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CEBP Focus: Biomarkers and Biospecimens

Minireview

International Efforts to Develop Biospecimen Best Practices

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Abstract

Variables introduced during the processes involved in biospecimen collection, processing, storage, and analysis are among the potential sources of bias in biomarker research. International efforts are under way to develop best practices to standardize biospecimen handling protocols. In general, documents on best practices address three major recurring themes: technical best practices on infrastructure and specimen handling, recommendations on informatics and data management, and recommendations on ethical, legal, and social issues. There are many areas of agreement among various international efforts, but no single set of practices has emerged as a unifying document. The ethical, legal, and social issues are particularly difficult to harmonize due to the many country-specific issues that are governed by a variety of local and federal rules and regulations. Given the increasingly international nature of research involving biomarkers and biospecimens, it will be necessary to continue to cooperate in the development of harmonized evidence-based best practices. Several international organizations including the International Cancer Genome Consortium are engaged in such efforts. *Cancer Epidemiol Biomarkers Prev; 19(4); 912–5. ©2010 AACR.*

Introduction

A number of studies have shown the effects of biospecimen collection, processing, and storage on the validity of biomarker measurements. As noted by Ransohoff and Gourlay (1), variables in specimen collection, storage, processing, and analysis are among the many potential sources of bias in biomarker research. In extreme cases, these variables could result in artifacts being misinterpreted as biomarkers. Such problems are often not recognized before large-scale laboratory analyses, and may only be uncovered, if at all, as a result of a careful review of the source of the biospecimens and documentation of their preanalytic handling. This problem is of particular significance when using technologies that assess multiple biomarkers within a single analysis, such as genomics, transcriptomics, proteomics, and metabonomics (2). Furthermore, biospecimens may have been acquired from collaborators who did not carefully document and communicate their biospecimen handling processes. Even if the optimal conditions are determined and documented within a laboratory, they may not be reported in the articles that result from use of the biospecimens.

International efforts are under way to address the lack of standardization of biospecimen processes for biomarker and other research efforts. The National Cancer Institute (NCI) Office of Biorepositories and Biospecimen Research (3) and the NCI Early Detection Research Network (4) are funding research efforts to address biospecimen standardization issues and to develop protocols that are based on rigorous scientific evidence. The Office of Biorepositories and Biospecimen Research's Biospecimen Research Network has initiated an extramural program to identify major sources of variability in biospecimen quality and stability with the goal of producing evidence-based standard operating procedures. In Europe, the Biobanking and Biomolecular Research Infrastructure program is pursuing similar goals, with the aim of sharing infrastructure, resources, and specimens for biomarker research throughout Europe (5).

In addition to the need for underlying research to support biomarker development and biospecimen processes, there has been growing recognition for the need for best practices to govern the collection, processing, storage, and dissemination of biospecimens for research, including biomarker studies. The Office of Biorepositories and Biospecimen Research published the NCI Best Practices for Biospecimen Resources (6), which were recently updated. Many international organizations such as the International Society for Biological and Environmental Repositories (7), the International Agency for Research on Cancer (8), and the Organisation for Economic Cooperation and Development (9) have been engaged in

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developing such guidelines for a variety of purposes. In the field of population-based biospecimen research, the Public Population Project in Genomics (10) has a central Internet repository of scientific information and tools aimed at facilitating the development, realization, and harmonization of research projects. The main documents describing efforts to develop best practices for biospecimen resources (also called biobanks, biological resource centers, or biorepositories) are summarized in Table 1.

