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Use of human specimens in research: the evolving United States regulatory, policy, and scientific landscape

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Abstract

The use of human specimens in research has contributed to significant scientific and medical advancements. However, the development of sophisticated whole genome and informatics technologies and the increase in specimen and data sharing have raised new questions about the identifiability of specimens and the protection of participants in human specimen research.

In the US, new regulations and policies are being considered to address these changes. This review discusses the current and proposed regulations as they apply to specimen research, as well as relevant policy discussions. It summarizes the ways that researchers and other stakeholders can provide their input to these discussions and policy development efforts. Input from all the stakeholders in specimen research will be essential for the development of policies that facilitate such research while at the same time protecting the rights and welfare of research participants.

Keywords

biorepositories; ethical issues; human specimen research; human subjects protection regulations; personalized medicine; research policy

Human specimens and human specimen biorepositories play a key role in scientific and medical advancement, and will continue to play a critical role in the future, particularly

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Conflicts of interest: W.E.G. operates tumor banks as part of the Breast, Pancreatic and Cervical SPOREs at the University of Alabama at Birmingham and the Pulmonary Hypertension Breakthrough Initiative and prospective tissue repositories as part of the Cooperative Human Tissue Network and the Comprehensive Cancer Center and is a member of ISBER. He is also a member of the ethics group of the U54 grant, Morehouse School of Medicine/Tuskegee University/University of Alabama at Birmingham Comprehensive Cancer Center Partnership.

towards efforts to develop individualized medicine and targeted therapies. However, their widespread use raises a number of challenges, particularly in relation to the current regulatory, policy and scientific landscape. Discussed in this paper is the potential importance of human specimens and human specimen biorepositories to research and the current and evolving regulatory, policy and scientific landscape in the US as it applies to such research.

Introduction

Importance of Human Specimens in Research

The use of human specimens in biomedical research has been critical to the development of current medical care. Although animal cell lines and specimens are useful in most research, molecular features of animal specimens frequently are different from those of matching human specimens just as animal diseases are, in general, different from human diseases. For example, it was recently reported that mice are a poor model for studying the genetics of human inflammatory disease.[1,2] The importance of archival clinical specimens in support of biomedical advances has been elegantly described by Korn as the “intellectual foundation of modern medicine”.[3] Indeed, since this publication, significant additional advances in medical care have been based on research using human specimens. Included are many major advances that have not only changed therapies of diseases, but also have resulted in new concepts of human biology.

Therapeutic advances and approaches to medical care now are beginning to target unique molecular features of pathways that have been identified in human specimens as important to the development of specific diseases. The potential uses of molecular targeting have resulted in approaches to treat the unique features of an individual patient's disease (e.g., personalized or individualized medical care). These approaches will require even greater use of human specimens both in medical research and to aid in clinical decisions.[4.5.6,7]

Specific targeting of features of molecular pathways has resulted in novel molecular directed therapies for once untreatable diseases, especially targeting specific molecules in different types of cancer. For example, the cellular surface receptor HER-2, was initially identified using archival human tissues and reported to be important in causing an aggressive subtype of breast cancer. Studies on human tissue led to the development of approaches to therapy that specifically target the HER-2 receptor.[8] Thus, a once poor prognostic feature of one type of breast cancer was changed by an effective strategy of molecular targeting to a good prognostic feature.[9,10,11] In addition, HER-2 targeted therapies are now being expanded to treat other forms of cancer, such as gastric cancer.[12]

Recent advances using human tissue have expanded and changed our concepts of human cellular biology resulting in potential new approaches to the treatment of a wide variety of diseases. For example, it was discovered that some messenger RNAs (mRNAs), which are the precursor molecules that permit the production of all proteins, were regulated in human and other cells by a newly identified category of small molecule, microRNA. [13] Up regulation or down regulation of specific proteins may be involved in the development, progression, or severity of specific diseases; the level of these proteins frequently are

affected by microRNAs.[13,14] Significantly, microRNAs are potential targets for specific therapies and the production of these proteins may be modulated by targeted microRNAs.[15,16] Several other paradigm-changing discoveries based on the use of human tissues also have altered our concepts of normal biology as well as causes of disease.[5,17] Given the demonstrated importance of human specimens to biomedical research and their role in developing approaches to targeted medicine, demand for human specimens has increased dramatically over the past several decades.[18] A number of types of human specimen biorepositories have been developed to help meet this demand.

Surgical Specimen Biorepositories

Because only a small proportion of tissues removed surgically are required for diagnosis, remnant tissues can be used to support biomedical research by constructing additional paraffin blocks for research or providing the remnant tissues as frozen and/or fresh viable tissue. The tissue required for diagnosis is embedded in paraffin and in addition to providing diagnostic information, also can be used in future research. Other innovative approaches to obtain samples for research may be applied to specimens that are too small or are in situ lesions; these include obtaining nitrocellulose blots as tissue aliquots.[19] These aliquots of residual surgical specimens may be stored for future research in various types of biorepositories.

