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Perspective on Biorepository Return of Results and Incidental Findings

Scott D. Jewell*

INTRODUCTION

Biorepositories and biobanking have gained considerable momentum in recent years.¹ Biorepositories consist of collections of biospecimens for science venues that rely on specimens for analysis.² The number and kinds of biorepositories would be too numerous to list. However, the growing membership of organized societies such as the International Society of Biological and Environmental Repositories (ISBER),³ the Biobanking and Biospecimen Resources Research Infrastructure,⁴ the Public Population Project in Genomics,⁵ the European, Middle Eastern, and African Society for Biopreservation and Biobanking,⁶ the Canadian Tumour Repository Network,⁷ and the National

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1. See, e.g., Alice Park, *Biobanks*, TIME, Mar. 23, 2009, at 63.
2. See *id.* (“Think of it as an organic bank account. You put your bio-material in and earn medical interest in the form of knowledge and therapies that grow out of that deposit . . .”).
3. INT’L SOC’Y FOR BIOLOGICAL & ENVTL. REPOSITORIES, <http://www.isber.org> (last visited Mar. 24, 2012).
4. BIOBANKING & BIOMOLECULAR RESOURCES RES. INFRASTRUCTURE, <http://www.bbmri.eu> (last visited Mar. 24, 2012).
5. PUB. POPULATION PROJECT GENOMICS, <http://www.p3g.org> (last visited Mar. 24, 2012).
6. EUR., MIDDLE EASTERN & AFR. SOC’Y FOR BIOPRESERVATION & BIOBANKING, <http://www.esbb.org> (last visited Mar. 24, 2012).
7. CANADIAN TUMOUR REPOSITORY NETWORK, <http://www.ctrnet.ca> (last visited Mar. 24, 2012).

Cancer Institute's (NCI) Office of Biorepositories and Biospecimen Research (OBBR)⁸ demonstrates worldwide interest and energy in the development of best practices and expertise in biobanking. One accepted definition of the term "repository" is ISBER's definition: "A repository is defined as an entity that receives, stores, processes and / or disseminates specimens It encompasses the physical location as well as the full range of activities associated with its operation."⁹ Another definition comes from the Department of Health and Human Services' Office for Protection from Research Risks: "Human Tissue Repositories collect, store, and distribute human tissue materials for research purposes. Repository activities involve three components: (i) the collectors of tissue samples; (ii) the repository storage and data management center; and (iii) the recipient investigators."¹⁰

Repositories of human biospecimens have rapidly developed to meet the demand for biospecimens—from individuals afflicted with diseases—for use in intense and competitive research initiatives seeking to discover new knowledge in the genomic era.¹¹ The increasing value and interest in human biorepositories have elevated concerns for human subjects as well as ethical issues related to the collection, holding, and use of biospecimens, especially where biospecimens may be used for future undefined research.¹² Furthermore, advancements in technology are more likely to prove the assumption that a deep interrogation into new knowledge could provide actionable medical treatments, such as directly targeting a biological pathway using an existing drug or intervention treatment that may have significance for future individual health outcomes.

8. NAT'L CANCER INST., OFF. BIOREPOSITORIES & BIOSPECIMEN RES., <http://www.biospecimens.cancer.gov/default.asp> (last visited Mar. 24, 2012).

9. Int'l Soc'y for Biological & Env'tl. Repositories, *2008 Best Practices for Repositories: Collection, Storage, Retrieval and Distribution of Biological Materials for Research*, 6 CELL PRESERVATION TECH. 5, 10 (2008).

10. Office for Prot. from Research Risks, *Issues to Consider in the Research Use of Stored Data or Tissues*, U.S. DEPT OF HEALTH & HUMAN SERVS. (Nov. 7, 1997), <http://www.hhs.gov/ohrp/policy/reposit.html>.

11. See Park, *supra* note 1.

12. Nils Homer et al., *Resolving Individuals Contributing Trace Amounts of DNA to Highly Complex Mixtures Using High-Density SNP Genotyping Microarrays*. PLOS GENETICS 9 (Aug. 2008), available at <http://www.plosgenetics.org/article/info%3Adoi%2F10.1371%2Fjournal.pgen.1000167>.

