ASIP Public Affairs

1996 Combined Pathology Statement

Statement by Pathology Organizations on Use of Human Tissues for Research August 28, 1996

Background

In July 1994 the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) convened a workshop to examine issues of informed consent for genetic research. These issues have been the subject of draft documents issued by the Ethical, Legal and Social Implications Working Group (ELSI) of the National Center for Human Genome Research (NCHGR). The recent "Consensus Statement" by Clayton et al (**JAMA**, 1995;274:1786-1792) was developed from that workshop, though the statement clearly indicates that it "is not the official policy of NIH or CDC." About the same time as this statement was published, proposed legislation (The Genetic Privacy and Nondiscrimination Act of 1995, S. 1416 and H.R. 2690; The Medical Records Confidentiality Act of 1995, S. 1360) and deliberations by a number of professional organizations raised concern among pathologists that research using human tissue may be restricted significantly by changes in concepts of informed consent and confidentiality related to genetic research. The issue of confidentiality has caused particular anxiety in many circles because of the potential consequences to individuals and their families from the misuse of genetic information by employers, health insurance providers, and others.

In January 1996 a group of pathologists representing most of the academic and clinical societies in that discipline participated in an invitational conference convened jointly by the Association of American Medical Colleges (AAMC) and the National Center for Human Genome Research (NCHGR). The meeting's purpose was to bring interested parties together to discuss balancing support for genetics research with legitimate concerns about protecting the rights and privacy of human subjects.

The College of American Pathologists produced a draft document for a broad group of pathology and other medical societies that was discussed at a meeting facilitated by the United States and Canadian Academy of Pathology and the American Society for Investigative Pathology on March 27, 1996. From that meeting, this final statement was prepared.

Principles or position recommendations to be adopted by interested organizations are presented in **Bookman Old Style Bold Type**. The remainder of the text either discusses further or specifically supports the recommendations. A summary of these recommendations is found on pages 9 and 10.

Definition of a Genetic Test/Genetic Research

There is a body of commentary asserting that genetic information is fundamentally different from other medical information. Three major characteristics of genetic information are proposed to account for this difference: power, predictiveness, and implications for individuals other than the patient. Authors of The Genetic Privacy and Nondiscrimination Act(1) are impressed with the pervasive nature of genetic information. Gostin(2) suggests that "Genomic data are qualitatively different from other health data because they are inherently linked to one person." Reilly(3) and Clayton(4) support this notion in acknowledging that genetic data may provide information about more than just the individual from whom

the data are derived.

Persuaded by these arguments, a number of jurisdictions (using terms such as genetic information,(1) genetic characteristics(5) , test of a person's genetic characteristics(6) , genetic testing(7) , and genetic screening or testing(8)) and organizations (9) (using similar terms) have developed definitions of varying breadth. In a sense, virtually all medical information and tests, directly or indirectly, derive from genes or gene products.

It is unlikely that an acceptable universal definition can be achieved. Moreover, the issue is not so much the definition of genetic tests, but, rather the inappropriate uses and misuses of information derived from genetic tests and research. There are, however, potential differences in the extent of harm that may result from the misuse of different kinds of medical information and, thus, there is a need for an operative definition of genetic information. Identification of genetic information as information used for the purpose of genetic counseling adequately distinguishes this information and permits regulations governing its use to be broadly and appropriately established.

Genetic information should be defined operatively as information used for the purpose of genetic counseling. Genetic tests should be defined as tests which provide information used for the purpose of genetic counseling. Genetic information should be subject to the same principles of privacy, confidentiality, and security as non-genetic medical information.(10)

It is important to realize that information developed in the course of genetic research, like that developed in the course of research generally, is not valid patient information for use in genetic counseling and therefore should not be considered genetic information as that term is used in statutory language (see discussion below, pages 6 - 8).

Confidentiality

The three ethical principles of the Belmont Report (11) **(respect for persons, beneficence, and justice) are the ethical foundation of practice for pathologists and guide decisions involving how tissues will be used.**

Information in the medical record is legally recognized as private and confidential. In certain uncommon cases, disclosure of this otherwise private information is permitted or even mandated by law for the public good (for example, in Tumor Registries). The same confidentiality considerations apply to patient information obtained during the course of research and investigation, even though the information is not a part of the medical record.