The Cooperative Human Tissue Network (CHTN) is a prospective biorepository model in which tissues are collected specifically to meet investigator requests.[20] Alternatively, tissues can be banked for future use in research biorepositories following a standard operating procedure (SOP); such a banking model is typically utilized by Specialized Programs in Research Excellence (SPORE)[21] and the National Cancer Institute Clinical Cooperative Group Banks.[22] Each of these two models, prospective and banking, has advantages and disadvantages. The prospective model has the advantage of providing specimens which exactly meet an investigator's needs and is a model in which generally all specimens are utilized; however, neither specimens nor clinical outcomes are immediately available from prospective biorepositories because both must be collected over time. The banking model typically has multiple specimens immediately available as well as clinical outcomes for the specimens provided. The banking model is most appropriate for cases in which it is necessary to collect clinical or longitudinal data and the participants are being followed over time. The disadvantages to the banking model are that the SOPs that are used in collecting and processing specimens may not meet investigator needs and requirements, especially for use with future technologies that may not yet be developed, and that many specimens may never be used. The underutilization of specimens in biobanks has recently been proposed as an important ethical issue.[23] While both types of biorepositories are useful models, careful attention is needed in the design of the biorepository to ensure that specimens are optimally utilized. [6,17]

While human specimens and human specimen biorepositories continue to be important to scientific and medical advances, the availability of large numbers of specimens and extensive associated demographic and clinical data, the powerful new genetic and genomic technologies such as whole genome sequencing and the enormous and rapid advances in

informatics, raise a number of evolving ethical, legal and social issues related to the use of human specimens. Discussed below are the current US regulations and policies as they relate to specimen research, including human specimen biorepositories, and the evolving scientific and policy landscape in the US.

The Current US Regulatory, Policy and Scientific Landscape

Federal Regulations That May Apply to Human Specimen Research

In the US, there are three important federal regulations that may apply to the use of human tissue and associated data in research, the "Common Rule," promulgated by the Department of Health and Human Services (HHS) and codified at Code of Federal Regulations (CFR) title 45 part 46, Subpart A[24], the US Food and Drug Administration (FDA) human subjects regulations at 21 CFR part 50[25], 56[26], and 812[27]and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (45 CFR part 160 and Subparts A and E of part 164)[28] and Security Rule (45 CFR part 160 and Subparts A and C of part 164).[28] Each of these regulations is discussed in further detail below.

The Common Rule

The Common Rule has been codified by 15 US federal departments and agencies and applies to all research involving human subjects that is "conducted, supported or otherwise subject to regulation by any federal department or agency which takes appropriate administrative action to make this policy applicable to such research." Each of these 15 federal department or agencies has a codification of the Common Rule which is equivalent to 45 CFR 46, Subpart A[1]. The Rule includes requirements for Institutional Review Board (IRB) review and informed consent for human subjects research.

The Common Rule defines "research" as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Sometimes the definition is challenging to interpret as the difference between "research" and uses of patient specimens and associated data in education or clinically relevant activities becomes blurred.[29] Therefore, researchers and pathologists should consult their local IRB for guidance before beginning activities involving human specimens.

The Common Rule defines a human subject as a living individual about whom an investigator conducting research obtains either data through intervention or interaction with the individual; or identifiable private information [45 CFR 46.102(f)]. Therefore, the Common Rule would apply when specimens or associated information are obtained for research from a living individual through intervention or interaction with the individual, such as a blood draw or cheek swab, or when residual specimens taken during the course of routine care are collected prospectively for research purposes. It would also apply when identifiable specimens are used for research (i.e., when the identity of the subject is or may readily be ascertained by the investigator or associated with the specimens).

[1]Although they have not issued the Common Rule in regulations, three other agencies comply with the Rule. For a complete list of agencies that follow the Common Rule, see http://www.hhs.gov/ohrp/humansubjects/commonrule/.

Furthermore, in order for research involving humans specimens to be considered human subjects research under the Common Rule, the individuals must be living. Thus, according to the Common Rule, as currently written, research involving material from deceased individuals (e.g. autopsy material) or the use of specimens that are completely anonymous (i.e. a link to subject identity does not exist), would not be subject to the Common Rule, although state and local regulations and policies may apply.

Under certain circumstances, research using coded specimens, that is, specimens for which identifying information has been replaced with a code, may not be considered human subjects research if certain conditions have been met[30]. The creation of a human specimen biorepository for research purposes is considered to be a research activity and would be considered to involve human subjects research if specimens and/or associated data are being collected through interaction or intervention with a living individual or if the human specimen repository includes the collection, distribution or use of identifiable private information.

For research using human specimens that is considered human subjects research, the Common Rule generally requires review by an Institutional Review Board (IRB) and informed consent from the subject/participant. However, research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens may be exempt from these requirements 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. [45 CFR 46.101(b)(4)].

Furthermore, the requirement for informed consent for use of human specimens may be waived by the IRB when all of the following conditions are met [45 CFR 46.116(d)]:

- 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
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.[2]

It is important to note that these requirements are based on the Common Rule as currently written. As discussed later in this paper, changes to these requirements are under consideration.[31]

The FDA Human Subjects Regulations

The second set of significant US federal regulations that may apply to the collection and use of human specimens for research are the Food and Drug Administration (FDA) regulations, 21 CFR 50[25], 56[26], and 812[27]. The FDA regulations apply to all clinical investigations

[2]This requirement was originally intended to apply to ‘deception research,’and generally believed to rarely, if ever, apply to research on human specimens.

regulated by the FDA under sections 505(i) and 520(g) of the Federal Food, Drug, and Cosmetic Act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the FDA. Among other products included within the scope are drugs for human use, medical devices for human use and biological products for human use. 21 CFR 50 covers informed consent requirements and 21 CFR 56 covers IRB review requirements. 21 CFR 812.2(a) applies to all clinical investigations of devices to determine safety and effectiveness unless the device investigation is exempt under 812.2(c).