Therefore, the research use of biospecimens from biorepositories—often well removed from the direct care of patients—has become an ethical concern when considering the potential benefits to patients and has opened a debate over the return of research results to individuals.¹³ Research results can include: 1) known events of importance such as the discovery of inheritable genes associated with increased managed healthcare for an individual or their family members;¹⁴ 2) primary results of unknown significance, such as a finding of new data or information generated from research testing that may affect some element of healthcare;¹⁵ and 3) secondary research findings such as mistakes uncovered in the management of research material (e.g., a discordant pathological diagnosis) that may or may not have a further effect on the healthcare of an individual.¹⁶ In these situations, the delivery of the data or information would include thorough reviews by scientists and physicians with appropriate knowledge to weigh the importance of the effectiveness of the research results. It should be noted that there is a systematic process that must occur between the generation of well-controlled and documented research results and the final determination of accurate measurement and validation to determine the usefulness of results for patient care. Laboratory tests for patient care are controlled

13. See, e.g., OFFICE OF BIOREPOSITORIES & BIOSPECIMEN RESEARCH, NAT'L CANCER INST., & NAT'L INSTS. OF HEALTH, WORKSHOP ON RELEASE OF RESEARCH RESULTS TO PARTICIPANTS IN BIOSPECIMEN STUDIES: WORKSHOP SUMMARY 3 (2011) [hereinafter WORKSHOP SUMMARY], available at http://biospecimens.cancer.gov/global/pdfs/NCI_Return_Research_Results_Summary_Final-508.pdf ("Proponents of sharing research results contend that human research participants should have the option of receiving potentially valuable information. Opponents maintain that the purpose of research is to generate general knowledge rather than individual data, and that research laboratories are not necessarily held to the same standards as clinical laboratories."); Laura M. Beskow & Wylie Burke, *Offering Individual Genetic Research Results: Context Matters*, 2 SCI. TRANSLATIONAL MED., June 30, 2010, at 1; Laura M. Beskow & Sondra J. Smolek, *Prospective Biorepository Participants' Perspectives on Access to Research Results*, 4 J. EMPIRICAL RES. ON HUM. RES. ETHICS, Sept. 2009, at 99, 99.

14. E.g., Beskow & Burke, *supra* note 13, at 1–2.

15. E.g., Lynn G. Dressler, *Biobanking and Disclosure of Research Results: Addressing the Tension Between Professional Boundaries and Moral Intuition*, in THE ETHICS OF RESEARCH BIOBANKING 85, 89 (J.H. Solbakk et al. eds., 2009).

16. E.g., Marianna J. Bledsoe et al., *Practical Implementation Issues and Challenges for Biobanks in the Return of Individual Research Results*, 14 GENETICS MED. 478, 482 (2012).

and managed in the United States by the Clinical Laboratory Improvement Amendments (CLIA).¹⁷

A number of concerns surrounding the return of results exist, several of which are not directly covered through the involvement of biorepositories. Individuals should have the opportunity to determine if their biospecimens can be used in research. The informed consent process is the best point to receive approval for the intended uses, broad or narrow, and to discuss the issues surrounding research results. It is unlikely that all uses and results can be defined. Even though there is a very small risk of having an individual's identity breached by non-approved users, many researchers prefer receiving biospecimens designated to be non-human subjects, which means having no identity or reasonable connection to the patient.¹⁸ Thus if an attempt to return research results did occur, the biorepository would not be able to provide certainty for the chain-of-custody (CoC) of the biospecimen to the individual's identity, which is purposefully broken in de-identification processes. The complexity of this process is easiest to explain to an individual by indicating that research results will not be returned.

A result from research that could carry an ethical justification to re-match the biospecimen to an individual would be one of a known inheritable genetic condition of significant healthcare management—especially if the individual was not already aware of the genetic inheritance.¹⁹ Even under these circumstances the use and availability of the results, compared to when the biospecimens were collected, need to be weighed against the value of communicating the information to an individual. The existing or monitoring institutional review boards (IRBs)²⁰ are already generally capable of determining the value of returning the results without further changes in the ethical or human-subjects standards.

Return of research results could also be considered based on the type of biorepository that manages the biospecimens.

17. See 42 C.F.R. § 493 (2011).

18. See Amy L. McGuire & Richard A. Gibbs, *No Longer De-Identified*, 312 SCIENCE 370, 370 (2006) (“At present, ethical concerns about the privacy of subjects whose sequenced DNA is publicly released have largely been addressed by ensuring that the data are ‘de-identified’ . . .”).

19. See, e.g., Dressler, *supra* note 15, at 93–94.

20. 45 C.F.R. § 46.109 (2011).