"There is no controversy among health care workers and researchers regarding the privacy(12) rights of patients and the obligation to safeguard confidentiality. There is also no disagreement with the fact that confidential information has been and will continue to be at risk for inappropriate disclosure. The operational challenge is, thus, one of security.(13) Since patient information of any kind is presumed to be confidential unless disclosure is expressly permitted by the patient (or the patient's legal representative) or is required by law, organizations and individuals must operate under rules of conduct and use physical systems that reasonably protect this information from inappropriate or unregulated disclosure.

Specimens removed from patients (referred to also as tissues) and sent to the pathology laboratory for examination become part of the patient's permanent medical record, either through processing into durable materials (e.g. slides, blocks, and reports) or through maintenance in some storage form (e.g. preserved in formalin; frozen; tissue culture). The laboratory that provides the primary diagnostic analysis of specimens is responsible for the maintenance and integrity of this part of the medical record. Within this maintenance responsibility is a parallel responsibility to provide appropriate material for research studies that have received institutional (i.e. Institutional Review Board [IRB]) approval.

The pathologist has an important responsibility both to meet the needs for optimal patient care and to contribute to advances in medical and scientific knowledge. The responsibilities are embodied in the concept of the pathologist as steward of patient material. Implicit in the pathologist's stewardship is the duty to maintain the confidentiality(14) of the information contained in the patient's medical record. This duty derives from millennia of medical tradition as well as from legislation and case law. What challenges this duty in our current time is both social and technological. The number of individuals and institutions with legitimate access to medical records is large and information technology has placed more and more components of the medical record in electronic form, adding new dimensions to the need for security of information.

Pathology departments must have a written policy about confidentiality and privacy rights. The policy must include specific procedures for access to the medical record; confirmation of IRB approval of research involving tissues when appropriate; a description of safeguards to prevent unauthorized access; procedures for the release of information; methods of assuring that everyone with access or who may gain legitimate access embraces the need for privacy, confidentiality, and security of patient information; procedures specific for records kept in electronic form; and procedures that specifically apply to the release of information for research.

Each institution that controls or uses specimens must have and enforce a written policy covering confidentiality. For issues involving research, this policy should be approved by the Institutional Review Board [IRB]. Confidentiality and security policies and procedures which involve compartmentalization of information should be promoted (15)

Where institutions and IRBs approve confidentiality policies and regard them as providing sufficient protections for patients from improper disclosure of information in the medical record, such approval should be regarded as adequate evidence of the ability to secure medical record information for all clinical and research applications.

Anonymized existing or prospective specimens should be, for research purposes, treated as specimens that were *never* linked to a source as defined by 45CFR46.

Specimens may be anonymized(16) or otherwise protected either by a source institution or by an independent tissue bank with IRB and institutionally approved confidentiality and security policies.

Current Federal regulations [45 CFR 46.101 (b)(4)] specify that existing specimens are exempt from IRB review if the information recorded by the investigator cannot be linked to the subject by anyone. Further,

regulations specify that specimens have to be existing at the time a study is proposed to qualify for exemption from 45 CFR 46.101(b)(4). The interpretation of these regulations should be reconsidered to permit anonymized specimens, whether existing or collected concurrently, to be exempt from IRB review.

Where specimens or data are identifiable or linked, researchers must agree to prohibitions restricting them from contacting patients who are the sources of specimens used in research or their families. The prohibition of patient contact does not preclude obtaining information from Tumor Registries. (17)

Under extraordinary circumstances when contact with the subject or source might be considered, researchers must make requests for contact through the appropriate IRB. If the IRB approves contact, the IRB will determine the method of contact.

Stewards of specimens should ensure that researchers have IRB-approved research proposals and have signed nondisclosure statements before releasing specimens to researchers. Publications and presentations must not permit the identification of individual sources of research specimens, without specific consent of the patient.

The central concept of the above recommendations is to preclude patient information from being inappropriately or inadvertently released to the patient's detriment. While the linkage of specimens to sources is possible with coding, source institutions and tissue banks must have methods approved by an IRB as properly protective of sources' privacy rights and confidentiality that preclude release of information. This specific point is addressed in the recommendation on page 5.

In the case of identifiable specimens, it must not be possible, without the patient's specific consent and IRB approval, either for research results to become part of the medical record or for patients to become aware of the results of research performed on their specimens. Information developed in the course of research is not generally regarded as valid for the clinical care of a patient. For this reason, research results should not become part of the medical record and physicians should not base their care of patients upon the results of research.

