. The IRB may approve a research protocol contingent upon its approval by other organizations (e.g., required reviews can be conducted in parallel).

(6) An IRB, in accordance with part 219 of Reference (c), shall approve all non-exempt research involving human subjects before any activities that involve human subjects can begin. An official cannot approve research that has been disapproved by the IRB in accordance with part 219 of Reference (c) (i.e., an IRB disapproval of a protocol cannot be overturned). The IRB must provide oversight of the ongoing research and review such research at intervals appropriate to the degree of risk, but not less than once per year.

(7) DoD institutions shall rely on an IRB whose membership meets the requirements in subparagraphs 3.a.(7)(a) through (d). In special circumstances, DoD institutions may rely on a non-Federal IRB if the conditions in subparagraph 3.a.(8) of this section are met.

(a) DoD IRBs shall consist of members who are Federal employees; Service members; individuals covered by sections 3371-3376 of title 5, U.S.C. (also known as "The Intergovernmental Personnel Act of 1970, as amended") (Reference (m)); or individuals appointed as experts or consultants in accordance with section 3109 of Reference (m).

(b) For DoD IRBs, the requirement to have a non-affiliated IRB member (section 219.107(d) of Reference (c)) can be fulfilled by a person who meets the criteria in subparagraph 3.a.(7)(a) of this section and is from an organization that is not part of the institution as defined on the institution's Federal assurance. DoD IRBs shall designate at least one alternate for the non-affiliated member. Although the presence of a non-affiliated member is not a requirement to have a quorum, the designation of one or more alternates will increase the likelihood that a non-affiliated member is present at the meetings.

(c) The IRB shall also have a scientist and a non-scientist to meet the requirements in section 219.107(c) of Reference (c). A member whose primary concerns are in a non-scientific area (i.e., the non-scientist) must be present to have a quorum at convened meetings. The non-affiliated position and the non-scientist position may be filled by the same person, or the non-affiliated position and the scientist position may be filled by the same person.

(d) The DoD institution shall consider including one or more community members on the IRB who are familiar with the perspectives of the human subjects (i.e., the community being recruited) commonly recruited and vulnerable subjects recruited by the institution. Community members may or may not be affiliated with the institution or have a scientific background. The appointment of the community members must comply with subparagraph 3.a.(7)(a) of this section.

(e) DoD IRBs may consult with subject matter experts (e.g., in science, in statistics, in ethics, for the subject population) who are not Federal employees or board members, but these consultants may not vote.

(8) DoD institutions engaged in non-exempt research involving human subjects and collaborating with a non-DoD institution's IRB may rely on a collaborating non-DoD institution's IRB if these minimum conditions are met:

(a) The DoD Component determines the collaborating non-DoD institution has an appropriate Federal assurance.

(b) The involvement of DoD personnel in the conduct of the research involving human subjects is secondary to that of the non-DoD institution.

(c) The DoD institution, the non-DoD institution, and the non-DoD institution's IRB have a written agreement defining the responsibilities and authorities of each organization in complying with the terms of the Federal assurances and this Instruction (i.e., have an Institutional Agreement for IRB Review or similar agreement). The DoD Component shall approve the terms of the agreement prior to the DoD institution's engagement in the research involving human subjects.

(d) The DoD Component must conduct an appropriate administrative review of the research involving human subjects to ensure it is in compliance with DoD policies and procedures prior to the DoD institution's engagement in the research.

b. DoD Component Review and Oversight

(1) At a minimum, the DoD Components must conduct an administrative review and approve all research involving non-exempt human subjects approved by a DoD institution when any of these conditions occur:

(a) The research will be conducted in a foreign country unless one of the following conditions apply:

1. The research will be conducted by an established DoD overseas research institution and the research will be conducted in the host country, or
2. The research will be conducted by a DoD overseas institution and will include only DoD personnel or U.S. citizens as human subjects.

(b) The research involves a collaboration with a non-DoD institution and the DoD institution is relying on the non-DoD institution's IRB, which is not composed of Federal employees (i.e., the research is approved by the IRB using the criteria described in subparagraph 3.a.(8)) of this section.

(c) The research permits a waiver of informed consent under paragraph (b) of section 980 of Reference (g).

(d) The research involves any fetal research covered under sections 289g–289g-2 of Reference (j).

(e) The research is required to be approved by either the ASD(R&E) or the Head of the OSD or DoD Component as delegated by the ASD(R&E) (e.g., the requirements in sections 7, 9, or 13 of this enclosure apply).

(2) The DoD Component administrative review must be conducted before the research involving human subjects can begin to ensure compliance with all applicable regulations and policies, including any applicable laws and requirements and cultural sensitivities of a foreign country if conducted in a foreign country. This Component review is not intended to be an additional IRB review.

4. RESEARCH INVOLVING HUMAN SUBJECTS CONDUCTED BY A NON-DoD INSTITUTION

a. Clause in Contracts and Agreements. The DoD Component must ensure the institution conducting the research involving human subjects is aware of its obligation to comply with the requirements of this Instruction and part 219 of Reference (c).

(1) Contracts for DoD-supported research involving human subjects must contain the Defense Federal Acquisition Regulation Supplement (DFARS) clause in accordance with section 252.235-7004 of title 48, CFR (Reference (n)). In addition to identifying contractor requirements and responsibilities, this clause also describes the role of the DoD Human Research Protection Official (HRPO). Comparable agreements not subject to section 252.235-7004 of Reference (n) (e.g., grants, assistance agreements, and cooperative research and development agreements) must contain language affirming the responsibilities of the non-DoD institution as required by Parts 22 (Appendix B), 37 (Appendix D), and 219 of Reference (c).

(2) The DFARS clause (or similar language) is not required to be included in an agreement with another Federal department or agency that has adopted the Common Rule. Approval by the HRPO is not required. The Federal department or agency may apply its own HRPP requirements in lieu of this

Instruction. However, the Federal department or agency must comply with the requirements in sections 7, 9, 13, and 17 of this enclosure and the requirements of Reference (f).

b. Non-DoD Institutional Responsibilities

(1) The non-DoD institution shall comply with the terms of the DFARS clause or comparable language used in the agreement with the DoD Component supporting the research involving human subjects, as provided in subparagraph 4.a.(1) of this section.

(2) When a non-DoD institution is conducting non-exempt research involving human subjects, the IRB review must consider the scientific merit of the research, as required by section 219.111 of Reference (c). The IRB may rely on outside experts to provide an evaluation of the scientific merit.

(3) IRBs may use expedited review procedures under section 219.110(a) of Reference (c) to review minimal risk, non-exempt research involving human subjects using materials (e.g., data, documents, records, or specimens) that have previously been collected for any purpose, provided the materials were not collected for the currently proposed research.

(4) To the extent provided in section 219.103 of Reference (c), the non DoD-institution shall promptly notify the HRPO of the following: when significant changes to the research protocol are approved by the IRB, the results of the IRB continuing review, if the IRB used to review and approve the research changes to a different IRB, when the institution is notified by any Federal department or agency or national organization that any part of its HRPP is under investigation for cause involving a DoD-supported research protocol, and all UPIRTSOs, suspensions, terminations, and serious or continuing noncompliance regarding DoD-supported research involving human subjects.

(5) Non-DoD institutions shall comply with requirements of this Instruction applicable to them. They are not required to comply with provisions of this Instruction either solely directed to actions of the DoD Components or specifically limited to DoD-conducted research involving human subjects.

c. DoD Component Review, Approval, and Oversight

(1) When the contract or other agreement may include research involving human subjects and if the non-DoD institution determines either the activity is not research involving human subjects or is exempt research involving human subjects, the HRPO must concur with the performing institution's determination before activity can begin.

(2) If the non-DoD institution determines the activity is non-exempt research involving human subjects, the HRPO must perform an administrative review of the research before the activities that involve human subjects can begin (e.g., human subject recruitment and data collection). Such review and approval shall be based on confirmation that the research and non-DoD institution are in compliance with applicable requirements of this Instruction and Parts 22 (Appendix B), 37 (Appendix D), and 219 of Reference (c). At a minimum, the HRPO must:

(a) Confirm the non-DoD institution has a Federal assurance appropriate for the research in question (see paragraph 2.a. of this enclosure).

(b) Review the research protocol and accept the IRB determination of level of risk and approval of the study for compliance with this Instruction.

(c) Review and accept IRB-approved substantive changes to an approved research protocol before they are implemented.

(d) Ensure the IRB conducts an appropriate continuing review at least annually.

(e) When the research involving human subjects is being conducted in a foreign country, confirm all applicable national laws and requirements of the foreign country have been met and confirm the IRB considered the cultural sensitivities in the setting where the research will take place.

(3) Upon receipt of notifications directed in subparagraph 4.b.(4) of this section, the supporting DoD Component shall promptly review the report and determine if further review of any or all the institution's research involving human subjects that is supported by the DoD Component is warranted. When appropriate, the DoD Component may defer its investigation to an ongoing Federal investigation. The DoD Component shall notify the ASD(R&E) in accordance with paragraph 3.f. of Enclosure 2 and section 16 of this enclosure.