The FDA regulations define a human subject differently than the Common Rule. The FDA regulations at 21 CFR 50.3(g) and 56.102(e) define a human subject as an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. (See 21 CFR 50.3(g) and 56.102(e)). The device regulations define a subject as an individual on whom or on whose specimen an investigational device is used. (See 21 CFR part 812).

Unlike the Common Rule, the FDA regulations do not require the research participant/ subject to be identifiable for the regulations to apply. Furthermore, unlike the Common Rule, the FDA exemptions to the requirement for informed consent are limited to emergency, life threatening situations, and military operations. This may pose challenges for some studies involving human specimens (e.g. the development of assays using archived specimens when it is difficult or impossible to contact the individual to obtain informed consent). In order to address this issue, the FDA issued guidance stipulating that the FDA would exercise enforcement discretion with regard to requiring informed consent when leftover human specimens that are not individually identifiable are used in FDA-regulated in-vitro diagnostic investigations, if certain conditions specified in the guidance are met.[32]

The Health Insurance Portability and Accountability Act, Privacy and Security Rules

The third major set of US federal regulations that may be relevant to some human specimen research is the Health Insurance Portability and Accountability Act (HIPAA) Privacy and Security Rules.[28] The Privacy Rule regulates the uses and disclosures of individually identifiable health information by “covered entities” (health care providers, health plans, and health care clearinghouses). While the Privacy Rule does not apply to the use of human specimens per se, it may apply to uses and disclosures of the health information that may be associated with the specimens. The Privacy Rule generally requires patient authorization for uses and disclosures of health information that is individually identifiable. [See 45 CFR part 164.508]. Authorization is a similar but not identical concept to informed consent. Informed consent is the process by which subjects are informed about the risks and benefits of participating in research whereas authorization is solely a permission to allow researchers to use or disclose defined protected health information.

The ways in which protected health information may be used and disclosed for research is summarized in Table 1. Patient authorization is not required if the information to be used or disclosed is de-identified according to the Privacy Rule's requirements at Section 164.514 (See Table 2) or a “Limited Data Set” (See Table 3) pursuant to a Data Use Agreement that meets the requirements of the Rule [See 45 CFR 164.514(e)]. Patient authorization for the

uses and disclosures of protected health information is also not required if an IRB has waived the requirement for authorization according to criteria stipulated in the Rule, for purposes “preparatory to research” or for research solely on decedents if certain representations are made to the IRB. The US Department of Health and Human Services has provided additional guidance on how the Privacy Rule applies to research[33], as well as guidance on de-identification.[34] The HIPAA Security Rule establishes national standards to protect individuals' electronic personal health information that is created, received, used, or maintained by covered entities.[28] The Security Rule (45 CFR Part 160 and Subparts A and C of Part 164) includes requirements for appropriate administrative, physical and technical safeguards to ensure the confidentiality, integrity, and security of electronic protected health information. These requirements may apply to research databases, such as those that may be associated with specimen collections, including those of individual investigators.

Other Applicable Regulations and Policies

In addition to the aforementioned US federal regulations, there may be state and local regulations or funding agency policies that may apply to human specimen research. For example, some states have their own human subjects regulations (e.g. New York, Maryland, Virginia, and California).[35] In addition, state laws concerning genetic testing, genetic or medical record privacy also may apply and these may vary considerably from state to state.[35] Certain human specimen research funded by the National Institutes of Health (NIH) may be subject to resource and data sharing policies, such as the NIH policy on genome-wide association studies. This policy calls for investigators funded by the NIH for genome-wide association studies to share de-identified genotypic and phenotypic data through a centralized NIH data repository.[36]

In other countries, there may be different ethical and privacy regulations and policies that may apply to the use of human specimens and associated data in research.[37]. These regulations and policies, especially in the European Union, are evolving rapidly and need to be considered when international collaborations are involved in research involving human specimens and/or data.

The Evolving Legal and Ethical Landscape Related to Human Specimen Research

Some of the aforementioned US regulations governing human subjects research were written a decade or two ago. Since that time, the research environment has evolved dramatically from research conducted in single laboratories to national and international multi-site collaborations between academia, government, industry and non-profit entities. Specimen and data sharing has also increased significantly, with many funding agencies now expecting broad sharing of research tools and data. Furthermore, the advent of affordable whole genome technologies, the increase in research databases, and implementation of electronic health records have raised new questions about privacy. At the same time, advances in technology are raising new questions regarding the identifiability of specimens and genomic data.