Occasionally specific examples are cited of physicians violating patient confidentiality during therapy or research. These are clear violations of medical ethics and cannot be tolerated by the medical community. There is no way to prevent, absolutely, such rare instances of abuse. Such abuse in research is best dealt with via sanctions against the offending individuals and institutions.

Research Uses

Existing statutory and case law recognizes the autonomy of patients' decisions over their bodies as well as related medical information. (18) Current regulations promulgated by the Office for Protection from Research Risks (OPRR) call for informed consent for research unless exceptions apply. The regulations apply to living individuals and exempt anonymous archived tissues from IRB review. They also permit more streamlined procedures when risks to the patient are minimal and obtaining consent is impractical.

The informed consent doctrine, as currently formulated, derives from notions of informed consent for

therapeutic intervention and for clinical research involving procedures performed on the subject.(19), (20), (21), (22) The patient, not the physician, has the final say over what will or will not be done with his or her body and hence over therapeutic options. The patient should then know the potential benefits and risks before making an informed decision over which, if any, therapeutic options to choose. The physician then bears the responsibility of bringing the pertinent information to the patient.

Although this informed consent doctrine is generally applied to research with human tissues, the interests of the patient are fundamentally different from those in which therapeutic intervention is at issue. The interests of a patient in the results of research are generally not specific to the individual. Usually, in fact almost always, a single research project does not establish irrefutable scientific fact and the results of a single investigation have no applicability to an individual patient. Disclosure of a single research project's results to a patient is at best not beneficial, and at worst could therefore be misleading or even harmful. Nonetheless, the societal interest in accumulated research findings is great. In the case of research on medically or surgically removed tissues, autopsy tissues and body fluids (tissue research), research projects do not immediately benefit the patient's health or alter treatment. To give a description of each and every research protocol which might be performed on a patient's tissue is an unreasonable burden for the patient and the researcher. The current informed consent doctrine, which requires detailed information about benefits and risks, is not well suited to research that does not involve patient therapy. General consent for use of the tissue in research should be sufficient. Society has a strong interest in research involving the use of human tissue which may be hampered by well-intended but intrusive regulations.

Some advocates recently have suggested that genetic testing involves greater risks from psychological and economic harms and therefore they recommend increased informed consent requirements.(23)Â However, the rules of privacy, confidentiality and security should be equally applied to all patient information. Genetic information, like other research information, would be adequately protected if the recommendations of this document are followed.

Citing genetic research in particular, Clayton (4) has suggested that tissues associated with general demographic data (e.g. sex, age, race) that are anonymous with respect to an individual subject's identity may not be anonymous with respect to classes of subjects (so- called communities of interest). Thus, research can develop information on all Caucasians or all females or all septuagenarians that may damage or otherwise put at risk individual members of the class. The risk here is primarily social (stigmatization; insurance discrimination and so on) and should be addressed through social mechanisms (law, regulation, code). Moreover, it is unrealistic to ask patients to foresee all adverse societal consequences of research as part of the informed consent process.

Similarly, the application of OPRR informed consent regulations to only living persons has been challenged with respect to genetic information. (15) Because genetic information about a deceased individual can provide information about individuals still living, it is argued, related survivors should be permitted to consent to research using the deceased relative's tissues. However, if safeguards are in place to prevent unauthorized disclosure of medical information, this argument becomes substantially less cogent.

Research on human specimens makes use of specimens collected in three different ways. In the case of

prospective collection, researchers use specimens collected specifically for research or as part of a research protocol. Informed consent must be obtained from the patient under OPRR regulations, and a patient's identity is clearly known to the researchers. Concurrent collection is preserving portions of therapeutic or diagnostic specimens left over after all the work necessary for the patient's care has been completed. In most laboratories this represents material that would otherwise be destroyed after a relatively short interval (days to weeks). Retrospective collection is the use of material already archived from specimens originally obtained for diagnostic and therapeutic purposes. The latter two methods of collection can produce specimens that are free of, or can be made free of patient direct identifiers (i.e. anonymized or linkable), and therefore may be appropriately used for research under a general consent.

For tissue research general consent for research should be sufficient. General consent forms should be worded broadly and include statements that tissues may be used in research approved by Institutional Review Boards and for educational purposes. Separate patient consent for each research study on archived or remnant tissues should not be required.