(4) DoD Components conducting a for-cause review of research conducted by a non-DoD institution shall evaluate and ensure the adequacy of human protection in DoD-supported programs and provide recommendations to the DoD Component about allowing continued DoD support of research involving human subjects, suspending the research until necessary changes have been made, or terminating the research.

5. EDUCATION AND TRAINING. The DoD Components shall ensure that all DoD personnel involved in the conduct, review, or approval of research involving human subjects, including the non-affiliated and prisoner representative members on the DoD IRB, receive initial and continuing education and training in compliance with the standards set forth by ASD(R&E) (see paragraph 1.f. of Enclosure 2 for details).

a. Initial and continuing education and training shall be commensurate with the duties and responsibilities of the DoD personnel.

b. All training and education of DoD personnel shall be documented.

c. Professional certification in the field of human research protection is encouraged for all DoD personnel involved in review and oversight of research involving human subjects.

d. When assessing whether to support or collaborate with a non-DoD institution for research involving human subjects, the DoD Components should evaluate the non-DoD institution's education and training policies to ensure the personnel are qualified to perform the research. The rigor of the evaluation should be appropriate for the complexity and risk of the research.

6. SELECTION OF HUMAN SUBJECTS AND EVALUATING RISK

    a. Selection of Human Subjects. The selection of human subjects reflecting gender and minority participation in DoD-conducted or -supported clinical research involving human subjects shall comply with section 252 of Public Law 103-160 (Reference (o)). The Head of the OSD or DoD Component may exercise the waiver authority under this law. This waiver authority may be delegated, as described in the Component's HRPP management plan, but not to an individual at the level of the institutional HRPP.

    b. Evaluating Risk. The phrase "ordinarily encountered in daily life or during the performance of routine physical or physiological examinations or tests" in the definition of minimal risk (section 219.102(i) of Reference (c)) shall not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain).

7. ADDITIONAL PROTECTIONS FOR HUMAN SUBJECTS. In addition to the requirements of part 219 of Reference (c), additional safeguards described in this section shall be provided for human subjects in all DoD-conducted research involving human subjects who may be considered vulnerable due to their association with groups or populations specifically defined by Federal regulations in subparts B-D of Reference (h) and this Instruction. Similarly, as provided in Reference (n) or Parts 22 (Appendix B) and 37 (Appendix D) of Reference (c), such additional safeguards shall also be provided in comparable DoD-supported research involving human subjects. For purposes of this Instruction, actions authorizing or requiring any action by an official of HHS about any requirements of subparts B-D of Reference (h) shall be under the authority of the ASD(R&E). Investigators, IRBs, IOs, and DoD Component personnel reviewing research protocols shall consider the need for appropriate similar safeguards for other vulnerable populations, such as: research involving human subjects and investigators in supervisor-subordinate relationships, human subjects with decisional or mental impairments, human subjects with a physical disability, or any other kind of human subjects in circumstances that may warrant provision of additional protections. As appropriate, qualified individuals (e.g., research monitors, ombudsmen, advocates) may be appointed to perform oversight functions or assist the human subjects.

    a. Pregnant Women, Fetuses, and Neonates as Subjects

        (1) Non-exempt research involving pregnant women, fetuses, or neonates as human subjects must meet the additional relevant protections of subpart B of Reference (h), unless modified by this Instruction. Research involving pregnant women as subjects may be exempt from the requirements of part 219 of Reference (c) and subpart B of Reference (h) if the research meets the exemption criteria at section 219.101(b) of Reference (c). If the pregnant woman is a prisoner, then paragraph 7.b. of this section also applies. If the pregnant woman is a minor, paragraph 7.d. of this section also applies. For purposes of applying paragraph 7.a., the phrase "biomedical knowledge" in subpart B of Reference (h) shall be replaced with "generalizable knowledge" throughout the subpart.

        (2) The applicability of subpart B of Reference (h) is limited to research involving:

(a) Pregnant women as human subjects involved in research that is more than minimal risk and includes interventions or invasive procedures to the woman or the fetus; or

(b) Fetus or neonate (see Glossary) as human subjects.

(3) Research involving human subjects using fetal tissue shall comply with sections 289g–289g-2 of Reference (j).

b. Prisoners as Subjects

(1) Research Intending to Include Prisoners as Subjects

(a) Research involving human subjects that includes prisoners must meet the additional relevant protections of subpart C of Reference (h), unless modified by this Instruction. If the prisoner is a pregnant woman, then paragraph 7.a. of this section also applies. If the prisoner is a minor, then paragraph 7.d. of this section also applies.

(b) Research intending to include prisoners as subjects cannot be reviewed by the IRB through an expedited review procedure.

(c) The IRB reviewing research intending to include prisoners as subjects shall be composed of at least one prisoner representative (see Glossary). The prisoner representative may be a prisoner, an employee of the prison, or an individual not affiliated with the prison. The prisoner representative shall have knowledge of the culture(s) of the prisoners and knowledge of the prison operations. At least one prisoner representative must be present for a quorum.

(d) Research involving prisoners at prisons or other types of institutions may be subject to additional review by institution authorities (e.g., Bureau of Prisons).

(2) Categories of Allowable Research Involving a Prisoner. In addition to the four categories of permissible research involving human subjects identified in subpart C of Reference (h), two additional categories are allowable.

(a) Epidemiological research that meets the following criteria can also be approved in accordance with the requirements of subpart C of Reference (h) and the requirements of this Instruction:

1. The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor associations for a disease.

2. The research presents no more than minimal risk.

3. The research presents no more than an inconvenience to the human subject.

4. Prisoners are not a particular focus of the research.

(b) Research involving human subjects that would meet the criteria described at section 219.101(b) of Reference (c) can be conducted, but must be approved by a convened IRB and meet the requirements of subpart C of Reference (h), this Instruction, and other applicable requirements.

(3) When a Subject Becomes a Prisoner

(a) When a previously enrolled human subject becomes a prisoner and the relevant research protocol was not reviewed and approved by the IRB in accordance with the requirements of subparagraphs 7.b.(1) and (2) of this section, the principal investigator shall promptly notify the IRB.

(b) If the principal investigator asserts to the IRB that it is in the best interest of the prisoner-subject to continue to participate in the research while a prisoner, the IRB Chair may determine that the prisoner-subject may continue to participate until the convened IRB can review this request to approve a change in the research protocol and until the IO and DoD Component office review the IRB's approval to change the research protocol. Otherwise, the IRB Chair shall require that all research interactions and interventions with the prisoner-subject (including obtaining identifiable private information) cease until the convened IRB can review this request to approve a change in the research protocol.

(c) The convened IRB, upon receipt of notification that a previously enrolled human subject has become a prisoner, shall promptly re-review the research protocol to ensure that the rights and wellbeing of the human subject, now a prisoner, are not in jeopardy. The IRB should consult with a subject matter expert having the expertise of a prisoner representative if the IRB reviewing the research protocol does not have a prisoner representative. If the prisoner-subject can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner-subject's confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research involving human subjects from continuing as approved, the convened IRB may approve a change in the study to allow this prisoner-subject to continue to participate in the research. This approval is limited to the individual prisoner-subject and does not allow recruitment of prisoners as subjects.

(d) This type of request for change in the research protocol cannot be reviewed and approved by the IRB using expedited review procedures. The research involving human subjects does not have to meet one of the six allowable categories of research as described in subparagraph 7.b.(2) of this enclosure.

(e) If the research involving human subjects is conducted by a non-DoD institution, the non-DoD institution shall promptly report all decisions in this matter to the HRPO. If the research is conducted by a DoD institution, the IRB shall promptly report all decisions in this matter to the IO and to the DoD Component office conducting the reviews identified in paragraph 3.b. of this enclosure. For all DoD-conducted or -supported research involving human subjects, the applicable DoD Component office conducting the reviews identified in paragraphs 3.b. or 4.c. of this enclosure must concur with the IRB before the human subject can continue to participate while a

prisoner. This approved change to a research protocol does not require ASD(R&E) approval.

c. Treatment of Detainees

(1) Research involving a detainee, as defined in DoD Directive 2310.01E (Reference (p)), as a human subject is prohibited.

(2) The prohibition in paragraph c.(1) of this section does not apply to activities covered by investigational new drug or investigational device provisions of Reference (d) when for the purpose of diagnosis or treatment of a medical condition in a patient. Such treatment (e.g., an investigational new drug) may be offered to detainees with the detainees' informed consent when the medical products are subject to Reference (d) as investigational new drugs or investigational medical devices, and only when the same product would be offered to members of the U.S. Military Services in the same location for the same medical condition and only when consistent with established medical practice involving investigational drugs and devices. Such permitted treatment involving detainees as subjects shall comply with all sections of this Instruction, including paragraphs 6.a., b., and d. of this section, as applicable.

d. Children as Subjects

(1) Research involving human subjects conducted or supported by the Department of Defense that recruits children to be subjects must meet the additional relevant protections of subpart D of Reference (h), unless modified by this Instruction. If the minor is a pregnant woman, then paragraph 7.a. of this section also applies. If the minor is a prisoner, paragraph 7.b. of this section also applies.