A number of cases in the media, both in the US and abroad have underscored some of the ethical, legal and social issues related to the use of human specimens in research. The Alder Hey organs scandal in the UK, involved the unauthorized removal, retention, and disposal of human tissue, including children's organs, from 1988 to 1995, and led to the Human Tissue Act 2004, and the creation of the Human Tissue Authority.[38,39] A number of cases in the US, have also highlighted important ethical issues related to the use of human specimens for research. Issues related to informed consent and the commercial use of tissue were highlighted in a recent best seller[40] concerning Henrietta Lacks, the daughter of a poor African- American tobacco farmer whose specimens were obtained without her knowledge or consent and used to develop cell lines which have been shared broadly and sold throughout the world. More recently, the posting of Henrietta Lacks' genomic sequence on a publicly available website without the consent of her family led to its removal.[41,42] The retention of blood spots obtained from newborn children for research without parental consent led to a lawsuit in Texas resulting in the destruction of approximately 5 million samples.[43,44] Other cases such as the Moore Case[45], Canavan Case[46], and Catalona Case[47, 48, 49]involved lawsuits regarding claims of private ownership of human specimens used in research. In none of these cases did courts find that research participants had any ownership rights to their tissue, although the courts noted the importance of informed consent.[50] To date, there is no federal law addressing the ownership of human tissue.

In another case that received attention in the US, specimens were collected from members of the Havasupai tribe for research on diabetes. The specimens were later used for studies of migration and other purposes that the tribe found objectionable. Tribal members sued the investigators and the university claiming fraud, breach of fiduciary duty, intentional infliction of emotional distress, negligence, conversion and lack of informed consent. The lawsuit also alleged that the researchers allowed wholesale transfer of blood samples from laboratory to laboratory and university to university and that many samples could not be accounted for. The lawsuit was settled with a payment of $700,000 to the tribe along with the return of the blood samples, any derivatives, and associated data and documentation.[51,52]

These cases demonstrate the importance of informed consent and transparency in specimen research. They also demonstrate the need to respect cultural perspectives in the conduct of such research, and the importance of having systems in place for tracking specimens when they are distributed for additional research and mechanisms for ensuring specimens are used consistent with informed consent.

These cases also illustrate the need for sound governance mechanisms and best practices for the collection, storage, distribution and use of human specimens in research. A number of best practices have been developed in this area. These include the International Society for Biological and Environmental Repositories Best Practices[53], the National Cancer Institute (NCI) Best Practices[54], and the Organisation for Economic Cooperation and Development (OECD) Guidelines for Human Biobanks and Genetic Research Databases.[55]

In the US, new regulations and policies are being considered to address the changes in the research environment.[56] The changes in the regulations being contemplated were discussed in an Advanced Notice of Proposed Rulemaking (ANPRM) entitled “Enhancing Protections

for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators" published on July 26, 2011.[31] The ANPRM discusses a number of changes to the Common Rule that are being contemplated to provide additional protections for participants of research, as well as reforms to reduce the burden to the research community.

The ANPRM addressed a number of issues related to human specimen research and invited comments on them. Among the issues for which public comments were solicited is whether specimens should in themselves be considered identifiable, whether consent should be required for unidentified specimens, and whether a broad (non-specific) consent for future use of tissues should be considered acceptable. In addition, a new category of research was discussed, an "excused" category of research involving secondary use of specimens and identifiable information in which consent is required but there is no IRB review, unless the researcher plans to contact subjects with individual research results. Issues related to the use of human specimens discussed in the ANPRM are summarized in Table 4. During the public comment period of 90 days, more than 1,100 comments were received in response to the proposed Rule.

A Notice of Proposed Rulemaking is only one, preliminary step in the regulation making process. The Administrative Procedure Act, Pub.L. 79-404, 60 Stat. 237, governs the way federal agencies may propose and establish regulations. This Act generally requires agencies to publish all proposed new regulations in the Federal Register at least 30 days before they take effect and provide a way for the public to comment on the proposed regulation. The agency can then decide whether to proceed with the rulemaking process and if so, incorporate the public comments into a Notice of Proposed Rulemaking. This Notice of Proposed Rulemaking is issued for public comment before finalizing and publishing a Final Rule. However, an agency may decide to take no further action at any step of this process. At the time of the writing of this article, a Notice of Proposed Rulemaking on the proposed changes to the Common Rule has not been issued.

The scientific and policy landscape is evolving to reflect new ethical issues and privacy challenges related to advancements in science and technology. Recent studies demonstrating the potential to identify individuals by their genomic data, even when stripped of traditional identifiers has raised new questions about how best to protect participants who contribute their specimens to research. Homer and colleagues demonstrated that they could detect an individual's SNP profile in a mixture of DNA from 1,000 individuals.[57] This led to a change in NIH's data sharing policies for whole genome association studies to provide further protection of aggregate genome wide association study data shared through the Database of Genonotypes and Phenotypes (dbGaP).[58,59] In another more recent study, researchers were able to identify anonymous DNA donors in the 1,000 Genomes Project by matching their DNA sequences to publicly available genealogy databases.[60]

Another area of considerable discussion related to human specimen research is when individual research results should be provided to research participants. The issue of when individual research results should be returned to research participants is not addressed explicitly in US federal regulations.

