

Cancer Epidemiology, Biomarkers & Prevention



Biospecimens and Biorepositories: From Afterthought to Science

Jimmie B. Vaught, Marianne K. Henderson and Carolyn C. Compton

Cancer Epidemiol Biomarkers Prev 2012;21:253-255.

Updated version Access the most recent version of this article at:
<http://cebp.aacrjournals.org/content/21/2/253>

Cited Articles This article cites by 19 articles, 9 of which you can access for free at:
<http://cebp.aacrjournals.org/content/21/2/253.full.html#ref-list-1>

Citing articles This article has been cited by 2 HighWire-hosted articles. Access the articles at:
<http://cebp.aacrjournals.org/content/21/2/253.full.html#related-urls>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.

Biospecimens and Biorepositories: From Afterthought to Science

Jimmie B. Vaught¹, Marianne K. Henderson², and Carolyn C. Compton¹

Abstract

Biospecimens are recognized as critical components of biomedical research, from basic studies to clinical trials and epidemiologic investigations. Biorepositories have existed in various forms for more than 150 years, from early small collections in pathology laboratories to modern automated facilities managing millions of samples. As collaborative science has developed, it has been recognized that biospecimens must be of consistent quality. Recent years have seen a proliferation of best practices and the recognition of the field of "biospecimen science." The future of this field will depend on the development of more evidence-based practices in both the research and clinical settings. As the field matures, educating a new generation of biospecimen/biobanking scientists will be an important need. *Cancer Epidemiol Biomarkers Prev*; 21(2); 253–5. ©2012 AACR.

Good Biospecimens Are Hard to Find

This editorial could also have been entitled "Biobanking¹: A Tricky Endeavor" but that was already used for the biospecimen session at the AACR conference on The Science of Cancer Health Disparities held in September 2011 (1). Biospecimens (blood, urine, tissue—fresh-frozen, paraffin-embedded, saliva, various cells) have been organized into formal collections in the United States for more than 150 years, starting in the Civil War era with the pathology specimens that resulted in the largest collection in the United States at the Armed Forces Institute of Pathology (2). Many smaller collections exist in pathology laboratories and clinics. And larger population-based collections are managed at multiple academic and clinical centers and at the NIH (Bethesda, MD; ref. 2).

Standards Were Late in Coming

Given the millions of samples collected for clinical and research purposes, for most of the history of biobanking, there has been a serious lack of attention to control the quality and consistency of collection, processing, and storage of biospecimens. A brief list of high-profile biospecimen-related problem areas include the following: (i)

high rates of false positives and false negatives in HER2 analyses traced to inconsistent biospecimen handling among laboratories (3); (ii) invalid results from early clinical proteomic and other biomarker studies related to differences in biospecimen handling protocols (4); and (iii) more recently, inadequate quality of tissue samples for The Cancer Genome Atlas pilot study (5). As these and other specimen-related issues have emerged over the past 10 years, efforts have been under way to develop best practices to guide biobank managers and investigators who rely on biospecimens for their research (6). In addition to technical approaches to biospecimen collection, processing, and storage, best practices also include guidance on important overarching issues such as quality management, ethical and regulatory requirements, and information systems management (7). The emerging ethical, regulatory, and societal issues facing biobanks are the most difficult to coordinate and standardize, including issues such as the return of research results, pediatric consent, and the accessibility of specimens and data (8).

Although "best practices" have been increasingly adopted, it has to be noted that they are generally based on empirical observations, that is, not evidence-based. There is still a lot that is not known about optimal biospecimen practices. For example, for many blood analyses, data concerning the effects of multiple freeze-thaw cycles and other preanalytic variables are difficult to find. Recently, the National Cancer Institute (NCI) and other programs have developed biospecimen research initiatives to systematically study such variables and produce evidence-based standards (9, 10).

The Issues Are Global

Many research initiatives are now international in nature. This presents special problems for studies involving biospecimens. Although as noted there is a proliferation

Authors' Affiliations: ¹Office of Biorepositories and Biospecimen Research, and ²Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, Maryland

Corresponding Author: Jimmie B. Vaught, Office of Biorepositories and Biospecimen Research, National Cancer Institute, 11400 Rockville Pike, Rockwall I, Suite 700, Bethesda, MD 20892. Phone: 301-451-7314; Fax: 301-480-4814; E-mail: vaughtj@mail.nih.gov

doi: 10.1158/1055-9965.EPI-11-1179

©2012 American Association for Cancer Research.

¹Generally biobank, biorepository, biospecimen resource, and biologic resource center all refer to the facilities and related processes that govern the collection, processing, and storage of biologic specimens.

of best practices, there is little international coordination of biospecimen standards, both from the operational and ethical/legal perspectives (6). As a result, investigators sharing samples and otherwise collaborating across borders must take care that quality standards are established prior to specimen collection. In addition, there are many political and regulatory obstacles to send specimens outside of various countries. However, a number of productive biospecimen networks have been developed, especially in Europe, Australia, and Asia that have been successful in establishing standards and sustainable business models (11).