There is not a one-size-fits-all category for biorepositories, and thus special consideration could be given to biorepositories that can meet the demands for the CoC. The infrastructure and management of biorepositories that can meet the demands to maintain ethical connectivity to research results would differ from the general biorepository and would certainly cost more to operate. Funding challenges would exist for these types of biorepositories and, like the funding models for clinical laboratories, these costs would need to be considered as part of the healthcare provided to patients.

Issues and concerns surrounding the return of research results as defined above are further discussed from the biorepository point of view below. Biospecimens held in biorepositories have been used for decades to generate research results. Then and now the policies on the return of research results have always sounded a clear “no” because research results by their nature have not been validated or proved meaningful or actionable in a clinical setting.²¹ The issue of return of results is a relatively new debate compared to the decades of existence of human biorepositories,²² yet when a transition from research to clinical action has occurred, significant time, effort, and testing have been needed to derive a meaningful data set for clinical action. The impetus for this rising debate is due to capabilities of genomic technology, the potential that genomic information can be linked to an individual, and the fact that genomic signatures may determine, predict, or direct treatment for health outcomes. Features of biorepositories that play an important role when results are returned include: biorepository structure and function, informed consent, CoC, IRB standards and decision-making, quality management programs (QMPs), funding, quality controls, proficiency testing, technologist certification, biorepository accreditation,²³ CLIA certification,²⁴ risk and disaster planning, and insurance. To ensure the proper and ethical return of research results to an individual, a biorepository should be held to the same standards that are in

21. See Dressler, *supra* note 15, at 91.

22. WORKSHOP SUMMARY, *supra* note 13, at 8 (“Although these issues have been in the public consciousness since the 1980s, interest has multiplied in recent years.”).

23. See *CAP Accreditation for Biorepositories*, C. AM. PATHOLOGISTS (2011), http://www.cap.org/apps/docs/laboratory_accreditation/lap_info/bio_brochure_042011.pdf.

24. See WORKSHOP SUMMARY, *supra* note 13, at 8–9.

place for clinical testing.

I. BIOREPOSITORY STRUCTURE AND FUNCTION

The complexity and breadth of the functions and services in human biorepositories make it difficult to apply prescribed requirements across the board. To appreciate the complexity of providing return of results, it is important to understand the basics of the structure and function of biorepositories. Human biorepository structures range from the individual investigator-managed biorepositories that may contain a few hundred biospecimens to large well-managed biorepositories with thousands to millions of biospecimens.²⁵ The operating premise for these biorepositories range from single user with minimal documentation and relatively low value to high-profile drug, device, or clinical trials with associated data and documentation of relative high cost and value.²⁶ Until recently, with the formation of biobanking societies and government influence on improved quality of research resources, the infrastructure and management of biorepositories could be considered haphazard at best.²⁷ While there are excellently managed, well-funded biorepositories that espouse the ability to move into the clinical translational space, suggesting that the return of research results is possible for biorepositories, as a broad based general concept it is impracticable. Biorepository structure and function are generally not funded well enough.²⁸ Requiring broad-based programs to get approval before returning research results would be an unfunded mandate on a system that has no method to force increases in revenue.²⁹ The result would be an action

25. See *Donating Tissue for Cancer Research: Biospecimens and Biorepositories*, NAT'L CANCER INST., <http://www.cancer.gov/cancertopics/factsheet/Information/donating-tissue-research> (last visited Apr. 4, 2012) (stating that the size of biorepositories varies greatly across the industry).

26. See *id.*

27. See Nat'l Cancer Inst., *Overview*, OFF. BIOREPOSITORIES & BIOSPECIMEN RES., <http://biospecimens.cancer.gov/about/overview.asp> (last visited Apr. 4, 2012) (stating that a primary purpose of the OBBR is to bring order to a haphazard system).

28. Gary E. Goodman, *Biorepositories: Let's Not Lose What We Have So Carefully Gathered!*, 15 *CANCER EPIDEMIOLOGY, BIOMARKERS, & PREVENTION* 599, 599 (2006) (citing a lack of stable funding as a major shortfall of many biorepositories).

