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Biorepository Proficiency Testing for the Quality Control of Biospecimens for the Global Biobanking Community

Contributed by members of the ISBER Biospecimen Science Working Group[1]

Introduction

Until now, proficiency testing programs have not existed for the quality assessment of biospecimens that are used in basic, translational, and clinical research studies, yet the discovery, validation, and clinical evaluation of biomarkers necessary for the advancement of global health depend upon the availability of a large number of standardized specimens. To meet this void, ISBER has launched a biorepository Proficiency Testing (PT) Program in partnership with the Integrated Biobank of Luxembourg (IBBL). The ISBER PT Program belongs to the category of interlaboratory comparison "schemes" involving simultaneous participation of biorepository laboratories located in different countries. Randomly selected aliquots from a source material prepared at IBBL (the test items) are being distributed and tested concurrently by all registered participants. After the completion of the testing, the participants' results will be returned to the Proficiency Testing provider (ISBER) and compared with the assigned value(s) derived from the reference laboratories to give an indication of the performance of the individual participants and of the group as a whole.

The ISBER PT Program allows biorepositories performing quality control assays and/or characterization of the biospecimens to assess the accuracy of their testing and to compare their results with those obtained in other laboratories around the world. It has been designed to include four schemes: DNA quantification and purity, RNA integrity, cell viability, and tissue antigenicity. The first two schemes were open for participation in the latter part of 2011. The cell viability and tissue antigenicity schemes will be added to the program in 2012.

Pilot PT Program for DNA Quantification and Purity and RNA Integrity

All the Standard Operating Procedures of the new ISBER PT program were written according to the requirements of the ISO/IEC 17043:2010 (the International Standard on "Conformity assessment – General requirements for proficiency testing"), reviewed by the ISBER PT Advisory Group and approved by the ISBER PT Coordinating Body (for more information, see http://www.isber.org/proficiency_testing/). Specific software has been configured for the needs of the biorepository PT schemes. A pilot program was conducted earlier this year among members of the ISBER Biospecimen Science Working Group[2] for the first two schemes, "DNA Quantification and Purity" and "RNA Integrity" assessment. The pilot program was fully successful. For the DNA Quantification and Purity scheme, the assigned value was 53.03 μg/ml (±3.25 μg/ml) and all participants obtained $|z| < 1$ scores. For the DNA ratio, the assigned value was 1.86 (±0.05) and all participants obtained $|z| < 1$ scores. For the RNA Integrity scheme, the assigned value was RIN 8.76 (±0.21) and 66.6% of participants obtained $|z| < 1$ scores, 22.2% of participants obtained $|z| < 2$ scores and 11.1% obtained $|z| < 3$ scores.

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Purpose

The ISBER PT Program provides inter-laboratory comparisons that are used to: (a) determine the performance of individual laboratories for biospecimen quality control tests and identify inter-laboratory differences; (b) identify testing problems that may be related to individual staff performance or calibration of instrumentation used in biospecimen quality control and provide guidance for remedial actions; (c) provide the necessary External Quality Assessment (EQA) tool for biorepositories that want to pursue accreditation; (d) determine the performance characteristics of new biospecimen quality control methods and their comparability with the current methods; and (e) provide additional confidence to biospecimen end-users.

Significance

The discovery, validation, and clinical evaluation of biomarkers depend upon the availability of a large number of standardized specimens. This poses a major challenge, given the multiple potential sources of specimens and the varying conditions under which they are collected. While the technology for multiplex platforms for the analysis of samples is flourishing, the current developmental bottleneck is achieving equal quality of the specimens used for the research and development (R&D) of new tests for diagnostic, prognostic, and therapy response markers. Many of the specimens that are currently used cannot be properly documented for origin, preparation, and quality. The lack of reliable guidelines for quality control of specimens and their derivatives to be used for research and clinical tests can negatively affect the research progress in support of the prevention, diagnosis, and treatment of life-threatening diseases. The delay in reasonable assessments such as proficiency tests to improve the quality of science also has a negative financial impact on research. Human specimens are the bridge between biomedical and clinical research and future patient care. While these activities may be regulated by quality assurance protocols and procedures, few guidelines are available to ensure the quality of the human specimens on which they depend.