From an ethical perspective, the issue of return of results and incidental findings has been debated for many years, and a number of groups have made recommendations in this area.[61,62] Arguments for return of results include respect for persons, beneficence, reciprocity, justice, and the duty to rescue.

Arguments against return of research results include the view that the original intent is an altruistic donation to help research, that return of research results would promote a therapeutic misconception, and perhaps most importantly, that harms can accrue when individual research findings that are incorrect or have not been validated are returned to participants or their physicians.

More recent discussions have focused on when and how research results and incidental findings should be returned to individuals from genomic biobanks.[63] However, the return of research results from genomic biobanks is complex, with not only ethical implications, but legal and practical implications; thus considerable caution in the return of such findings is needed.[64,65]

The issues raised by the advent of genomic technologies are being explored by the Presidential Commission for the Study of Bioethical Issues, a panel of experts who advises the President on bioethical issues arising from advances in biomedicine and related areas of science and technology. The Commission recently issued a report entitled, “Privacy and Progress in Whole Genome Sequencing”.[66] The Commission recommended strong baseline protections for whole genome sequence data and urged federal and state governments to ensure a consistent floor of individual privacy protections covering whole genome sequence data across state lines. They also recommended that clinicians and researchers use robust and understandable informed consent procedures when conducting whole genome sequencing and that the federal government facilitate broad public access to the important clinical advances that result from whole genome sequencing. As its next project, the Commission has taken up the return of incidental findings, including those arising during the course of genomic research and other research on human specimens.

While the Commission's recommendations do not constitute official policy guidance, these discussions and other policy development efforts may have a significant impact on biorepositories and the use of human specimens in research and should be followed closely by the research community.

Summary and Conclusions

As the scientific and policy landscape continues to evolve in the US, it will be important for researchers and other stakeholders to provide input as new regulations and policies are developed. Researchers, research participants, and other relevant stakeholders can follow publication of regulations and policies in the Federal Register[67] and Regulations.gov[68] and provide comments through Regulations.gov during the public comment period. Additionally, the International Society for Biological and Environmental Repositories (ISBER)[69] Science Policy Committee tracks policy and regulatory developments in the US and abroad, disseminates information to ISBER members and provides comments on behalf of ISBER. Nonetheless, comments from individuals as well as groups representing them are

also important. Active engagement of all the relevant stakeholders will be essential to help inform the development of policies related to the use of specimens in research that will allow important research to proceed, while at the same time protecting participants of such research, their privacy and the confidentiality of their data. Responsible stewardship of specimens used for research will be critical to ensure that public trust is maintained in the research enterprise.

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References

1. Seok J, Warren HS, Cuenca AG, et al. Inflammation and Host Response to Injury, Large Scale Collaborative Research Program. Genomic responses in mouse models poorly mimic human inflammatory diseases. Proc Natl Acad Sci U S A. 2013; 110(9):3507–12. [PubMed: 23401516]
2. Grizzle WE, Moore HM. Mice model findings and the future of human tissue in disease research. Biopreservation and Biobanking. 2013:111–2.10.1089/bio..2013.1132
3. Korn D. Contribution of the human tissue archive to the advancement of medical knowledge and the public health. Research involving human biological materials: ethical issues and policy guidance. National Bioethics Advisory Commission. 2000; 2:E1–E30. Available for download at http://bioethics.georgetown.edu/nbac/pubs.html.
4. Grizzle, WE.; Srivastava, S.; Manne, U. Translational Pathology of Neoplasia. In: Srivastava, S.; Grizzle, WE., editors. Translational Pathology of Early Cancer. IOS Press BV; Amsterdam, The Netherlands: 2012. p. 7-20.
5. Grizzle, WE.; Srivastava, S.; Manne, U. The biology of incipient, pre-invasive or intraepithelial neoplasia. In: Srivastava, S.; Grizzle, WE., editors. Translational Pathology of Early Cancer. IOS Press BV; Amsterdam, The Netherlands: 2012. p. 21-39.
6. Grizzle, WE.; Bell, WC.; Sexton, KC. Issues in collecting, processing and storing human tissues and associated information to support biomedical research. In: Srivastavas, S.; Grizzle, WE., editors. Translational Pathology of Early Cancer. IOS Press BV; Amsterdam, The Netherlands: 2012. p. 531-549.
7. Srivastava, S.; Grizzle, WE. Biomarkers and the genetics of early neoplastic lesions. In: Srivastava, S.; Grizzle, WE., editors. Translational Pathology of Early Cancer. IOS Press BV; Amsterdam, The Netherlands: 2012. p. 41-64.
8. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001; 344(11): 783–92. [PubMed: 11248153]
9. Jackish C. HER-2-positive metastatic breast cancer: optimizing trastuzumab-based therapy. The Oncologist. 2006; 11(1):34–41. [PubMed: 16971738]
10. Nahta R, Esteva FJ. Trastuzumab: triumphs and tribulations. Oncogene. 2007; 26:3637–3643. [PubMed: 17530017]
11. Von Minckwitz G, Schwedler K, Schmidt M, et al. Trastuzumab beyond progression: overall survival analysis of the GBG 26/BIG 3-05 phase III study in HER2-positive breast cancer. Eur J Cancer. 2011; 4:2273–2281. [PubMed: 21741829]
12. Ruschoff J, Dietel M, Baretton G, et al. HER2 diagnostics in gastric cancer-guideline validation and development of standardized immunohistochemical testing. Virchows Arch. 2010; 457(3): 299–307. [PubMed: 20665045]