29. See *id.* (noting that most biorepository funding occurs on a trial-by-trial grant basis).

that can't be implemented without significant funding. It makes more sense to determine the interest and scope of biorepositories that can enter the space of translational medicine with intent to return results to individuals and then set requirements for those biorepositories to meet the appropriate standards. Biorepositories establishing best practices are working towards preventing errors in transcription, building robust information systems to manage the inventory, improving quality control and quality assurance procedures, creating management and backup processes for freezers and other equipment, ensuring the safety of technologists, documenting standard operating procedures, making appropriate decisions in distribution and regulatory requirements, and managing a host of other subtle issues that arise in running a biorepository.³⁰ The varying structures and complexities of biorepositories raise the awareness that standardization is both important and necessary to provide return of results. However, the CoC could be very problematic. Some biorepositories do carry the protected health information (PHI) of the patient and connectivity to the biospecimens. This doesn't mean the standard operating procedures maintain CoC, but it does make the process possible. However, many biorepositories do not store or maintain PHI.³¹ Under these circumstances if the use of biospecimens produces significant findings, identification practices would be difficult to connect with certainty to an individual who donated the biospecimen for research. To judge if a biorepository is aligned and able to manage the return of results, both internal and external adjudication of its operation should be implemented. The responsibility to individuals to provide research results is a serious undertaking, which demands fool-proof processes and procedures to connect with certainty the research data to the identity of an individual.

30. E.g., Walter C. Bell et al., *Organizational Issues in Providing High-Quality Human Tissues and Clinical Information for the Support of Biomedical Research*, 576 *Methods Molecular Biology* 1, 1–28 (2010); Samir N. Khleif et al., *AACR-FDA-NCI Cancer Biomarkers Collaborative Consensus Report: Advancing the Use of Biomarkers in Cancer Drug Development*, 16 *CLINICAL CANCER RES.* 3299, 3302 (2010); Brian R. Leyland-Jones et al., *Recommendations for Collection and Handling of Specimens from Group Breast Cancer Clinical Trials*, 26 *J. CLINICAL ONCOLOGY* 5638, 5639–41 (2008).

31. E.g., *Privacy*, ORBIT, <http://www.aurorahealthcare.org/services/orbit/bg.html> (click on the “Privacy” tab at the top of the page) (last visited Apr. 4, 2012).

A. INFORMED CONSENT, CHAIN OF CUSTODY, AND IRB STANDARDS AND DECISION MAKING

Biorepositories may receive patient-consented biospecimens but without holding the patient identifiable information. In these situations the clinical site would hold the patient's identifying documentation. The associated IRB protocol may or may not allow reconnection to the patient's identity. In some biorepositories the biospecimen collections may exist with complete anonymity of the origin of the person who contributed the biospecimens. Thus not all biorepositories would be able to return results to individuals without the appropriate CoC or an IRB approval or consent to re-connect to an individual.

Assuming that consent from all patients will be required, the identifiability of a patient may not be a jurisdiction of the biorepository and the processes to maintain CoC would be needed for every patient set of biospecimens while the reconnection event will be rare. To maintain this functionality would be very costly to the biobanking and research enterprise.

Bioinventory software is also a key element in the safeguard of the CoC. Several choices in software selection exist, but the costs range from inexpensive homegrown products to commercial products costing several thousands of dollars, and enterprise systems costing hundreds of thousands of dollars.³² Reliable options that include complete auditing transaction systems to manage CoC and security for the protection of human subjects information would be required if return-of-results programs are implemented. Surprisingly, many software bioinventory systems do provide these defaults, but again the often-missing link is the connecting data to the link to an individual's identity.

A confounding issue in the return of results involves the authority of the IRB, which would have approved the consent to collect biospecimens. If there is a decision to return results, which is then managed under CLIA law, who makes the decision to return results to the individual? How is this decision

32. *E.g., The Multiple Myeloma Research Foundation (MMRF) and Translational Genomics Research Institute (TGen) Announce Innovative Molecular Profiling and Biobanking Collaboration for Landmark Multiple Myeloma Study*, TRANSLATIONAL GENOMICS RES. INST. (Apr. 2, 2012), <http://www.tgen.org/news/index.cfm?newsid=2055> (announcing the use of VARI/TGen Bioinventory software).

made? Qualified individuals who have the appropriate ability and authorization should make these decisions. This brings an additional burden on the IRB and requires that the IRB be made up of individuals who are both well versed in the protection of human subjects but also are able to assess the clinical significance of the reported data. CLIA is clearly a requirement and the process on the engagement of CLIA-licensed assay reporting is well known, but the decision and criteria for moving a research result to a clinical event is not defined and would require a separate body of specialists.