Biorepositories (which store and distribute biological samples) and research facilities (which receive and use these samples in their research projects) may perform quality control (QC) assays on the samples. However, until now, no single source PT Program intended for multiple users has existed for the assessment of performance of an on-site QC testing activity. This has precluded investigators and clinicians from comparing results of tests performed in different laboratories. At present, widespread characterization assays include DNA quantification and purity assessment by spectrophotometry or fluorometry, RNA integrity assessment by RNA Integrity Number (RIN) measurement, cell viability assays by trypan blue exclusion, calcein, ATP measurement, or other assays. These assays are useful but are not sensitive enough to assess common preanalytical variations, such as delays before blood centrifugation, the total time of tissue cold ischemia, or the duration of sample cryopreservation. This is why new biospecimen QC methods are needed. ISBER will incorporate new QC methods in future PT programs as they become validated.

A PT Program corresponding to such assays fulfills the needs of repositories worldwide that perform quality control tests on their samples. Additionally, the PT Program can be invaluable to public and private research laboratories, which are the end-users of the samples. The benefits are that the PT Program includes the assurance of accuracy and precision of the participant laboratories. These benefits are valuable because ISBER is an international society, and the greatest (and unique) advantage of these PT Programs lies in their international character.

Potential impact

PT is expected to have a significant impact on the collection and sharing of biospecimen information and biospecimens themselves including: (a) implementation of a specimen quality management system; (b) adoption of appropriate and validated quality controls, according to GCLP (Good Clinical Laboratory Practice); and (c) assignment of values (quantitative or qualitative) to biological samples. The proposed strategy to impact the domain of biobanks through PT Programs is in line with the strategy outlined by government agencies, eg the United States National Cancer Institute (NCI) *Best Practices for Biospecimen Resources* (http://biospecimens.cancer.gov/practices/2010bp.asp), which are in turn based on ISBER's *Best Practices* (http://www.isber.org/bp/BestPractices2008.pdf, most recently published in *Cell Preservation Technology*, 2008, 6:5-58; DOI: 10.1089/cpt.2008.9997). ISBER's Education and Training Committee is now finalizing the 3rd edition of the ISBER *Best Practices*, hallmarked by intensive international input. Novel QC tools that will be developed in the next 5 years will be incorporated in the ISBER PT programs, to enhance their widespread adoption and validation.

The application of the ISBER PT program will affect current research and clinical practice paradigms at different levels:

1. *Potential impact on biospecimen science and biorepositories*. The ISBER PT Program represents an important development in the biorepository community, and in promoting collaboration between academic repositories and the diagnostic and pharmaceutical industries. Presently, multi-centric (often international) human clinical studies are increasing in frequency and will be important in future patient care. Therefore, research biorepositories need to guarantee comparability of such samples without institute-dependent intrinsic bias. Sample validation/characterization is the only way to guarantee that samples distributed to industry or academic researchers meet the required quality specifications and correspond to an activity that can be accredited by an external body. The acceptance of biological samples and associated data between countries will be facilitated if biobanks can offer or propose validation protocols for their samples and ensure the accuracy of their results. PT Programs represent one way of achieving this goal. PT Programs are expected to improve the quality management systems of biorepositories and are designed to promote the quality and the economic health of the biorepository industry by diminishing the actual "asymmetric information" gap between biospecimen providers and biospecimen end-users.
2. *Potential impact on personalized medicine industries*. The schemes of the ISBER PT program represent an essential infrastructural development in the field of biomarker

identification and validation. There is rising awareness of the problem of clinical sample variability. In addition, the development of a normative framework that applies to both biorepository and research communities must be assessed. The diagnostic and pharmaceutical industries are facing the new challenge of "personalized medicine" as a result of the amount and diversity of data created through the use of molecular biology and pharmacogenomics technologies. These technologies have also created opportunities for the development of new tests to determine patients' response to a drug and to screen out inappropriate drug candidates. Since the measurement of analytical data or the limitation of measurement is dependent on the access to highly standardized and accurately characterized specimens, the ISBER PT Program is expected to ultimately contribute to personalized medicine development.

The potential of the ISBER PT Program lies in the development and implementation of schemes providing objective characterization of biospecimens that are independent of the specific processing method that has been used for their preparation and storage. The advancement of collaboration between academic repositories and the diagnostic and pharmaceutical industries is an important development for the biorepository community. The accreditation of laboratories for the performance of these quality control assays can be a future outcome of PT programs and could represent a major service of technical assistance to biorepositories and/or end-users of samples.