13. McNally LR, Manne U, Grizzle WE. Post-transcriptional processing of genetic information and its relation to cancer. Biotech Histochem. in press.
14. Volinia S, Calin GA, Chang-Gong L, et al. A microRNA expression signature of human solid tumors defines cancer gene targets. PNAS. 2006; 103(7):2257–2261. [PubMed: 16461460]
15. Krützfeldt J, Rajewsky N, Braich R, et al. Silencing of microRNAs *in vivo* with 'antagomirs'. Nature. 2005; 43810.1038/nature04303
16. Wu Y, Crawford M, Mao Y, et al. Therapeutic delivery of MicroRNA-29b by cationic lipoplexes for lung cancer. Mol Ther Nucleic Acids. 2013:2–e84. PMID: 23591808. PMCID: PMC3650246.
17. Grizzle, WE.; Sexton, KC.; Bell, WC. Human Tissue Biorepository. In: Cheng, L.; Zhang, D.; Eble, J., editors. Molecular Genetic Pathology. 2nd. Vol. 1. Springer Science+Business Media; 2013. p. 483-497.
18. Hughes SE, Barnes RO, Watson PH. Biospecimen use in cancer research over two decades. Biopreservation and Biobanking. 2010; 8(2):89–97. [PubMed: 24845937]
19. Gaston SM, Soares MA, Siddiqui MM, et al. Tissue-print and print-phoresis as platform technologies for the molecular analysis of human surgical specimens: Mapping tumor invasion of the prostate capsule. Nat Med. 2005; 11(1):95–101. [PubMed: 15619629]
20. National Cancer Institute CHTN Cooperative Human Tissue Network. [Accessed 25 May 2013] http://www.chtn.nci.nih.gov
21. National Cancer Institute Translational Research Program. [Accessed 25 May 2013] http://trp.cancer.gov
22. National Cancer Institute (NCI) Cooperative Group Banks: Biorepositories for NCI-sponsored Clinical Trials. [Accessed 25 May 2013] http://cgb.cancer.gov
23. Cadigan RJ, Dragana L, Haldeman K, et al. Neglected ethical issues in biobank management: Results from a U.S. study. Life Sciences, Society and Policy. 2013; 9:1. published on-line March 2013.
24. [Accessed 25 May 2013] Code of Federal Regulations Title 45 Public Welfare Department of Health and Human Services Part 45 Protection of Human Subjects. http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html
25. Food and Drugs. Food and Drug Administration Department of Health and Human Services; Code of Federal Regulations Title 21. Chapter ISubchapter A. General Part 50. Protection of Human Subjects http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?CFRPart=50&showFR=1 [Accessed 25 May 2013]
26. Food and Drugs. Food and Drug Administration Department of Health and Human Services; Code of Federal Regulations Title 21. Chapter ISubchapter A. General Part 56. Institutional Review Boards.http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=56 [Accessed 25 May 2013]
27. Food and Drugs. Food and Drug Administration Department of Health and Human Services; Code of Federal Regulations Title 21. Chapter ISubchapter H. Medical Devices Part 812 Investigational Device Exemptions.http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=812 [Accessed 25 May 2013]
28. U. S. Department of Health and Human Services. [Accessed 17 June 2013] Combined Text of All Rules. [45 CFR Parts 160, 162, and 164]. Available for download at: http://www.hhs.gov/ocr/privacy/hipaa/administrative/combined/index.html
29. Bell WC, Sexton KC, Grizzle WE. How to efficiently obtain human tissues to support specific biomedical research projects. Cancer Epidemiol Biomarkers Prev. 2009; 18(6):1676–9. [PubMed: 19435863]
30. [Accessed 25 May 2013] OHRP Guidance on Research Involving Coded Private Information or Biological Specimens. http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf
31. Human subjects research protections: enhancing protections for research subjects and reducing burden, delay, and ambiguity for investigators. Federal Register. Jul 26.2011 76 CFR 44512. HHS-OPHS-2011 005.
32. FDA. [Accessed 25 May 2013] Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable; p. 34http://www.fda.gov/cdrh/oivd/guidance/1588.html