B. QUALITY MANAGEMENT PROGRAMS

Technological advancements have put a greater emphasis on the quality of biospecimens since the resulting data from these improved sensitivities have been shown to be problematic if not conducted using an appropriate biospecimen—such as seen with the development of an RNA measurement or RNA integrity number value.³³ Thus the improvements in the management of biospecimens for both collection and storage have focused on quality assurance and quality control procedures.³⁴ Clinical trial groups of the NCI sponsor a cooperative group-banking committee tasked with harmonizing procedures and, where possible, documenting measures of quality control and management of these biospecimens.³⁵ While efforts to improve quality, or least the documentation to assess or point to a measure or degree of quality, are ongoing using the Biospecimen Reporting for Improved Study Quality standards,³⁶ very few biorepositories in academia, especially those with minimal resources, fully implement a QMP. These programs are modeled after groups that maintain good laboratory or manufacturing practice, such as is used in handling pharmaceutical-grade compounds. These programs are costly, but they easily point out where mistakes are made in an operation and enforce the necessary changes to improve the procedure, pro-

33. See *How the RNA Integrity Number (RIN) Works*, AGILENT TECH. (June 2004), http://www.agilent.com/about/newsroom/lscs/background/rna_integrity.pdf.

34. See Leyland-Jones, *supra* note 30, at 5639.

35. Cooperative Group Banks, *Quality Assurance*, NAT'L CANCER INST., <http://cgb.cancer.gov/biospecimens/qualityassurance.html> (last viewed Apr. 11, 2012).

36. See Helen M. Moore et al., *Biospecimen Reporting for Improved Study Quality*, 9 BIOPRESERVATION & BIOBANKING 57, 58–59 (2011).

cess, and ultimately the product. In the biorepository the product is the identity, quality, and correct biospecimen. In the clinical setting the combination of CLIA, an accreditation review like the American College of Pathologists (CAP),³⁷ and the laboratories internal quality management review team provides the level of scrutiny and oversight to enforce corrective action plans. The biorepository with research biospecimen inventory should also be required to meet the stringency of assurance. Again the QMP can be a significant consumer of the operating cost of a biorepository with research biospecimens that are simply too large to be managed at this present state of funding for biorepositories.³⁸

C. FUNDING

A well-funded biorepository can implement provisions of tracking and managing biospecimens into and out of the biorepository. However, in general, biorepositories are funded at a minimal operational level even if the biorepository has significant value, standards, and diverse services.³⁹ Greater than average funding is needed to maintain a system with sufficient numbers of well-trained operating personnel as well as equipment and software systems for biorepository inventory and management. While software systems and the implementation of operation activities such as the use of barcodes have improved significantly, many biorepositories still function with homegrown software systems and manual operating procedures. A system that would implement the standards and processes discussed above for the return of research results would require significantly more operating funding to manage the potential to provide this level of service.⁴⁰ Return of research results or incidental findings and thus the need to connect back to the patient would most probably be a rare event. However,

37. See *CAP Accreditation for Biorepositories*, *supra* note 23.

38. See Goodman, *supra* note 28, at 599.

39. See, e.g., Geoffrey S. Ginsburg et al., *Centralized Biorepositories for Genetic and Genomic Research*, 299 JAMA 1359, 1359 (2008) (noting that institutions often have "limited resources and inconsistent funding").

40. Bledsoe, *supra* note 16, at 480 ("Setting up systems to return individual research results has infrastructure implications and costs, including the need to set up systems for decision-making and processes for implementing the return of findings, staffing and funding for recontact, informatics systems for reporting and auditing and tracking of specimens, etc.").

the expense to maintain the procedures to provide this service with CoC assurance would be significant to the operational funding for the average biorepository.

D. QUALITY CONTROLS, CERTIFICATION, AND PROFICIENCY

New technology purposes to provide more detailed insights into the molecular signatures of biological systems. In turn, these technologies will also provide increased sensitivities and a greater demand on the quality of procurement and management of biospecimens that are used in the generation of research data. Biobanking organizations are central drivers in efforts to improve the accuracy and stringencies in the practices of biorepositories and to ensure that biological and environmental resources provide the best services.⁴¹ At present, biorepositories self-measure quality control because professional services to administer these activities are not implemented. One assessment of self-certification is to arrange both internal and external reviews of the biorepository operations to certify high standards of operation. Proficiency analysis is an important measure of laboratory procedures such as the isolation of nucleic acids to qualify procedures and routine consistency and accuracy in assay performance. Certification of technologists is another indicator of competency in operations. These proficiency and certification measures, coupled with internal and external reviews, ensure vetted processes to manage return of research results.