Table 1. Selected international technical best practices and guidelines

Document name	Institution	Web link*
Tissue banking for biomedical research	National Cancer Center, Singapore	http://www.bioethics-singapore.org/uploadfile/52533%20PMHT%20AppendixB-Dr%20Kon.pdf
Biorepository protocols	Australasian Biospecimen Network,/Australia	http://www.abrn.net/pdf/ABN_SOPs_Review_Mar07_final.pdf
European Human Frozen Tumor Tissue Bank (TUBAFROST)	TUBAFROST/European Union	http://www.tubafrost.org/research/moreinfo/deliverables/TUBAFROST%20Deliverable%203.1.pdf
Human tissue and biological samples for use in research (operational and ethical guidelines)	Medical Research Council, UK	http://www.mrc.ac.uk/consumption/idcplg?IdcService=GET_FILE&dID=9051&dDocName=MRC002420&allowInterrupt=1
2008 Best practices for repositories: collection, storage, retrieval and distribution of biological materials for research	International Society for Biological and Environmental Biorepositories	http://www.isber.org/Pubs/BestPractices2008.pdf
National Cancer Institute: best practices for biospecimen resources	National Cancer Institute, United States	http://biospecimens.cancer.gov/bestpractices/
Common minimum technical standards and protocols for biological resource centers dedicated to cancer research	International Agency for Research on Cancer	http://www.iarc.fr/en/publications/pdfs-online/wrk/wrk2/Standards_ProtocolsBRC.pdf
OECD Best practice guidelines for biological resource centers	Organization for Economic Cooperation and Development	http://www.oecd.org/dataoecd/7/13/38777417.pdf
Recommendation Rec(2006)4 of the Committee of Ministers to member states on research on biological materials of human origin	Council of Europe Committee of Ministers	https://wcd.coe.int/ViewDoc.jsp?id=977859&BackColorInternet=9999CC&BackColorIntranet=FFBB55&BackColorLogged=FFAC75
Case studies of existing human tissue repositories: "best practices" of a biospecimen resource for the genomic and proteomic era	RAND Corporation, Inc.	http://prostatenbnpilot.nci.nih.gov/docs/03RAND.pdf
Fundamentals of cryobiology	CryoBiosystems, Inc.	http://www.cryobiosystem-imv.com/Cryobiology/Basesfondamentalesdelacryobiologie/tabid/251/PageContentMode/1/language/en-US/Default.aspx?PageContentMode=1
Quality of collections of biological resources†	Institut National de la Santé et de la Recherche Médicale, France	http://www.p3gobservatory.org/download/projet+norme+Biobanque+Eng.pdf
Transport of infectious substances	World Health Organization	http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_CSR_LYO_2005_22r%20.pdf
UN Recommendations on the transport of dangerous goods (model regulations)	United Nations Economic Commission for Europe	http://www.unece.org/trans/danger/publi/unrec/rev13/13files_e.html

*Readers should be aware that electronic links to documents may change rapidly. This list is certified accurate as of January 1, 2010.

†Nonconsolidated English version of an official French Norm (NF-S 96-900).

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Local laboratories, biorepositories, pathology departments, and institutions may or may not adopt all or parts of these practices, as well as develop their own reference protocols. Therefore, none of these best practice documents have, thus far, been universally applied. Unfortunately, these multiple initiatives to develop best practices have not been well coordinated, leading to confusion over their adoption as well as inconsistencies in the specific recommendations. In general, documents on best practices address three major recurring themes: technical best practices on infrastructure and specimen handling, recommendations on informatics and data management, and recommendations on ethical, legal, and social issues.

Technical best practices

The goal of technical best practices is to assure that specimens are obtained and stabilized as appropriate (frozen or formalin-fixed, for example) and remain stable as they undergo further procedures and analyses. A comprehensive quality management plan with appropriate standard operating procedures is essential to all technical operations involving biospecimens. Supplementary Table S1 provides an overview of available best practices on biobank infrastructure and on biospecimen acquisition, preservation and storage, processing, and shipping. Many of these guidelines are based on experience and of the "art of the possible" and have been proposed as "points to be considered" rather than claiming to include evidence-based practices for biospecimen handling. Therefore, these guidelines remain heterogeneous. Whereas some topics are well documented, such as DNA acquisition and processing for genomics, there is still a lack of detailed recommendations for complex fields such as epigenomics or metabonomics.

Informatics and data management

The data (clinical, epidemiologic, demographic, biospecimen quality, etc.) associated with biospecimens are critical for their overall value and utility for research. Best practices include assuring that data are collected according to recognized standards, in particular, in identifying the pathologic status of the biospecimen, determining the common data elements that need to be collected, establishing quality control for data collection, and assuring that data are collected according to privacy rules and other human subjects data protection rules and regulations. As stated in the NCI Best Practices, "An informatics system should support all aspects of biospecimen resource operations, including, but not limited to, tracking of research participants enrollment and consent; biospecimen collection, processing, storage, and dissemination; quality assurance/quality control processes and documentation; collection of, or electronic linkage to research participant (i.e., clinical) data; data security; and management reporting functions; e.g., generating reports on inventory, collection, utilization and quality assurance. In addition, the system should store a minimum, common set of clinical and experimental annotation data." Whenever appropriate, informatics systems within biospecimen resources should be integrated with the institution's data systems (in particular in a clinical context) and other systems and data as applicable to the study design (e.g., large databases in population studies). One of the major obstacles to the efficiency and accuracy of data exchanges among biospecimen resources is the lack of interoperability of informatics systems. Best practices dictate that information systems should be interoperable to both integrate clinical and research data, and to enhance the ability to establish biospecimen resource networks that can readily exchange information.