33. [Accessed 25 May 2013] U S Department of Health and Human Services Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule. Available for download at http://privacyruleandresearch.nih.gov/pr_02.asp
34. [Accessed 25 May 2013] U S Department of Health and Human Services Guidance Regarding Methods for De-identification of Protected Health Information in Accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. http://www.hhs.gov/ocr/privacy/hipaa/understanding/coveredentities/De-identification/guidance.html
35. Hakimian, R.; Taube, S.; Bledsoe, M.; Aamodt, R. National Cancer Institute Cancer Diagnosis Program: 50-State Survey of Laws Regarding the Collection, Storage, and Use of Human Tissue Specimens and Associated Data for Research. Bethesda, MD: National Institutes of Health; 2004. NIH publication 05 5628http://cdp.cancer.gov/humanSpecimens/survey/index.htm [Accessed 25 May 2013]
36. U. S. Department of Health and Human Services, National Institutes of Health. [Accessed on 25 May 2013] Genome-Wide Association Studies (GWAS). http://gwas.nih.gov/
37. U.S. Department of Health and Human Services Office for Human Research Protections. [Accessed on 25 May 2013] International Compilation of Human Research Standards. http://www.hhs.gov/ohrp/international/intlcompilation/intlcompilation.html
38. [Accessed 25 May 2013] The Royal Liverpool Children's Inquiry: Summary and Recommendations. The House of Commons. Jan 30. 2001 http://www.official-documents.gov.uk/document/hc0001/hc00/0012/0012_i.pdf
39. The National Archives. Legislation.gov.uk. [Accessed 25 May 2013] Human Tissue Act 2004. http://www.legislation.gov.uk/ukpga/2004/30/contents
40. Skloot, R. The Immortal Life Of Henrietta Lacks. New York: Crown Publishing, Random House, Inc.; 2010.
41. Skloot R. The Immortal Life of Henrietta Lacks, the Sequel. New York Times. Mar 23.2013
42. Travis J. Privacy Flap Forces Withdrawal of DNA Data on Cancer Cell Line. Science Insider 2013. Mar 26.2013
43. Grody WW, Howell RR. The fate of newborn screening blood spots. Pediatric Research. 2010; 67(3):237. [PubMed: 20154576]
44. Fikac, P. [Accessed 25 May 2013] State to destroy newborns' blood samples. The Houston Chronicle. Dec 22. 2009 http://www.chron.com/news/houston-texas/article/State-to-destroy-newborns-blood-samples-1599212.php
45. Moore v Regents of the University of California. 793P2d479. (Cal Rptr 146 1990)
46. Greenberg v Miami Children's Hospital Research Institute. 264(F Supp 2d):1064. (SD Fla 2003).
47. Washington University v Catalona. 437(FSupp2d):985. (ED Mo 2006).
48. Washington University v Catalona. 400F3d:667. (8thCir 2007).
49. Kaiser J. Court decides tissue samples belong to university, not patients. Science. 2006; 312:346. [PubMed: 16627702]
50. Hakimian R, Korn D. Ownership and use of tissue specimens for research. JAMA. 2004; 292:2500–2505. [PubMed: 15562130]
51. Kiefer, M. [Accessed on 25 May 2013] Havasupai Tribe ends regents lawsuit with burial. The Arizona Republic. Apr 22. 2010 Available for download at http://www.azcentral.com/arizonarepublic/local/articles/2010/04/22/20100422arizona-havasupai-tribe-regents-lawsuit.html
52. Mello MM, Wolf LE. The Havasupai Indian tribe case: lessons for research involving stored biologic samples. N Engl J Med. 2010; 363:204–207. [PubMed: 20538622]
53. Campbell L, Betsou F, Garcia DL, Giri JG, Pitt KE, Pugh RS, et al. ISBER 2012 Best Practices for Repositories: Collection, storage, retrieval and distribution of biological materials for research. Biopreservation and Biobanking (3rd). 2012; 10:79–161. Available for download at http://www.isber.org/?page=BPR. [PubMed: 24844904]
54. National Cancer Institute 2011 Best Practices for Biospecimen Resources. [Accessed on 25 May 2013] Available for download at http://biospecimens.cancer.gov/practices/
55. Organisation for Economic Cooperation and Development (OECD) Guidelines for Human Biobanks and Genetic Research Databases. [Accessed on 25 May 2013] 2009. Available for

download at http://www.oecd.org/sti/biotech/guidelinesforhumanbiobanksandgeneticresearchdatabaseshbgrds.htm

56. Emanuel EJ, Menikoff J. Reforming the regulations governing research with human subjects. NEJM. 2011; 365(12):1145–1150. [PubMed: 21787202]
57. Homer N, Szelinger S, Redman M, et al. Resolving individuals contributing trace amounts of DNA to highly complex mixtures using high-density SNP Genotyping Microarrays. PLOS Genetics. Aug 29.2008
58. NCBI Database of Genotypes and Phenotypes. [Accessed 25 May 2013] http://www.ncbi.nlm.nih.gov/gap
59. Zerhouni EA, Nabel EG. Protecting aggregate genomic data. Science. 2008 Oct 3.322(5898):44. [PubMed: 18772394]
60. Gymrek M, McGuire AL, Golan D, Halperin E, Erlich Y. Identifying Personal Genomes by Surname Inference. Science. 2013; 339(6117):321–324. [PubMed: 23329047]
61. Wolf SM, Lawrenz FP, Nelson CA, et al. Managing incidental findings in human subjects research: analysis and recommendations. J Law Med Ethics. 2008; 36:219–248. [PubMed: 18547191]
62. Fabsitz RR, McGuire A, Sharp RR, et al. National Heart, Lung and Blood Institute working group: Ethical and practical guidelines for reporting genetic research results to study participants: updated guidelines from a National Heart, Lung and Blood Institute working group. Cir Cardiovasc Genet. 2010; 3:574–580.
63. Wolf SM, Crock BN, Van Ness B, et al. Managing incidental findings and research results in genomic research involving biobanks and archived data sets. Genetics in Medicine. 2012; 14:361–384. [PubMed: 22436882]
64. Bledsoe MJ, Grizzle WE, Clark BJ, Zeps N. Practical implementation issues and challenges for biobanks in the return of individual research results. Genetics in Medicine. 2012; 14:478–483. [PubMed: 22323073]
65. Bledsoe MJ, Clayton EW, McGuire AL, Grizzle WE, O'Rourke PP, Zeps N. Return of research results from genomic biobanks: cost matters. Genetics in Medicine. 2013; 15:103–105. [PubMed: 22935716]
66. The Presidential Commission for the Study of Bioethical Issues. [Accessed on 25 May 2013] Privacy and Progress in Whole Genome Sequencing. Oct. 2012 Available for download at http://bioethics.gov/node/764
67. National Archives and Records Administration. [Accessed on 27 May 2013] The Federal Register. https://www.federalregister.gov/
68. Regulations.gov. [Accessed on 27 May 2013] http://www.regulations.gov/#!home
69. The International Society for Biological and Environmental Repositories. [Accessed on 17 June 2013] http://www.isber.org/