(2) The footnote in section 219.101(i) of Reference (c), prohibiting specific exemptions described in section 219.101(b) from applying to children, is also applicable to DoD-conducted or -supported research involving human subjects unless otherwise clarified in this Instruction.

e. DoD Personnel as Subjects

(1) Military Personnel as Subjects

(a) Service members shall follow their command policies regarding the requirement to obtain command permission to participate in research involving human subjects while on-duty. Additionally a Service member's ability to perform his or her military duties may be affected by participating during off-duty time (i.e., on leave or during non-duty hours). Therefore, Service members shall follow their Component and command's policies for approving off-duty employment or activities. The IRBs of DoD institutions or HRPOs may require Principal Investigators to confirm that a Service member's commander supports the member's participation in DoD-supported research involving human subjects.

(b) Superiors (e.g., military and civilian supervisors, unit officers, and noncommissioned officers (NCOs)) are prohibited from influencing the decisions of their subordinates (e.g., junior enlisted personnel and

equivalent civilians) regarding participation as subjects in research involving human subjects covered by this Instruction.

(c) Superiors of Service members (e.g., unit officers, senior NCOs, and equivalent civilians) in the chain of command shall not be present at any human subject recruitment sessions or during the consent process in which members of units under their command are afforded the opportunity to participate as human subjects. When applicable, the superiors so excluded shall be afforded the opportunity to participate as human subjects in a separate recruitment session.

(d) For research involving Service members as human subjects that has been determined to be greater than minimal risk and when recruitment occurs in a group setting, the IRB shall appoint an ombudsman. The ombudsman shall not be associated in any way to the research and shall be present during the recruitment in order to monitor that the voluntary involvement or recruitment of the Service members is clearly and adequately stressed and that the information provided about the research is clear, adequate, and accurate. The ombudsman may also be the research monitor (see section 8 of this enclosure). For research involving Service members as human subjects, that has been determined to be NO greater than minimal risk and when recruitment occurs in a group setting, the IRB shall determine when it is appropriate to appoint an ombudsman for the purposes described in this paragraph. The decision to require the appointment of an ombudsman should be based in part on the human subject population, the consent process, and the recruitment strategy.

(2) DoD Civilians as Subjects

(a) DoD Civilians shall follow their organization's policies regarding the requirement to obtain permission to participate in research involving human subjects.

(b) Supervisors (e.g., military and civilian supervisors or anyone in the supervisory structure) are prohibited from influencing the decisions of their subordinates regarding participation as subjects in research involving human subjects covered by this Instruction.

(c) Supervisors (e.g., military and civilian supervisors or anyone in the supervisory structure) shall not be present at any human subject recruitment sessions or during the consent process in which DoD civilians under their supervision are afforded the opportunity to participate as human subjects. When applicable, supervisors so excluded shall be afforded the opportunity to participate as human subjects in a separate recruitment session.

(d) For research involving civilians as human subjects and when recruitment occurs in a group setting, the IRB shall discuss appointing an ombudsman for the purposes described in subparagraph e.(1)(d) of this section. The decision to require the appointment of an ombudsman should be based in part on the human subject population, the consent process, and the recruitment strategy.

8. RESEARCH MONITOR

   a. For DoD-conducted research involving human subjects determined by the IRB to involve more than minimal risk to human subjects (as defined in section 219.102(i) of Reference (c)), and, to the extent provided pursuant to Parts 22 (Appendix B), 37 (Appendix D), and 219 of Reference (c) and Reference (n), comparable DoD-supported research, the IRB shall approve an independent research monitor by name. Additionally, the research monitor may be identified by an investigator or appointed by an IRB or IO for research involving human subjects determined to involve minimal risk. There may be more than one research monitor (e.g., if different skills or experiences are necessary). The monitor may be an ombudsman or a member of the data safety monitoring board.

      (1) The duties of the research monitor shall be determined on the basis of specific risks or concerns about the research. The research monitor may perform oversight functions (e.g., observe recruitment, enrollment procedures, and the consent process for individuals, groups or units; oversee study interventions and interactions; review monitoring plans and UPIRTSO reports; and oversee data matching, data collection, and analysis) and report their observations and findings to the IRB or a designated official.

      (2) The research monitor may discuss the research protocol with the investigators, interview human subjects, and consult with others outside of the study about the research. The research monitor shall have authority to stop a research protocol in progress, remove individual human subjects from a research protocol, and take whatever steps are necessary to protect the safety and well-being of human subjects until the IRB can assess the monitor's report. Research monitors shall have the responsibility to promptly report their observations and findings to the IRB or other designated official.

      (3) The IRB must approve a written summary of the monitors' duties, authorities, and responsibilities. The IRB or HRPP official shall communicate with research monitors to confirm their duties, authorities, and responsibilities.

      (4) The research monitors shall have expertise consonant with the nature of risk(s) identified within the research protocol, and they shall be independent of the team conducting the research involving human subjects.

   b. The Heads of the OSD and DoD Components may waive the requirement to have a research monitor on a case-by-case basis when the inclusion of a research monitor is not necessary to provide additional protections for human subjects. This waiver authority may be delegated to a DoD official, as described in the Component's HRPP management plan, but not at or below the position of the institution's DoD IO.

9. UNIQUE DoD LIMITATIONS ON WAIVER OF INFORMED CONSENT

   a. Sections 219.116(c) and (d) of Reference (c) identify conditions where an IRB may waive informed consent for DoD-conducted and DoD-supported research involving human subjects. Section 980 of Reference (g) imposes limitations on waiving informed consent when using DoD appropriated funds. Section 980 of Reference (g) is applicable ONLY to DoD funded research involving a human being as an experimental subject as defined in the Glossary. The definition of research involving

a human subject as an experimental subject is not the same as the definition of research involving human subjects. Section 980 of Reference (g) is not applicable to exempt research involving human subjects.

b. When the research meets the Glossary definition of research involving a human being as an experimental subject, informed consent must be obtained in advance from the experimental subject or the subject's legal representative consistent with part 219 of Reference (c) if the subject cannot consent. If consent is to be obtained from the experimental subject's legal representative, the research must intend to benefit the individual subject. The determination that research is intended to be beneficial to the individual experimental subject must be made by an IRB consistent with part 219 of Reference (c).

c. The requirement of paragraph 9.b. of this section may be waived by the ASD(R&E) if all the following conditions are met:

(1) The research is necessary to advance the development of a medical product for the Military Services.

(2) The research may directly benefit the individual experimental subject.

(3) The research is conducted in compliance with all other applicable laws and regulations.

d. The ASD(R&E) may delegate the waiver authority described in paragraph 9.c. to the Heads of the OSD and DoD Components if they have appropriate policies and procedures in their management plans. This authority is further delegable only to a DoD Component official who is a Presidential Appointee with Senate Confirmation.

10. PROTECTING HUMAN SUBJECTS FROM MEDICAL EXPENSES IF INJURED

a. DoD-Supported Research Involving Human Subjects. All non-exempt research involving human subjects shall, at a minimum, meet the requirement of section 219.116(a)(6) of Reference (c). The Common Rule does not require payment or reimbursement of medical expenses, provision of medical care, or compensation for research-related injuries.

b. DoD-Conducted Research Involving Human Subjects. The DoD Components shall establish procedures to protect human subjects from medical expenses (not otherwise provided or reimbursed) that are the direct result of participation in DoD-conducted non-exempt research involving human subjects that involves more than minimal risk. Such procedures may consist of utilizing the Secretarial Designee program as described by section 108.4(i) of Reference (c) during the period of the human subject's involvement in the research, which may be extended further upon the approval of the USD(P&R). DoD Components may supplement this Secretarial Designee procedure with additional procedures consistent with applicable authority. This requirement does not apply when the Department of Defense is supporting the research but is not engaged in the non-exempt research involving human subjects (i.e., when the non-exempt research involving human subjects is performed solely by non-DoD institutions).

c. DoD Collaborative Research Involving Human Subjects

(1) When collaborating with a non-DoD institution, the DoD Components shall establish procedures comparable to those required by paragraph 10.b. of this section to protect human subjects from medical expenses (not otherwise provided or reimbursed) that are the direct result of participation

in non-exempt research involving human subjects and that are a direct result of research activities performed by DoD personnel. This does not apply to expenses resulting from the injury due to actions performed by the non-DoD institution(s).