Evolution of Biospecimen Types

Traditionally, the major division among biorepository types has been between tissue and blood samples collected in surgical and pathology suites for clinical research applications and those collected for population-based studies, generally blood, urine, and saliva samples. As new technologies such as tissue and expression microarrays (12) have evolved, so have the specimen types and the methods to collect them changed (13). More recently, methods have been developed to isolate and study circulating tumor cells with high-resolution imaging techniques (14). A major factor affecting these trends is the availability of new analytic technologies. As smaller and smaller samples are needed for analyses, collection methodologies continue to evolve as well. For example, where microgram quantities of DNA were needed for early genomic analyses, nanogram quantities are now sufficient and DNA from saliva is increasingly used (15). And methods such as laser capture microdissection provide additional tools for specialized analytic applications (16).

Technologies and Economics

As sample types have evolved, so have the technologies necessary to process and store the increasing variety of biospecimens. One key to this process is the increasing recognition that biospecimen management is an expensive proposition. A large epidemiologic biorepository that processes and houses millions of samples each year can cost millions of dollars to construct and operate. The requirements for such a large facility include sophisticated equipment monitoring and alarm systems; back-up generators for power failures; quality management protocols; and well-developed procedures for processing, storing, and shipping samples (17). For studies where extra aliquots of samples are maintained in freezers whereas others are undergoing analyses, storage costs alone can be \$10,000 or more on an annual basis.

Economic factors, along with the need for other space-saving and efficiency measures, have led to the development of new technologies. Among these are automated sample aliquoting and nucleic acid extraction instruments that have greatly increased the productivity of biorepo-

sitories (18, 19). Additional efforts have gone into developing alternative storage models. Although the Centers for Disease Control and Prevention has been collecting and analyzing newborn blood spot cards for many years, newer dry-state techniques, for example, from Biomatrix (20) and GenVault (21) have led to additional advances, reducing costs while maintaining blood, nucleic acids, proteins, and saliva samples at ambient temperatures.

The Molecular Epidemiology Perspective

Biospecimens for molecular epidemiology studies have continued to focus on genetics and genomics (i.e., genome-wide association studies, high-density sequencing, and exome sequencing) in the last few years and this trend will continue (22, 23). But the need to measure metabolites, such as estrogens/androgens (24), small-molecule proteins and pathways, large proteins, and even components of the microbiome (25), has expanded. The increasing need for blood and blood products, tissues, and other body fluids is driven by new analytic tests. There is still a need to understand optimal ways to process and store specimens for these tests and future applications and methods to store specimens in more cost-effective, energy-efficient ways. These needs include new automation where appropriate, initially in the processing, handling, and testing areas as thousands of samples often need to be analyzed.

In terms of molecular epidemiologic study initiatives, the genetic focus with an attempt to identify gene-environment interactions has necessitated larger and larger sample sizes. With this in mind, investigators are pooling samples from a variety of international study sites (26). This globalization of investigations introduces the hazard of variable collection, processing and storage conditions among sample sets, and the accompanying chance that assay results will differ due to these varied conditions. As is the case for clinical studies, evidence-based protocols that are widely recognized and adopted are needed to minimize the problems associated with comparison of assay results across collections.

For additional information, see the *Focus: Biomarkers and Biospecimens* section published in the April 2010 issue of *Cancer Epidemiology, Biomarkers, and Prevention* (19:901–1015).

Degree Programs and Beyond

As was the case in the development of molecular epidemiology 2 decades ago, where training of epidemiologists in laboratory science had to be integrated and developed over time, biospecimen science has evolved informally and "on the job" under the leadership of experts in pathology, epidemiology, clinical chemistry, biochemistry, molecular biology, and related disciplines. Until now, there has been no formal training in the new field of biospecimen science. Recently, a new masters degree program in biobank management was initiated in France

by the International Agency for Research on Cancer (27). Similar ideas are being discussed in other parts of Europe and the United States. Also, as biorepositories become "professionalized," several organizations are developing formal evaluation programs, such as the International Society for Biological and Environmental Repositories Self-Assessment Tool and Biorepository Proficiency Testing Program (28) and the formal accreditation and certification of biorepositories by the U.S. College of American Pathologists (29).

As degree programs, evidence-based practices, proficiency testing, accreditation programs, and biospecimen

research and publications grow and expand in scope, it is obvious that the field of biobanking has evolved from the earlier view that simply embedding or freezing biospecimens with no consideration of preanalytic variables was sufficient, into a true scientific discipline. But, it is still a tricky endeavor.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received December 15, 2011; accepted December 21, 2011; published online February 7, 2012.