Table 1

Ways in Which Protected Health Information Can be Used and Disclosed by Covered Entities For Research Under the HIPAA Privacy Rule [45 CFR parts 160, 162, and 164]

- With individual's authorization for research [See 45 CFR part 164.508]
- Without individual's authorization if one of the following applies and other conditions in the Rule have been met [See 45 CFR part 164.512]:
  - IRB or Privacy Board waiver
  - Preparatory to research (with certain representations)
  - Limited data set (with data use agreement)
  - De-identified dataset
  - Research solely on decedents
  - Informed consent, waiver of informed consent, or permission before compliance date

Table 2

De-Identified Data Set[34]

The Privacy Rule allows a covered entity to de-identify data by removing all 18 elements that could be used to identify the individual or the individual's relatives, employers, or household members; these elements are enumerated in the Privacy Rule. The covered entity also must have no actual knowledge that the remaining information could be used alone or in combination with other information to identify the individual who is the subject of the information. Under this method, the identifiers that must be removed are the following:

1. Names.
2. All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP Code, and their equivalent geographical codes, except for the initial three digits of a ZIP Code if, according to the current publicly available data from the Bureau of the Census:
   - **a.** The geographic unit formed by combining all ZIP Codes with the same three initial digits contains more than 20,000 people.
   - **b.** The initial three digits of a ZIP Code for all such geographic units containing 20,000 or fewer people are changed to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older.
4. Telephone numbers.
5. Facsimile numbers.
6. Electronic mail addresses.
7. Social security numbers.
8. Medical record numbers.
9. Health plan beneficiary numbers.
10. Account numbers.
11. Certificate/license numbers.
12. Vehicle identifiers and serial numbers, including license plate numbers.
13. Device identifiers and serial numbers.
14. Web universal resource locators (URLs).
15. Internet protocol (IP) address numbers.
16. Biometric identifiers, including fingerprints and voiceprints.
17. Full-face photographic images and any comparable images.
18. Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification.

[3]Excerpt taken from “Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule”. U.S. Department of Health and Human Services.

[4]Note Covered Entities may also use statistical methods to establish de-identification instead of removing all 18 identifiers, [See 45 CFR part 164.514(b)].

Table 3

Limited Dataset Under the Privacy Rule[1]

A limited data set is described as health information that excludes certain, listed direct identifiers (see below) but that may include city; state; ZIP Code; elements of date; and other numbers, characteristics, or codes not listed as direct identifiers. The direct identifiers listed in the Privacy Rule's limited data set provisions apply both to information about the individual and to information about the individual's relatives, employers, or household members. The following identifiers must be removed from health information if the data are to qualify as a limited data set:

1	Names.
2	Postal address information, other than town or city, state, and ZIP ode.
3	Telephone numbers.
4	Fax numbers.
5	Electronic mail addresses.
6	Social security numbers.
7	Medical record numbers.
8	Health plan beneficiary numbers.
9	Account numbers.
10	Certificate/license numbers.
11	Vehicle identifiers and serial numbers, including license plate numbers.
12	Device identifiers and serial numbers.
13	Web universal resource locators (URLs).
14	Internet protocol (IP) address numbers.
15	Biometric identifiers, including fingerprints and voiceprints.
16	Full-face photographic images and any comparable images.

[1] Excerpt taken from “Protecting Personal Health Information in Research: Understanding the HIPAA Privacy Rule”. U.S. Department of Health and Human Services.

Table 4

Specimen-Related Issues on Which Comments Were Solicited in the Advanced Notice of Proposed Rulemaking, "Human subjects research protections: enhancing protections for research subjects and reducing burden, delay, and ambiguity for investigators"[5].

- Specified data security protections calibrated to the level of identifiability
- Identifiability of specimens
- Consent requirements for research use of specimens stripped of identifiers
- Acceptability of broad consent for specimen research
- Whether there should be an "excused" category of research involving secondary use of specimens and identifiable information in which consent is required but there is no IRB review, unless PI plans to contact subjects with individual research results

[5] Federal Register. July 26, 2011. 76 CFR 44512. HHS-OPHS-2011-005.