General consent forms are designed to meet consent requirements for research where specific consent is either not required or waived [45CFR 46.116(c) and (d)]. IRBs must be aware of confidentiality policies in organizations conducting or contributing to research and must agree that such policies adequately protect patients from inappropriate disclosure of protected information (i.e. minimal risk).

There is great value in previously collected specimens that are not associated with current consent procedures. Researchers should not be prevented from using this important resource. Therefore, use of these archival tissue collections should fall under the guidelines proposed herein, even if no general consent initially was obtained. General consent must be obtained for research and educational uses of tissues collected after January 1, 1998.

Where identity can be determined by the institution or the tissue bank (i.e. identity is linkable), research using the specimen should be permitted under the general consent procedure(24) when IRB-approved confidentiality and security policies are operational.

Other Considerations

The distinction between use of tissue for diagnosis and research is often unclear. In some cases, particular examinations, tests, and procedures may be considered investigational although they provide insight into the patient's condition. Indeed, pathologists receive the tissue and or fluids in the first place to perform diagnostic measures for the patient. This implies the use of professional judgment in the handling and work-up of the specimen.

Consent forms should also include consent for use of tissues in education.

Excess/residual tissue and/or fluids should be available for use as clinical controls and for validating new tests. For instance, plasma from a clinical blood test may be used in the clinical laboratory to insure the quality of an instrumental analysis.

In some cases, pathologists, especially forensic pathologists, must retain tissues and/or fluids for medical-legal purposes.

In all non-diagnostic uses, confidentiality beyond the immediate use must be maintained, except for medical examiners in which the information is made public by law.

Conclusion

Pathologists, and other medical specialists, as recipients of tissue and medical specimens, consider themselves stewards of patient tissues whose duty it is to protect the best interests of both the individual patient and the public. The stewardship of slides, blocks and other materials includes providing, under appropriate circumstances, patient materials for research. The decision to do that should be based on the specific (i.e. direct patient care) and general (i.e. furthering medical knowledge) interests of the patient and of society. The same principles of responsibility should apply to all medical professionals who receive and use specimens. This document proposes specific recommendations whereby both interests can be fostered safely, ethically, and reasonably.

The following is a summary of the specific recommendations given above.

1. Genetic information should be defined operatively as information used for the purpose of genetic counseling. Genetic Tests should be defined as tests which provide information used for the purpose of genetic counseling. Genetic information should be subject to the same principles of privacy, confidentiality, and security as non-genetic medical information.

2. The three ethical principles of the Belmont Report (respect for persons, beneficence, and justice) are the ethical foundation of practice for pathologists and guide decisions involving how tissues will be used.

3. Pathology departments must have a written policy about confidentiality and privacy rights. The policy must include specific procedures for access to the medical record; confirmation of IRB approval of research involving tissues when appropriate; a description of safeguards to prevent unauthorized access; procedures for the release of information; methods of assuring that everyone with access or who may gain legitimate access embraces the need for privacy, confidentiality, and security of patient information; procedures specific for records kept in electronic form; and procedures that specifically apply to the release of information for research.

4. Where institutions and IRBs approve confidentiality policies and regard them as providing sufficient protections for patients from improper disclosure of information in the medical record, such approval should be regarded as adequate evidence of the ability to secure medical record information for all clinical and research applications.

5. Anonymized existing or prospective specimens should be, for research purposes, treated as specimens that were **never** linked to a source as defined by 45CFR46.

6. Where specimens or data are identifiable or linked, researchers must agree to prohibitions restricting them from contacting patients who are the sources of specimens used in research or their families. The

prohibition of patient contact does not preclude obtaining information from tumor registries.

7. Stewards of specimens should ensure that researchers have IRB- approved research proposals and have signed nondisclosure statements before releasing specimens to researchers. Publications and presentations must not permit the identification of individual sources of research specimens, without specific consent of the patient.

8. For tissue research, general consent for research should be sufficient. General consent forms should be worded broadly and include statements that tissues may be used in research approved by Institutional Review Boards and for educational purposes. Separate patient consent for each research study on archived or remnant tissues should not be required.

9. Where identity can be determined by the institution or the tissue bank (i.e. identity is linkable), research using the specimen should be permitted under the general consent procedure when IRB-approved confidentiality and security policies are operational.