E. ACCREDITATION AND CLIA

Biobanking is not a new phenomenon across scientific disciplines, yet the focus of increased interest and improvements in the practices of biorepositories is directly related to the advancements in analytical genomic technology.⁴² Unfortunately a standard to ensure research biorepositories are well managed and controlled to meet the rigor of clinical reporting requirements has never been a goal.⁴³ Beyond the biorepository quality control, proficiencies, and technologist certifications, the most important achievements would be accreditation and a license under the CLIA. As noted above, a CLIA license is the re-

41. See, e.g., Int'l Soc'y for Biological & Env'tl. Repositories, *supra* note 9 (outlining best practices to improve sample quality).

42. See Ginsburg, *supra* note 39, at 1359.

43. See Bledsoe, *supra* note 16, at 479–80.

quirement to be able to return results to individuals.⁴⁴ Movement to develop biorepositories that qualify for the stringent requirements of CLIA is nowhere more evident than in the CAP's plan to launch a Biorepository Accreditation Program (BAP) in 2012.⁴⁵ While the initial phases of the CAP BAP program will not provide biorepositories with an approach to CLIA accreditation, it is very significant because the majority of CAP accreditation programs validate the consistent quality of biospecimen.⁴⁶ Given time for the CAP's BAP program to mature, and good actionable reasoning to return results, biorepositories may become involved in the clinical space, and the CLIA application will then apply in some areas of biobanking. Although proficiency, certification, and quality control are important working elements in biobanking, accreditation and CLIA license are the documents that must be in place to pave the road for return of research results.

F. RISK, DISASTER PLANNING, AND INSURANCE

Return of research results places an expectation that, when individual's biospecimens are stored, not only will the biospecimens be used in initial research to generate data, but that remainder aliquots of biospecimens could also be used to generate more data. With each data generation potentially ending in a process that could qualify for the return of results to individuals, risk attributed to mismanagement is heightened.⁴⁷ In a similar context, liability and insurance costs for a biorepository may result or increase if reporting errors were a consequence of mismanagement by the biorepository that could affect the health decisions of an individual. In addition, if the perception of increased value of the biorepository contents and risk increase, the biorepository's institution will need to carry a larger insurance coverage in case of disasters that result in the loss of the contents. Presently most biorepositories likely have emergency planning for the common freezer failure. Emergencies can be classified as a more minor single event that can be handled by the biorepository personnel. However, disasters are

44. See *supra* INTRODUCTION.

45. See *CAP Accreditation for Biorepositories*, *supra* note 23.

46. *Frequently Asked Questions About the CAP's Biorepository Accreditation Program*, C. AM. PATHOLOGISTS para. 1 (Feb. 16, 2012), http://www.cap.org/apps/docs/laboratory_accreditation/lap_info/bap_faq.pdf.

47. See Bledsoe, *supra* note 39, at 479–80.

events that can jeopardize or destroy a large portion or an entire biorepository such as building structure failure or major damage due to natural disasters or fire. Insurance coverage needs to cover the perceived value of a biorepository collection. However, including insurance coverage to manage return of results represents a new cost to the risk management of the biorepository in order to manage both the potential loss of the biospecimens and any lawsuits from individuals.

CONCLUSION

Return of research results to individuals when an actionable discovery has been found does have an ethical consideration that should be discussed and, where possible, implemented. However, at this time, the state of biobanking as outlined above points to many gaps in a system that is not applicable for clinical settings or the corollary that is the return of results. Although a developing accreditation program from CAP⁴⁸ and a proficiency program⁴⁹ started by ISBER and the International BioBank of Luxembourg bring documented standards for biorepositories, the lack of CLIA license, which is required for the return of results, continues to be a significant deficit in the credibility of biorepositories to perform and manage that activity. Regardless of the accreditation and license structural processes that, in time, could be managed by a few biorepositories that want to function in that space, other operational issues to provide the functionality needed to accomplish the return of results will need to be met. These include funding, long-term risk management, and insurance. Furthermore, if funding and risk management solutions existed to develop and operate the infrastructure to return research results, the most significant issue that remains is the validation of research findings in the context of the meaningfulness to an individual's healthcare. Prior to enacting policies or requirements to return research results guidelines should be established on the healthcare benefits and appropriateness of the results.

48. *CAP Accreditation for Biorepositories*, *supra* note 23.

49. *ISBER Proficiency Testing (PT) Program*, INT'L SOC'Y FOR BIOLOGICAL & ENVTL. REPOSITORIES, http://www.isber.org/proficiency_testing/ (last visited Apr. 2, 2012).