(2) When DoD personnel are conducting the research involving human subjects at the collaborating institution and the Department of Defense does not have the primary involvement, the DoD Components are not required to have procedures to protect human subjects from medical expenses. For this purpose the determination of primary involvement shall be based on consideration of the type and portion of the DoD involvement in the collaborative research (e.g., research staff, human subjects, facilities, equipment, IRB, and all other assets).

(3) When the collaboration is such that it is difficult to separate DoD involvement from that of the non-DoD institution, the Head of the OSD or DoD Component may waive this requirement to have procedures to protect human subjects from medical expenses. This waiver authority may be delegated, as described in the Component's HRPP management plan, but not at or below the position of the institution's DoD IO.

11. COMPENSATION TO HUMAN SUBJECTS FOR PARTICIPATION IN RESEARCH

a. DoD-Conducted Research Involving Human Subjects

(1) When the Human Subjects Are On-Duty Federal Personnel

(a) Federal personnel (civil servants or Service members) participating as human subjects in DoD-conducted research while on duty (i.e., not on leave and participating during their duty hours) may be compensated up to $50 for each blood draw if the research meets the purpose of section 30 of title 24, U.S.C. (Reference (q)). Payment for blood draws may come directly from a Federal or non-Federal source. By permitting compensation for blood draws, Reference (q) provides an exception to section 5536 of Reference (m), which prohibits Federal personnel from being paid by any source other than their regular Federal salaries while they are on duty.

(b) Federal personnel participating as human subjects in DoD-conducted research while on duty may only be compensated for blood draws as described in this paragraph and may not be otherwise compensated for general research participation.

(2) When the Human Subjects Are Off-Duty Federal Personnel

(a) Federal personnel (civil servants or Service members) participating as human subjects in DoD-conducted research while off duty may be compensated up to $50 for each blood draw if the research meets the purpose of Reference (q). Payment for blood draws may come from a Federal or non-Federal source.

(b) Additionally Federal personnel while off duty may be compensated for research participation other than blood draws in the same way as human subjects who are not Federal personnel (i.e., compensated for participation in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research).

However, payment to off-duty Federal personnel for research participation other than blood draws must not be directly from a Federal source (payment from a Federal contractor or other non-Federal source is permissible).

(3) When the Human Subjects Are Not Federal Personnel

(a) Non-Federal personnel participating as human subjects in DoD-conducted research may be compensated up to $50 for each blood draw if the research meets the purpose of Reference (q). Payment for blood draws may come directly from a Federal or non-Federal source.

(b) Additionally non-Federal personnel may be compensated for research participation other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research. Payment for general research participation may come directly from a Federal or non-Federal source.

b. Non DoD-Conducted Research Involving Human Subjects

(1) When the Human Subjects Are On-Duty Federal Personnel

(a) Federal personnel (civil servants or Service members) participating as human subjects in research conducted by a non-DoD institution (whether or not the research is Federally funded) may be compensated up to $50 for each blood draw if the research meets the purpose of Reference (q). By permitting compensation for blood draws, Reference (q) provides an exception to section 5536 of Reference (m), which prohibits Federal personnel from being paid by any source other than their regular Federal salaries while they are on duty.

(b) Federal personnel participating as human subjects in non-DoD-conducted research while on duty may only be compensated for blood draws as described in this paragraph and may not be otherwise compensated for general research participation, even if the research is not Federally funded or conducted.

(2) When the Human Subjects Are Off-Duty Federal Personnel

(a) Federal personnel (civil servants or Service members) participating as human subjects in Federally-funded human subject research conducted by a non-DoD institution may be compensated up to $50 for each blood draw if the research meets the purpose of Reference (q). However, if the research is not Federally funded, the human subjects may be compensated for blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the blood draw unless it is prohibited by this Instruction or another policy (i.e., the $50 limitation per blood draw does not apply).

(b) Additionally Federal personnel while off duty may be compensated for research participation other than blood draws in the same way as human subjects who are not Federal personnel (i.e., compensated for participation in a reasonable amount as approved by the IRB

according to local prevailing rates and the nature of the research). However, payment to off-duty Federal personnel for general research participation must not be directly from a Federal source (payment from a Federal contractor or other non-Federal source is permissible).

(3) When the Human Subjects Are Not Federal Personnel

(a) Non-Federal personnel participating as human subjects in DoD-funded research may be compensated up to $50 for each blood draw if the research meets the purpose of Reference (q).

(b) Additionally non-Federal personnel may be compensated for participation in DoD-supported research for other than blood draws in a reasonable amount as approved by the IRB according to local prevailing rates and the nature of the research. Payment for general research participation may come directly from a Federal or non-Federal source.

12. SERVICE MEMBERS AND THEIR STATUS AS ADULTS. For purposes of legal capacity to participate in DoD-conducted or -supported research involving human subjects, all active duty Service members and all Reserve Component members in a Federal duty status are considered for purposes of this Instruction to be adults. The participation of such members is not subject to requirements of paragraph 7.d. of this enclosure or subpart D of Reference (h) regarding research involving children or minors. When Service members are under 18 years of age, students at Service Academies, or trainees, the IRB shall carefully consider the recruitment process and the necessity to include such members as human subjects.

13. CLASSIFIED RESEARCH INVOLVING HUMAN SUBJECTS. For all DoD-conducted non-exempt research involving human subjects that involves classified information as defined in Executive Order 13526 (Reference (r)), and, to the extent provided pursuant to Parts 22, 37, and 219 of Reference (c) and Reference (n), comparable DoD-supported research, the additional requirements in this section apply. The involvement of classified information may be limited to information needed for IRB approval and oversight of the research; information needed to inform the human subjects during the consent process; and information provided by the human subjects during the course of the research. If this activity is part of a classified program, this section does not apply if the information required to be contained in the research protocol or needed by either the IRB or the human subjects is not classified.

a. Secretary of Defense approval is required for all classified non-exempt research involving human subjects. Submission for approval shall be from the Head of the OSD or DoD Component conducting or supporting the non-exempt research involving human subjects. The request shall be coordinated with the ASD(R&E) and General Counsel of the Department of Defense after the IRB has approved the research.

b. Waivers of informed consent are prohibited.

c. Informed consent procedures shall include:

(1) Identification of the Department of Defense as the supporting institution of the research, unless the research involves no more than minimal risk. The Secretary of Defense may grant an exception to this requirement on the grounds that providing this information could compromise intelligence sources or methods.

(2) A statement that the research involving human subjects is classified and an explanation of the impact of the classification.

d. IRB approval process shall meet the following requirements:

(1) IRB review shall be conducted using a full board review. Use of an expedited review procedure is prohibited.

(2) At least one non-affiliated member shall be a non-Federal employee (other than as an individual appointed as an expert or consultant in accordance with section 3109 of Reference (m) for purposes of service on the IRB).

(3) Any IRB member who disagrees with a majority decision approving a project may appeal the decision to the Secretary of Defense. The appeal shall be included in the DoD Component's submission to the Secretary of Defense.

(4) The IRB shall determine whether potential human subjects need access to classified information to make a valid, informed consent decision.

e. Disclosure or use of classified information must comply with the requirements of Reference (r) for access to and protection of classified information.

14. ADDITIONAL PROTECTIONS FOR CONFIDENTIALITY. This section outlines certain authorities that the DoD Components may consider using, subject to applicable requirements, for particular sensitive research activities when additional protections for confidentiality would improve participation and results.

a. Confidential Information Protection and Statistical Efficiency Act (CIPSEA) for Non-Statistical Agencies. Any DoD Component may use the authority pursuant to sections 501-513 of Reference (k) to assure that data or information acquired by the DoD Component under a pledge of confidentiality for exclusively statistical purposes shall be used exclusively for statistical purposes and may not be disclosed in identifiable form for any other purpose, except with the informed consent of the respondent. Use of this authority is subject to the requirements of sections 512 and 523-525 of Reference (k) and of Reference (l), including that the research involving human subjects is conducted by a DoD Component or other Federal agency and not by a contractor, grantee, or other non-Federal entity, and that use of the authority is reported annually to OMB by the DoD Component.

b. CIPSEA for Statistical Agencies. Any DoD Component or unit thereof designated a statistical agency by the OMB pursuant to section 522 of Reference (k) and Reference (l) may designate agents (e.g., contractor, grantee, or other non-Federal entity under a qualifying agreement) that may assure that data or information acquired for the Component under a pledge of confidentiality for exclusively statistical purposes shall be used exclusively for statistical purposes, and may not be disclosed in identifiable form for any other purpose, except with the informed consent of the respondent. Use of this authority is subject to the requirements of sections 512 and 523-525 of Reference (k) and of Reference (l).

c. Certificate of Confidentiality. A DoD Component or a contractor, grantee, or other non-Federal entity conducting DoD-supported research involving human subjects may request from the National Institutes of Health (NIH) of the Department of HHS a Certificate of Confidentiality pursuant to section 241(d) of Reference (j). Such a Certificate of Confidentiality authorizes persons engaged in biomedical, behavioral, clinical, or other research related to mission areas of the NIH to protect the privacy of

human subjects of sensitive research against compulsory disclosure in any Federal, State, or local judicial, administrative, or legislative proceeding to identify human subjects. Issuance of any Certificate of Confidentiality is at NIH's discretion and is subject to the requirement of section 241(d) of Reference (j) and any other NIH guidelines.