Pathology societies that have approved this document:
Academy for Clinical Laboratory Physicians and Scientists
American Academy of Oral and Maxillofacial Pathology
American Board of Oral and Maxillofacial Pathology
American Association of Neuropathologists
American Registry of Pathology
American Society for Investigative Pathology
American Society of Clinical Pathologists
American Society of Cytopathology
Arthur Purdy Stout Society of Surgical Pathologists
Association for Molecular Pathology
Association of Directors of Anatomic and Surgical Pathology
Association of Pathology Chairs
College of American Pathologists
Society for Toxicologic Pathology
United States and Canadian Academy of Pathology
Universities Associated for Research and Education in Pathology

1. S. 1416, The Genetic Privacy and Nondiscrimination Act of 1995, 15 November 1995.

2. Gostin, LO: Genetic Privacy. **J Law Med Ethics** 1995; 23:320-330.Â

3. Reilly, PR: Panel Comment: The Impact of the Genetic Privacy Act on Medicine. **J Law Med Ethics** 1995; 23:378-381.

4. Clayton, EW: Panel Comment: Why the Use of Anonymous Samples for Research Matters. **J Law Med Ethics** 1995; 23:375-377.

5. California Health and Safety Code 1374.7(c) (1994).

6. California Insurance Code 10147(e) (1994).

7. New Hampshire Revised Statutes Annotated, chapter 141- H:1(IV) (1995).

8. Ohio Revised Code 1742.42, 1742.43; 3901.49; 3901.491; 3901.50; 3901.501 (1993).

9. e.g. The National Academy of Sciences/National Research Council.

10. This definition focuses on validated medical information that is important enough clinically to warrant counseling patients and their family members as to risks of future diseases.

11. **The Belmont Report**, The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, Department of Health and Human Services, April 18, 1979.

12. Privacy includes both the notion of respect for personal autonomy (see **Research Uses**) and an interest in freedom from uninvited and unwarranted intrusions. It implies freedom to live as one desires in one's own space. A constitutional right to privacy has been applied in certain limited contexts.

13. Security is the notion of unlikelihood of undesired disclosure or leak of confidential information, intentional or not.

14. Confidentiality is the notion that information released will not be freely disseminated. It implies that the information will be held in confidence - a trust, if not a fiduciary duty, to not disclose the information to others without the person's consent, actual or implied, or otherwise in his/her interest.

15. An example of compartmentalization is maintaining patient identity and clinical information separate from research data through the use of coding.

16. The term "anonymized" has been used in place of "rendered anonymous". The literature uses four terms: anonymous where no identification was ever attached connecting the specimen to a person; anonymized where linkages have been irreversibly removed, rendering the specimen equivalent to an anonymous specimen; linked or identifiable where the specimen is unidentified for research purposes, but can be linked to the source through use of a code; and identified where a specific patient identifier is included with the specimen.

17. 42 USC 241 et seq. (Title III of the Public Health Service Act) and PL 102-515 (Cancer Registry Amendment Act)

18. There is no corpus of statutory or case law that clearly defines physical ownership of removed specimens. Most general surgical consents permit institutions and individuals to use removed tissue for education and research in addition to use for the direct care of the patient. It is equally unclear if a patient gives his or her tissue specifically for research whether or not the tissue becomes the property of those to

whom it is given. Human tissue cannot be legally sold, but it can be given away. In fact, the Uniform Anatomical Gift Act specifically permits the gift of tissue even at death.

Pathologists, in the course of ordinary medical practice, substantially transform specimens from their original state. The durable materials thus produced (slides and blocks) can fairly be claimed as the property of the entity which produced them. Even in this framework, the hospital or pathologist may be reasonably considered to hold the tissue in trust, primarily for the patient, but also for society at large.

19. Faden RR and Beauchamp TL: **A History and Theory of Informed Consent.** Oxford University Press, New York, 1986.

20. Lederer SE: **Subjected to Science: Human Experimentation in America Before the Second World War**. Johns Hopkins University Press, Baltimore, 1995.

21. Levine RJ: **Ethics and Regulation of Clinical Research**, 2nd edition, Urban & Schwarzenberg, Inc., Baltimore, 1986.

22. Meldelson D: Historical evolution and modern implications of the concepts of consent to, and refusal of, medical treatment in the law of trespass. **J Legal Med** 1996; 17:1-71

23. Clayton EW, Steinberg KK, Khoury MJ et al: Informed consent for genetic research on stored tissue samples. **JAMA** 1995;274: 1786-1792.

24. Consent forms should be worded so that patients may either consent or decline consent (e.g. "I **CONSENT** or I**DECLINE TO CONSENT** to the use of my tissues for research").