Ethical, legal, and social issues

These issues are as important as the technical practices for biospecimen resources, and are often controversial (11) and subject to change. The following issues must be considered for best practices:

- Informed consent: defining the "moral contract" between researchers and the study participants and setting the framework for the allowable use of biospecimens and data;
- Custodianship: planning and implementing and policies to assure the long-term stability of biospecimens and the handling of specimens and data in the event that the resource is forced to close due to funding shortfalls or other special circumstances;
- Privacy: assuring the privacy of patients and other biospecimen donors through adherence to legally defined principles and rules, such as the Health Insurance Portability and Accountability Act (HIPAA) privacy rule and other federal, state, and local regulations;
- Access: developing policies governing information on specimen availability and on sharing specimens and data within the context of specified study design;
- Intellectual property: adopting guidelines to assure proper and legal handling of specimen and data sharing through material transfer agreements and similar documentation, acknowledging the specific input of scientists involved in biospecimen and data collection and management as a key element in the "added scientific value" of biospecimens for research.

Many of these issues, such as informed consent and material transfer agreements, are governed by law or binding regulations at the international, national (federal), local, or institutional level. The NCI Best Practices and other guidelines documents do not establish new policies, but rather provide guidance to biospecimen resources concerning the critical factors to consider when establishing and using a biospecimen collection. At the international level, the International Cancer Genome Consortium (12) has developed a set of policies for informed consent, custodianship, data access and sharing, and intellectual property, that provides a framework for large, multicentric studies focused on genetics and genomics. However,

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guidance on these issues is constantly evolving due to advances in technology that make it difficult to assure that biospecimens cannot be used to identify a person, changes in the public perception of the appropriate use of human tissue for research, and considerations on the stringency of informed consent policies regarding future unexpected research uses of biospecimens.

Conclusions

Although the varied international efforts to establish best practices for biospecimen use in biomarker and other research efforts have greatly contributed to convergence in principles for technical, informatics, and ethical/legal/social issues, many issues remain unresolved. For example, there are many preanalytic variables involved in collecting blood and tissue that have not been studied, which will continue to affect biomarker validation and other studies. One of the critical problems in such studies is the absence of reliable biomarkers of the biological quality of biospecimens. As biospecimen research becomes more established as a scientific field of endeavor, and the resulting evidence-based protocols are incorporated into best practices documentation, the situation will improve. Currently, the need to further support research towards the development of rigorous, verifiable, and controllable protocols is recognized as the main priority in biospecimen research. In addition, it will be necessary for international organizations to coordinate the efforts to establish consistent guidelines. Such efforts are under way in organizations such as the International Society for Biological and Environmental Repositories, the Public Population Project in Genomics Observatory, and the Marble Arch Group (13). International cooperation in the establishment of best practices is essential due to major international collaborative studies that require sharing biospecimens and data collected at multiple institutions, such as the International Cancer Genome Consortium (14).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Ransohoff DF, Gourlay ML. Sources of bias in specimens for research about molecular markers for cancer. J Clin Oncol 2010;28:698–704.
2. Ransohoff DF. Bias as a threat to the validity of cancer molecular-marker research. Nat Rev Cancer 2005;5:142–9.
3. NCI Office of Biorepositories and Biospecimen Research. Available from: http://biospecimens.cancer.gov/.
4. NCI Early Detection Research Network. Available from: http://edrn.nci.nih.gov/.
5. Yuille M, van Ommen GJ, Brechot C, et al. Biobanking for Europe. Brief Bioinform 2008;9:14–24.
6. NCI Best Practices for Biospecimen Resources. Available from: http://biospecimens.cancer.gov/practices/.
7. Campbell JD, Skubitz APN, Somiari SB, Sexton KC, Pugh RS, International Society for Biological and Environmental Repositories (ISBER). 2008 Best Practices for Repositories: Collection, Storage, Retrieval and Distribution of Biological Materials for Research. Cell Preserv Technol 2008;6:3–58.
8. Caboux E, Plymoth A, Hainaut P. Common minimal technical standards and protocols for biological resource centers dedicated to cancer research. IARC Working Group Reports 2007:1–38.
9. Organisation for Economic Co-operation and Development. Available from: http://www.oecd.org/dataoecd/7/13/38777417.pdf.
10. Knoppers BM, Fortier I, Legault D, Burton P. The Public Population Project in Genomics (P3G): a proof of concept? Eur J Hum Genet 2008;16:664–5.
11. Vaught JB, Lockhart N, Thiel KS, Schneider J. Ethical, legal and policy issues: dominating the biospecimen discussion. Cancer Epidemiol Biomarkers Prev 2007;16:2521–3.
12. International Cancer Genome Consortium: goals, structure, policies and guidelines. Available from: http://www.icgc.org/files/ICGC_April_29_2008.pdf.
13. Riegman PH, Morente MM, Betsou F, et al. Biobanking for better healthcare. Mol Oncol 2008;2:213–22.
14. International Cancer Genome Consortium. Available from: http://www.icgc.org.