15. RECORD KEEPING

    a. Part 219 of Reference (c) requires all institutions engaged in DoD-conducted or -supported research involving human subjects to retain records for at least 3 years after the completion of the research. Research involving human subjects may be covered by other Federal regulations that impose longer record keeping requirements. The DoD Components may rely on the non-DoD institutions to keep the required records that were generated by the institution, or the DoD Components may make arrangements to transfer the records.

    b. The DoD Components shall also retain records regarding the oversight of DoD Component-supported research involving human subjects for at least 3 years after the completion of the research, HRPP education or training program, or other action relevant to the HRPP. Additionally, the DoD Components shall keep all records regarding DoD Component waivers, exemptions, and extensions, and all DoD Component requests for exceptions, waivers, exemptions, and extensions submitted to the ASD(R&E) for action for at least 3 years after the completion of the research.

    c. The DoD Components may be required to retain records for longer than specified in paragraphs 15.a. and 15.b. of this section. For example, some Health Insurance Portability and Accountability Act documentation is required to be retained for 6 years (in accordance with DoD 6025.18-R (Reference (s))). For complete recordkeeping guidance and instruction, the DoD Components shall consult their respective records disposition schedules.

    d. Records maintained by non-DoD institutions that document compliance or noncompliance with this Instruction shall be made accessible for inspection and copying by authorized representatives of the Department of Defense at reasonable times and in a reasonable manner as determined by the supporting DoD Component.

16. NONCOMPLIANCE WITH THIS INSTRUCTION. The DoD Components shall respond to allegations of noncompliance with this Instruction. For allegations that involve more than one DoD Component or a non-DoD institution, the involved institutions should jointly determine and assign executive responsibility for responding to the allegation(s). For allegations involving a non-DoD institution, the DoD Component supporting the research involving human subjects shall ensure the allegation is properly investigated and reported to the DoD Component. All findings of serious or continuing noncompliance with this Instruction that have been substantiated by inquiry or investigation shall be reported to the ASD(R&E) in a timely manner.

17. APPLICABILITY TO OTHER REQUIREMENTS. Compliance with this Instruction does not imply that all other applicable requirements have been met for DoD-conducted and -supported research involving human subjects. No DoD agency within the Intelligence Community shall sponsor, contract for, or conduct non-exempt research involving human subjects except in accordance with paragraph 2.10 of Executive Order 12333 (Reference (t)). Additionally, research involving human subjects using surveys, materials under the purview of the FDA, or individually identifiable health information may be subject to additional Federal or DoD requirements, such as those identified in Reference (s), DoD 5400.11-R

(Reference (u)), and DoDI 6000.08 (Reference (v)). States may have differing definitions and protections for vulnerable populations. Research involving human subjects conducted in foreign countries may be subject to additional national and local requirements.

18. CCHRPP MEMBERSHIP. The CCHRPP shall be composed of senior officials at the GO/FO, SES, or equivalent level. The Heads of the OSD and DoD Components with a DoD Component HRPP management plan shall each identify one member to represent their Component to the ASD(R&E). The Chair shall be designated by the ASD(R&E). The CCHRPP shall be supported by an Executive Secretariat (O-6 or equivalent level) composed of representatives from the DoD Components' human research protection oversight offices.

GLOSSARY

PART I. ABBREVIATIONS AND ACRONYMS

ASD(HA)	Assistant Secretary of Defense for Health Affairs
ASD(R&E)	Assistant Secretary of Defense for Research and Engineering
CCHRPP	Coordinating Committee for Human Research Protection Programs
CFR	Code of Federal Regulations
CIPSEA	Confidential Information Protection and Statistical Efficiency Act of 2002
DFARS	Defense Federal Acquisition Regulation Supplement
DoDD	Department of Defense Directive
FDA	Food and Drug Administration
GO/FO	general or flag officer
HHS	Health and Human Services
HRPO	human research protection official
HRPP	Human Research Protection Program
IO	institutional official
IRB	institutional review board
NCOs	noncommissioned officers
NIH	National Institutes of Health
OMB	Office of Management and Budget
OT&E	operational test and evaluation
RDT&E	research, development, test and evaluation
SES	Senior Executive Service
UPIRTSO	unanticipated problems involving risks to subjects or others
U.S.C.	United States Code
USD(P&R)	Under Secretary of Defense for Personnel and Readiness

PART II. DEFINITIONS

Unless otherwise noted, these terms and their definitions are for the purpose of this Instruction.

administrative review. A review of a research protocol and supporting documents (e.g., safety review, scientific review, IRB minutes) related to DoD-supported research involving human subjects which ensures the institution engaged in the research involving human subjects has met the requirements of all applicable regulations and policies. This review is NOT an IRB review.

classified research involving human subjects. Research involving human subjects where the protocol or other information required by the IRB for review and oversight or required or provided by the research subjects includes classified information, as defined in Reference (q).

clinical investigations. Any research or experiments that involve a test article, one or more human subjects, and are performed under the requirements of Reference (d). Clinical investigations are a subcategory of research involving human subjects.

continuing noncompliance. A pattern of noncompliance (see definition of noncompliance) that suggests the likelihood that, without intervention, instances of noncompliance will recur. A repeated unwillingness to comply with this Instruction or a persistent lack of knowledge of how to comply with this Instruction.

Common Rule. The regulation adopted by multiple Federal departments and agencies for the protection of human subjects in research. The Department of Defense's implementation of the Common Rule is part 219 of Reference (c); the Department of HHS's implementation of the Common Rule is subpart A of Reference (h).

detainee. Defined in Reference (p).

DoD-conducted research involving human subjects. Research involving human subjects that is performed by DoD personnel. Intramural research is one type of DoD-conducted research involving human subjects. See "engaged in research involving human subjects."

DoD personnel. DoD civilian employees and members of the military services.

DoD civilian employee. An individual meeting the definition of "employee" consistent with section 2105 of Reference (m). It includes employees of DoD Non-Appropriated Fund Instrumentalities; DoD civilian employees filling full-time, part-time, intermittent, or on-call positions; and individuals serving under personal services contracts consistent with section 2.101 of Reference (n). It excludes employees of contractors (other than personal services contractors) and foreign nationals of host countries.

Service members. Individuals appointed, enlisted, or inducted for military service under the authority of the Department of Defense. The Military Services are the Army, the Navy, the Air Force, the Marine Corps, the Coast Guard, and the Reserve Components, which includes the Army and the Air National Guards of the United States. Members of the Reserve Components are included when in a duty status.

DoD-supported research involving human subjects. Research involving human subjects for which the Department of Defense is providing at least some of the resources (see "research involving human subjects"). Resources may include but are not limited to funding, facilities, equipment, personnel (investigators or other personnel performing tasks identified in the research protocol), access to or information about DoD personnel for recruitment, or identifiable data or specimens from living individuals. It includes both DoD-conducted research involving human subjects (intramural research) and research conducted by a non-DoD institution.

engaged in research involving human subjects. An institution is engaged in research involving human subjects when its personnel are conducting activities covered by section 219.101(a) of Reference (c) and this Instruction. An institution that is funding, providing equipment, providing access to or information about potential human subjects (but not recruiting human subjects), providing data or specimens (either identifiable or not), or overseeing the research from a regulatory or compliance standpoint is not engaged in the research involving human subjects (but is supporting the research (see "DoD-supported research involving human subjects")).

exempt research involving human subjects. Research involving human subjects where the only involvement of the human subjects in the research will be in one or more of the categories identified in section 219.101(b) of Reference (c).

experimental subject. See "research involving a human being as an experimental subject."

Federal assurance. A written document in which an institution (not an IRB) commits to a Federal department or agency their compliance with the requirements set forth in the Common Rule. Institutions engaged in non-exempt research involving human subjects conducted or supported by the Department of Defense or other Federal departments and agencies that have adopted the Common Rule must have a

Federal assurance approved or accepted by the Federal agency supporting the research. The elements of a Federal assurance are outlined in section 219.103(b) of Reference (c).

fetus. The product of conception from implantation until delivery as defined in subpart B of Reference (h).

HRPO. An individual who is delegated the responsibilities as defined in paragraph (a)(2) of section 252.235-7004 of Reference (n). There may be more than one HRPO in a DoD Component. Some DoD Components may use a different title for the person(s) with the defined responsibilities.