References

- American Association for Cancer Research. Fourth Conference on The Science of Cancer Health Disparities [cited 2012 Jan 10]. Available from: <http://www.aacr.org/home/scientists/meetings-workshops/cancer-health-disparities.aspx>.
- Eiseman E, Haga S. A handbook of human tissue sources: a national resource of human tissue samples. Santa Monica, CA: RAND Corporation; 2000.
- Wolff AC, Hammond ME, Schwartz JN, Hagerty KL, Allred DC, Cote RJ, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor testing in breast cancer. *Arch Pathol Lab Med* 2007;131:18–43.
- Ransohoff DF, Gourlay ML. Sources of bias in specimens for research about molecular markers for cancer. *J Clin Oncol* 2010;28:698–704.
- Silberman S. The flesh files. *Wired* 2010;157.
- Vaught J, Caboux E, Hainaut P. International efforts to develop biospecimen best practices. *Cancer Epidemiol Biomarkers Prev* 2010;19:912–5.
- NCI Best Practices for Biospecimen Resources [cited 2012 Jan 10]. Available from: <http://biospecimens.cancer.gov/bestpractices>.
- Knoppers BM, Hudson TJ. The art and science of biobanking. *Hum Genet* 2011;130:329–32.
- Moore HM, Compton CC, Alper J, Vaught JB. International approaches to advancing biospecimen science. *Cancer Epidemiol Biomarkers Prev* 2011;20:729–32.
- Hatzis C, Sun H, Yao H, Hubbard RE, Meric-Bernstam F, Babiera, et al. Perioperative ischemia and tissue preservation effects on RNA integrity and microarrays of breast cancer. *J Natl Cancer Inst* 2011;103:1–13.
- Vaught J, Kelly A, Hewitt R. A review of international biobanks and networks: success factors and key benchmarks. *Biopreserv Biobanking* 2010;7:143–50.
- Sherman ME, Howatt W, Blows FM, Pharoah P, Hewitt SM, Garcia-Closas M. Molecular pathology in epidemiologic studies: a primer. *Cancer Epidemiol Biomarkers Prev* 2010;19:966–72.
- Ergin B, Meding S, Langer R, Kap M, Viertler C, Schott C, et al. Proteomic analysis of PAXgene-fixed tissues. *J Proteome Res* 2010;9:5188–96.
- Marrinucci D, Bethel K, Lazar D, Fisher J, Huynh E, Clark P, et al. Cytomorphology of circulating tumor cells: a small case series. *J Oncol* 2010;2010:861341.
- Bahlo M, Stankovich J, Danoy P, Hickey PF, Taylor BV, Browning SR. Saliva-derived DNA performs well in large-scale, high-density single-nucleotide polymorphism microarray studies. *Cancer Epidemiol Biomarkers Prev* 2010;19:794–6.
- Xu C, Houck JR, Fan W, Wang P, Chen Y, Upton M, et al. Simultaneous isolation of DNA and RNA from the same cell population obtained by laser capture microdissection for genome and transcriptome profiling. *J Mol Diagn* 2008;10:129–34.
- Baird PM, Frome RJ. Large-scale repository design. *Cell Preserv Technol* 2005;3:265–66.
- Elliott P, Peakman TC. The UK biobank sample handling and storage protocol for the collection, processing and archiving of human blood and urine. *Int J Epidemiol* 2008;37:234–44.
- European, Middle Eastern and African Society for Biopreservation and Biobanking [cited 2012 Jan 10]. Available from: http://www.esbb.org/market_fold/automation.html.
- Lee SB, Crouse CA, Kline MC. Optimizing storage and handling of DNA extracts. *Forensic Sci Rev* 2010;22:131–43.
- Davis JC, Shon J, Wong DT, Jaffe S, McEvoy J. A DNA-based biological sample tracking method. *Cell Preserv Technol* 2005;3:54–60.
- Hunter DJ, Chanock SJ. Genome-wide association studies and "the art of the soluble". *J Natl Cancer Inst* 2010;102:836–7.
- National Heart, Lung and Blood Institute. The Exome Project [cited 2012 Jan 10]. Available from: <http://www.nhlbi.nih.gov/resources/exome.htm>.
- Stanczyk FZ, Jurow J, Hsing AW. Limitations of direct immunoassays for measuring circulating estradiol levels in postmenopausal women and men in epidemiologic studies. *Cancer Epidemiol Biomarkers Prev* 2010;19:903–6.
- NIH Human Microbiome Project. Clinical sampling [cited 2012 Jan 10]. Available from: http://hmpdacc.org/micro_analysis/microbiome_sampling.php.
- National Cancer Institute. Cohort Consortium [cited 2012 Jan 10]. Available from: <http://epi.grants.cancer.gov/Consortia/cohort.html>.
- Gormally E, Hardy I, di Donato JH, Caboux E, Hofman P, Hainaut P. Development of a curriculum at the master level for managers of biobanks and biological resource centers: a pilot program. *Biopreserv Biobanking* 2011;9:308.
- International Society for Biological and Environmental Repositories [cited 2012 Jan 10]. Available from: <http://www.isber.org>.
- College of American Pathologists Accreditation for Biorepositories [cited 2012 Jan 10]. Available from: http://www.cap.org/apps/docs/laboratory_accreditation/lap_info/bio_brochure_042011.pdf.