HRPP. An institution's system of interdependent elements that implement policies and practices to protect human subjects involved in research. An HRPP may or may not include a Federal assurance. If the HRPP includes a Federal assurance, it may contain policies and procedures for an IRB belonging to the institution or for a relationship with an IRB external to the institution.

human subject. A living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or obtains identifiable private information as defined in section 219.102(f) of Reference (c). (FDA regulations include a different definition of human subject. With respect to research subject to FDA regulations, the FDA definition in section 50.3(g) of Reference (d) also applies.)

identifiable private information. Defined in section 219.102(f) of Reference (c).

intervention and interaction. An intervention includes both physical procedures by which data are gathered 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. See section 219.102(f) of Reference (c) for more information. Examples include, but are not limited to, a physical procedure, a drug, a manipulation of the human subject or subject's environment, the withholding of an intervention that would have been undertaken if not for the research purpose, or communication such as a survey or interview.

intramural research. Research (see "research involving human subjects") that is conducted by an entity that is part of the Department of Defense.

institution. An organization or entity defined in a Federal assurance or HRPP.

IO. The senior person authorized to establish and responsible to maintain the HRPP for the institution. Responsible for a Federal assurance and the IRBs internal to the institution, if these elements are part of the HRPP.

neonate. Newborns as defined in subpart B of Reference (h).

non-affiliated IRB member. Defined in section 219.107(d) of Reference (c). This member is not connected with the institution(s), as defined in the institution's Federal assurance that is creating or relying on the IRB, or a member of the immediate family of a person who is associated with the institution creating or relying on the IRB.

noncompliance. Failure of a person, group, or institution to act in accordance with this Instruction, its references, or applicable requirements.

non-DoD institution. An entity that is not part of the Department of Defense.

non-exempt research involving human subjects. An activity that meets the definitions of research and human subject but does not meet the criteria where the only involvement of the human subjects in the research are in one or more of the categories identified in section 219.101(b) of Reference (c).

ombudsman. A person who acts as an impartial and objective advocate for human subjects participating in research.

OSD Component. Defined in DoD Instruction 5025.01 (Reference (w)).

OT&E. Defined in section 139(a)(2)(A) of Reference (g).

prisoner. Defined in subpart C of Reference (h). Includes military personnel in either civilian or military custody or detainment.

prisoner representative. An individual member on the IRB who shall have working knowledge of the human subject population to be recruited, a reasonable familiarity with the operations of the prison or confinement facility, and any other legally imposed restrictive conditions involved in the research, and appropriate background and expertise to serve in this capacity.

private information. Defined in section 219.102(f) of Reference (c).

research. Any activity that is a systematic investigation, including RDT&E, designed to develop or contribute to generalizable knowledge as defined in section 219.102(d) of Reference (c).

research involving human subjects. Activities that include both a systematic investigation designed to develop or contribute to generalizable knowledge AND involve a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or identifiable private information. Activities covered by section 219.101(a) of Reference (c) (including exempt research involving human subjects) and this Instruction.

The following activities conducted or supported by the Department of Defense are NOT research involving human subjects:

Activities carried out solely for purposes of diagnosis, treatment, or prevention of injury and disease in Service members and other mission essential personnel under force health protection programs of the Department of Defense, including health surveillance pursuant to section 1074f of Reference (g) and the use of medical products consistent with DoD Instruction 6200.02 (Reference (x)).

Authorized health and medical activities as part of the reasonable practice of medicine or other health professions undertaken for the sole purpose of patient treatment.

Activities performed for the sole purpose of medical quality assurance consistent with section 1102 of Reference (g) and DoDD 6025.13 (Reference (y)).

Activities performed solely for an OT&E project where the activities and project meet the definition of OT&E as defined in section 139(a)(2)(A) of Reference (g).

Activities performed solely for assessing compliance of individuals and organizations with requirements applicable to military, civilian, or contractor personnel or to organizational units, including such activities as occupational drug testing, occupational health and safety reviews, network monitoring, and monitoring for compliance with requirements for protection of classified information.

Activities, including program evaluation, customer satisfaction surveys, user surveys, outcome reviews, and other methods, designed solely to assess the performance of DoD programs where the results of the evaluation are only for the use of Government officials responsible for the operation or oversight of the program being evaluated and are not intended for generalized use beyond such program.

Survey, interview, or surveillance activities and related analyses performed solely for authorized foreign intelligence collection purposes, as authorized by DoDD 5240.01 (Reference (z)).

research involving a human being as an experimental subject. An activity, for research purposes, where there is an intervention or interaction with a living individual for the primary purpose of obtaining data regarding the effect of the intervention or interaction. Research involving a human being as an experimental subject is a subset of research involving human subjects. This definition relates only to the

application of section 980 of Reference (g); it does not affect the application of part 219 of Reference (c). This definition does not include activities that are not considered research involving human subjects, activities that meet the exemption criteria at section 219.101(b) of Reference (c), and research involving the collection or study of existing data, documents, records, or specimens from living individuals.

research monitor. Individuals with expertise consonant with the nature of risk(s) identified within the research protocol, whose role is to protect the safety and well-being of human subjects.

secretarial designee program. Defined in section 108.3 of Reference (c).

serious noncompliance. Failure of a person, group, or institution to act in accordance with this Instruction and its references such that the failure could adversely affect the rights, safety, or welfare of a human subject; place a human subject at increased risk of harm; cause harm to a human subject; affect a human subject's willingness to participate in research; or damage or compromise the scientific integrity of research data.

UPIRTSO. Any incident, experience, or outcome that meets ALL three of the following conditions:

Is unexpected (in terms of nature, severity, or frequency) given the procedures described in the research protocol documents (e.g., the IRB-approved research protocol and informed consent document) and the characteristics of the human subject population being studied.

Is related or possibly related to participation in the research (in this Instruction, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).

Suggests that the research places human subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized, even if no harm has actually occurred.

Appendix D

Biographic Sketches of Committee Members, Consultants, and Staff

COMMITTEE MEMBERS

James F. Childress, PhD (*Chair*), is University Professor and John Allen Hollingsworth Professor of Ethics at the University of Virginia, where he directs the Institute for Practical Ethics and Public Life. At the University of Virginia, he is also Professor of Religious Studies in the College and Graduate School of Arts and Sciences and Professor of Research in Medical Education in the School of Medicine. His research interests include theory and method in biomedical ethics and the role of biomedical ethics in public policy. He is a member of the Institute of Medicine (IOM) and, among other activities, he chairs the Health Sciences Policy Board and previously chaired the IOM Committee on Increasing the Rates of Organ Donation in 2005–2006 and the IOM Planning Committee for Symposium on dual loyalties in military in 2008. Dr. Childress was the Vice Chair of the National Task Force on Organ Transplantation and he also served on the Board of Directors of the United Network for Organ Sharing (UNOS), the UNOS Ethics Committee, the Biomedical Ethics Advisory Committee, the Recombinant DNA Advisory Committee, and several Data and Safety Monitoring Boards for NIH clinical trials. In 1996, President Clinton appointed him to the National Bioethics Advisory Commission. Dr. Childress is also a Fellow of the American Academy of Arts and Sciences, as well as of the Hastings Center, and he has been the Joseph P. Kennedy Sr. Professor of Christian Ethics at the Kennedy Institute of Ethics at Georgetown University. He received his BA from Guilford College, his BD from Yale Divinity School, and his MA and PhD from Yale University.

Alexander M. Capron, LLB, is University Professor at the University of Southern California, where he holds the Scott H. Bice Chair of Healthcare Law, Policy and Ethics in the Gould School of Law and is a Professor of Law and Medicine in the Keck School of Medicine. He serves as the Co-Director of the Pacific Center for Health Policy and Ethics, a campus-wide interdisciplinary research and education center. His areas of interest in research include genetic databanks and biobanks, euthanasia and end-of-life care, conflicts of interest in research and practice, and the work of national ethics commissions. Professor Capron served as the first Director of Ethics, Trade, Human Rights and Health Law at the World Health Organization and was appointed by President Clinton to the National Bioethics Advisory Commission. He has served as President of the American Society of Law Medicine and Ethics, as President of the International Association of Bioethics, and as Chair of the Biomedical Ethics Advisory Committee of the U.S. Congress. Professor Capron chaired the Board of Advisors of the American Board of Internal Medicine and served on the Recombinant DNA Advisory Committee at the National Institutes of Health and on various panels at the Institute of Medicine. He is a Member of the Institute of Medicine and of the American Law Institute, Founding Fellow of the Hastings Center, and a Fellow of the American Association for the Advancement of Science. Professor Capron received a BA from Swarthmore College and an LLB from Yale University, where he was an officer of the *Yale Law Journal*.

Carolyn C. Compton, MD, PhD, is President and CEO of Critical Path Institute. She was formerly Director of the NCI Office of Biorepositories and Biospecimen Research. In addition to human biospecimen science, her research interests include translational studies in colon cancer, pancreatic cancer, and wound healing. Before working at NCI, Dr. Compton was the Strathcona Professor and Chair of Pathology and the Pathologist-in-Chief of McGill University Health Center. Prior to this, she had been a Professor of Pathology at the Harvard Medical School and the Massachusetts General Hospital, where she had been the Director of Gastrointestinal Pathology for many years. Currently, she is an adjunct Professor of Pathology at the Johns Hopkins Medical School. Dr. Compton holds several national and international leadership positions in professional organizations such as the College of American Pathologists, the Cancer and Leukemia Group B, the American Joint Committee on Cancer, and the American Society of Clinical Oncology. She is also a member of the editorial boards of Cancer, Biopreservation and Biobanking, and Clinical Proteomics. She received her BA in Biology at Brin Mawr College, her MD from Harvard Medical School, and PhD in Anatomy from the Harvard Graduate School of Arts and Sciences. She trained in both Anatomic Pathology and Clinical Pathology at Harvard's Brigham and Women's Hospital.

Kelly Edwards, PhD, is Associate Professor in the Department of Bioethics and Humanities at the University of Washington School of Medicine and Adjunct Associate Professor in the Department of Environmental and Occupational Health Sciences. She is also a core faculty for the Institute for Public Health Genetics in the School of Public Health. Dr. Edwards' research interests include community-based research practices, environmental justice, everyday ethics in research practice, feminist and narrative approaches to bioethics, and integrating ethics into training programs and public policy. She is the Co-Chair of the Biobank Working Group for the Clinical Translational Science Awards Key Function Committee in Ethics, Director of the Community Outreach and Ethics Core for the NIEHS-funded Center for Ecogenetics and Environmental Health, and Core Lead for the Ethics of Partnership Core for the NHGRI-funded Center for Genomics and Healthcare Equality. Dr. Edwards was the recipient of funding from the Greenwall Foundation Presidential Award for research resulting in the publication "Testing Justice: A Normative Framework for Genetic Research and Practice" and an edited volume from Oxford University Press (2011): *Achieving Justice in Genomic Translation*. She received an AB in Philosophy from Occidental College, an MA in Medical Ethics, and a PhD in Philosophy of Education from the University of Washington.

Bradley A. Malin, PhD, is the Director of the Health Information Privacy Laboratory (HIPLab), an Associate Professor of Biomedical Informatics, and an Associate Professor of Computer Science at Vanderbilt University. His research focuses on the development and evaluation of data privacy technologies, with an emphasis on personal biomedical information. Malin served as the Organizing Chair of the workshop on the HIPAA Privacy Rule's De-Identification Standard for the HHS Office of Civil Rights in 2010 and for the Electronic Health Information & Privacy Conference in 2009. He was also the Scientific Program Chair of the Privacy Aspects of Data Mining Workshop at the IEEE International Conference on Data Mining. He served on the committees of the ACM International Health Informatics Symposium, the ACM/IEEE Model-Based Trustworthy Health Information Systems Workshop (MOTHIS), and the IEEE Conference on Healthcare Informatics, Imaging, and Systems Biology. In 2010, Malin received the Presidential Early Career Award for Scientists and Engineers (PECASE), the highest honor bestowed by the U.S. government on outstanding scientists and engineers beginning their independent careers. Malin received his BS in Biological Sciences, his MS in Knowledge Discovery and Data Mining, MPhil in Public Policy and Management, and his PhD in Computer Science at Carnegie Mellon University.

Guido Marcucci, MD, is Professor of Medicine, the John B. and Jane T. McCoy Chair in Cancer Research, and the Associate Director of Translational Research at the Ohio State University Comprehensive Cancer Center, where he also works as an attending physician of the Leukemia/Lymphoma and Bone Marrow Transplant Services. He is the Director of the Comprehensive Cancer Center Leukemia Tissue Bank and the co-director of the Cancer and Leukemia Group B (CALGB) Leukemia Tissue Bank. Prior to his current position, Dr. Marcucci was the Associate Professor of Medicine and Molecular Virology, Immunology and Medical Genetics and Pharmaceutics, as well as an NIH T32 Fellow of the Division of Hematology-Oncology at the Comprehensive Cancer Center. His research focuses on tissue banking and development and validation of biomarkers for treatment prediction and prognostication in leukemia, including whole-genome gene and microRNA expression and epigenetic profiling. He chairs the CALGB Leukemia Correlative Science Committee and currently oversees the molecular screening for FLT3 mutations that tests the eligibility of North American AML patients for CALGB 10603, a multi-institutional trial involving also major European academic institutions. Dr. Marcucci serves as member of the AML working group for the NCI Leukemia Steering Committee, and he is member of the ASCO Scientific Program Committee. He earned his MD degree from the Catholic University of Sacred Heart in Rome, Italy, where he graduated summa cum laude. He completed his internal medicine internship and residency at the State University of New York at Buffalo and a 2-year medical oncology fellowship at the Roswell Park Cancer Institution.

Robert L. Reddick, MD, is the Chair and Frank Townsend Professor of Pathology, Past Interim Dean of the Graduate School of Biomedical Sciences, and Director of the Histology and Electron Microscopy Labs at the University of Texas Health Science Center at San Antonio. Prior to his current position, Dr. Reddick was a Professor of Pathology and Chair of the Department of Pathology at the University of North Carolina at Chapel Hill Medical School. His current research projects include studies of mouse models of atherosclerosis and studies of the genetic basis of aging. Dr. Reddick is a member of the United States and Canadian Academy of Pathology and the American Society of Investigative Pathology. He is also a member of the AFIP Scientific Advisory Board and the Texas Society of Pathologists. He served in the United States Army Walter Reed Institute of Dental Research in 1966–1968. Dr. Reddick received his BA in chemistry, his MS in experimental pathology, and his MD at the University of North Carolina at Chapel Hill, where he proceeded to be named the first Kenneth M. Brinkhous, M.D. Distinguished Professor.

Frederick J. Schoen, MD, PhD, is Professor of Pathology and Health Sciences and Technology at Harvard Medical School and Director of Cardiac Pathology and Executive Vice-Chairman in the Department of Pathology at the Brigham and Women's Hospital (BWH). As Executive Vice-Chair, he has leadership responsibility for the allocation of human tissue-based resources for clinical trials and translational research, especially those related to advanced molecular diagnostics. Dr. Schoen is also Co-Director of the BWH Biomedical Research Institute (BRI) Technology in Medicine Initiative and BWH liaison to the Center for Integration of Medicine and Innovative Technology (CIMIT). He is an active teacher/director of courses in pathology, cardiovascular pathology, and biomaterials, medical devices, and tissue engineering at Harvard and MIT, some of which utilize large collections of archived gross pathology specimens. Dr. Schoen's research focuses on cardiovascular pathology, heart valve substitutes, biomaterials, and tissue engineering. In 2009, Dr. Schoen was appointed by Massachusetts Governor Deval Patrick to serve as a member of the Office of the Chief Medical Examiner (OCME) Medico-Legal Commission, which oversees Forensic Pathology activities in the Commonwealth. He also serves or has served on many national and international academic and governmental advisory committees, grant review committees and editorial boards, and is consultant and scientific advisor to numerous medical device companies. Dr. Schoen earned his BSE in Materials and Metallurgical Engineering from the University of Michigan, his PhD in Materials Science from Cornell University, and his MD from the University of Miami School of Medicine.

Michael L. Shelanski, MD, PhD, is the Delafield Professor and Chairman of the Department of Pathology and Cell Biology at Columbia University and the Director of Pathology Service at New York Presbyterian Hospital, Columbia-Presbyterian Center. He is also the Co-Director of the Taub Institute for Research on Alzheimer's Disease and the Aging Brain, the Director of the Alzheimer's Disease Research Center, and the Director of the Medical Scientist Training Program at Columbia University. Dr. Shelanski was the Associate Professor of Neuropathology and Assistant Pathologist and Senior Associate at Harvard Medical School in 1974–1978. His areas of expertise include Cell Biology, Neurobiology of Disease, and Medical Education of physician scientists. His research focuses on the mechanism of memory disruption and synaptic dysfunction in Alzheimer's disease. Dr. Shelanski is on the Board of Directors of the Burke Research Institute and the Board of Directors of the N. Bud Grossman Center for Memory Research and Care. He is the President of the External Advisory Board of Institut du Cerveau et de la Moelle épinière and was the Associate Editor of the *Journal of Neuroscience* in 1999–2004. He is a member of the Institute of Medicine. Dr. Shelanski received his MD and PhD from the University of Chicago.

Robert West, MD, PhD, is Associate Professor of Pathology and Co-Director of the Immunodiagnosis Laboratory at Stanford University Medical Center. He is also a Staff Pathologist for the Palo Alto Veterans Administration. His research focuses on gene expression profiling of soft tissue tumors to examine stromal expression patterns in carcinomas, as well as RNA-seq expression studies of potential therapeutic gene targets in epithelial cancers and soft tissue tumors. Dr. West is an Editorial Board member of the *American Journal of Surgical Pathology*. He is a member of United States and Canadian Association of Pathologists and the American Society for Investigative Pathology. In 1993, Dr. West was a recipient of the Research Award from the American Federation for Clinical Research and was honored with the Rosenblatt Award of Pathology at Washington University in 1999. Dr. West received his BS in Biology at Brown University and his MD and PhD in immunology at Washington University.

Ignacio I. Wistuba, MD, is the Jay and Lori Eisenberg Professor in the Department of Pathology with a joint appointment in the Department of Thoracic/Head and Neck Medical Oncology (THNMO) at The University of Texas MD Anderson Cancer Center. Dr. Wistuba is a surgical and molecular pathologist with a strong record of scientific achievements in the study of lung and gastrointestinal cancers that includes more than 200 peer-reviewed papers and several book chapters. He is the director of the Thoracic Molecular Pathology Laboratory at the MD Anderson Cancer Center and Director of the THNMO Laboratory Research Program. Dr. Wistuba has established a tissue bank resource of lung cancer specimens with annotated clinical data. He also coordinates the distribution of specimens for molecular analysis to several institutional and national research projects including U.S. Department of Defense, NCI-funded studies, United Against Lung Cancer, V Foundation, and Cancer Prevention and Research Institute of Texas (CPRIT). Dr. Wistuba's research interests include the elucidation of the molecular abnormalities involved in the early pathogenesis of lung cancer, the identification of molecular markers for prognosis, the identification of new molecular targets and the validation of biomarkers for targeted-therapy, and the identification of molecular markers associated to metastasis development. A major aspect of Dr. Wistuba's efforts involves overseeing correlative laboratory biomarker studies for lung cancer prevention and therapy trials (MD Anderson BATTLE program) and preclinical studies of animal lung carcinogenesis. Dr. Wistuba earned his MD from the Austral University of Chile and his Pathology degree from the Catholic University of Chile.

Susan M. Wolf, JD, is the McKnight Presidential Professor of Law, Medicine & Public Policy and the Faegre & Benson Professor of Law at the

University of Minnesota, as well as Professor of Medicine. She is also a faculty member at the Center for Bioethics and the founding Chair of the University's Consortium on Law and Values in Health, Environment & the Life Sciences. Much of her research focuses on the return of incidental findings and individual research results to participants, including in large-scale research using biobanks and archives. Ms. Wolf spent several years practicing law at Paul, Weiss, Rifkind, Wharton & Garrison in New York. In 1984, she became a National Endowment for the Humanities (NEH) Fellow and then Associate for Law at The Hastings Center, a research institute in New York specializing in biomedical ethics. She also taught law and medicine at New York University Law School for 6 years as an Adjunct Associate Professor. Ms. Wolf has been a Fellow in the Program in Ethics and the Professions at Harvard University and is currently a Fellow of the American Association for the Advancement of Science (AAAS). She is a member of the Institute of Medicine, past member of the American Society for Bioethics & Humanities (ASBH) Board of Directors and former Chair of the Association of American Law Schools (AALS) Section on Law, Medicine and Health Care. Ms. Wolf has served on a variety of governmental and institutional panels, including the American Bar Association (ABA) Coordinating Group on Bioethics and the Law, American Society for Reproductive Medicine (ASRM) Ethics Committee, and Memorial Sloan-Kettering Cancer Center Ethics Committee. She is Executive Editor of the *Minnesota Journal of Law, Science & Technology*. Ms. Wolf received her AB summa cum laude from Princeton University and her JD from Yale Law School, with graduate work at Harvard University.

CONSULTANTS

Jeffrey T. Mason, PhD, is the Director of the Laboratory of Proteomics and Protein Science at the Washington, DC, Veterans Affairs (VA) Medical Center. Prior to taking his position at the VA, he was the Chairman of the Department of Biophysics at the Armed Forces Institute of Pathology (AFIP). Dr. Mason received his PhD in Physical Biochemistry from the University of Virginia in 1982 and remained at the university as a Research Assistant Professor in the Biochemistry Department before joining the AFIP in 1986. While at the AFIP, Dr. Mason also served as the Administrative Director of the AFIP Magnetic Resonance Imaging Center and Co-Director of the Brain Injury Research Center, a collaborative program between the AFIP and the Defense and Veterans Brain Injury Center. Dr. Mason served as the Chairman of the AFIP Research Committee and was a member of the AFIP Institutional Review Board. He was the Department of Defense representative to the National Advisory General Medical Sciences Council of the National Institutes of Health (NIH) and served on the Council's work-

ing group for the evaluation of the Minority Opportunities in Research (MORE) programs and the Council's Scientific Workforce Development Committee. Dr. Mason has served on numerous NIH and VA Study Sections and VA Advisory Panels, and has served on the editorial boards of several scientific journals. In 2001 and 2011, Dr. Mason received the Department of the Army Commander's Award for Civilian Service and in 2010 he was elected as a Fellow of the Washington Academy of Sciences.

Pilar Ossorio, JD, PhD, is Associate Professor of Law and Bioethics at the University of Wisconsin at Madison, and Program Faculty in the Graduate Program in Population Health at the UW. Prior to taking her position at UW, she was Director of the Genetics Section at the Institute for Ethics at the American Medical Association, and taught as an adjunct faculty member at the University of Chicago Law School. Dr. Ossorio received her PhD in Microbiology and Immunology in 1990 from Stanford University. She went on to complete a postdoctoral fellowship in cell biology at Yale University School of Medicine. Throughout the early 1990s Dr. Ossorio also worked as a consultant for the federal program on the Ethical, Legal, and Social Implications (ELSI) of the Human Genome Project, and in 1994 she took a full time position with the Department of Energy's ELSI program. In 1993 she served on the Ethics Working Group for President Clinton's Health Care Reform Task Force. Dr. Ossorio received her JD from the University of California, Berkeley, School of Law (Boalt Hall) in 1997. She is a fellow of the American Association for the Advancement of Science's (AAAS's), a member of the editorial board of the *American Journal of Bioethics*, chair of an NHGRI advisory group on ethical issues in large scale sequencing, and a member of UW's institutional review board for health sciences research. Dr. Ossorio is a past member of AAAS's Committee on Scientific Freedom and Responsibility, a past member of the National Cancer Policy Board (Institute of Medicine), and has been a member or chair of several working groups on genetics and ethics.

STAFF

David A. Butler, PhD, is Scholar and Director of the Medical Follow-Up Agency at the Institute of Medicine (IOM). He received his BS and MS in engineering from the University of Rochester and his PhD in public-policy analysis from Carnegie Mellon University. Before joining the IOM, Dr. Butler served as an analyst for the U.S. Congress Office of Technology Assessment, was Research Associate in the Department of Environmental Health of the Harvard School of Public Health, and performed research at Harvard's Kennedy School of Government. He has directed several IOM studies on environmental-health and risk-assessment topics, including ones

that produced *Damp Indoor Spaces and Health*, *Clearing the Air: Asthma and Indoor Air Exposures*, *Veterans and Agent Orange: Update 1998* and *Update 2000*, and the series *Characterizing the Exposure of Veterans to Agent Orange and Other Herbicides Used in Vietnam*. Dr. Butler was also a coeditor of *Systems Engineering to Improve Traumatic Brain Injury Care in the Military Health System*.

Lauren N. Savaglio, MS, is Research Associate at the Institute of Medicine. She received her BS in political science and international relations from Arizona State University and her MS in global health from George Mason University (GMU), where her research interests included pesticide use in agriculture and the nutritional status of those infected with HIV/AIDS. She is also an Adjunct Professor in GMU's Department of Global and Community Health and Department of Nutrition, where she teaches public health, nutrition, and environment courses. Before going to the IOM, she practiced as an emergency medical technician at INOVA Fair Oaks Hospital in Virginia, performed HIV/AIDS research for Whitman-Walker Health, and served in the Peace Corps in Togo, West Africa.

Rachel S. Briks, BS, is Program Assistant at the Institute of Medicine Board on the Health of Select Populations. She received her BS in community health from the University of Maryland, College Park, in May 2010. Before joining the IOM, she interned at AED Center on AIDS and Community Health and worked as a clerk for the Centers for Disease Control and Prevention National Center for Health Statistics through the Student Temporary Employment Program (STEP).

Latarsha Carithers, PhD, was a winter 2011 Christine Mirzayan Science and Technology Policy Fellow at the National Academies. She is current Project Manager with the Office of Biorepository and Biospecimen Research at the National Cancer Institute. Dr. Carithers completed her PhD in pathobiology and molecular medicine at Columbia University in February 2011. Her doctoral work was funded by a National Research Service Award from the NIH and focused on developing mouse models of breast cancer to study the biological function of the protein encoded by the breast cancer susceptibility gene 1 (BRCA1). Prior to graduate school, she received her BS from Spelman College and participated in summer biomedical research programs at Morehouse School of Medicine, Stanford University, and the National Cancer Institute. As a Mirzayan Fellow, Dr. Carithers worked with the Institute of Medicine on the Board on the Health of Select Populations where she gained a broad understanding of how science and policy intersect.