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Review

Ensuring Sample Quality for Biomarker Discovery Studies – Use of ICT Tools to Trace Biosample Life-cycle

SILVIA RIONDINO[1,2*], PATRIZIA FERRONI[3*], ANTONELLA SPILA[1], JHESSICA ALESSANDRONI[1], ROBERTA D'ALESSANDRO[1], VINCENZO FORMICA[2], DAVID DELLA-MORTE[1,2], RAFFAELE PALMIROTTA[3], UMBERTO NANNI[4], MARIO ROSELLI[2] and FIORELLA GUADAGNI[1,3]

[1]*BioBIM - Multidisciplinary Interinstitutional BioBank, IRCCS San Raffaele Pisana – Research Center, Rome, Italy;*
[2]*Medical Oncology, Policlinico Tor Vergata Biospecimen Cancer Biorepository (IIV Bio. Ca. Re), Department of Internal Medicine, University of Rome "Tor Vergata", Tor Vergata Clinical Center, Rome, Italy;*
[3]*San Raffaele Rome University, IRCCS San Raffaele Pisana, Research Center, Rome, Italy;*
[4]*Department of Computer, Control and Management Engineering "Antonio Ruberti", "Sapienza" University, Rome, Italy*

Abstract. *The growing demand of personalized medicine marked the transition from an empirical medicine to a molecular one, aimed at predicting safer and more effective medical treatment for every patient, while minimizing adverse effects. This passage has emphasized the importance of biomarker discovery studies, and has led sample availability to assume a crucial role in biomedical research. Accordingly, a great interest in Biological Bank science has grown concomitantly. In biobanks, biological material and its accompanying data are collected, handled and stored in accordance with standard operating procedures (SOPs) and existing legislation. Sample quality is ensured by adherence to SOPs and sample whole life-cycle can be recorded by innovative tracking systems employing information technology (IT) tools for monitoring storage conditions and characterization of vast amount of data. All the above will ensure proper sample exchangeability among research facilities and will represent the starting point of all future personalized medicine-based clinical trials.*

*These Authors contributed equally to this study.

Correspondence to: Prof. Fiorella Guadagni, MD, Ph.D., Interinstitutional Multidisciplinary Biobank, IRCCS San Raffaele Pisana – Research Center, Via di Val Cannuta 247, 00166, Rome, Italy. Tel: +39 0652253733, Fax: +39 0652255668, e-mail: fiorella.guadagni@sanraffaele.it

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With the advent of "omic" sciences, the significance and applications of precision medicine could allow the design of personalized health therapy regimens, based on individual biological variability. To this purpose, it is mandatory to identify the factors that predispose an individual to disease, recognize the features of progression, and predict patient response to treatment. Under this light, the availability of a large number of standardized biological specimens has assumed a crucial role in the field of biomedical research, especially since many research activities are seriously invalidated by the different methodological approaches employed during sample handling and storage.

In the present review we consider certain issues related to proper management of biospecimens in order to enable biological resource Centres to establish shared searchable collections of samples, that might pose the basis for future personalized medicine-based clinical trials.

A systematic literature review was performed by searching PubMed-Medline, Scopus and Web of Science. Inclusion criteria regarded relevant research studies, among those published in English. For the selection of the search terms we referred to previous literature reviews and the key words of leading papers on the topic of biomarker discovery and biobanking as provided by ISBER guidelines (www.isber.org. Last access to databases: July 2015.

Personalized Therapy, Lessons from Molecular Medicine

In recent decades we have witnessed a substantial change in our approach to medicine. A great shift has been witnessed,

going from a global approach, that considers the various clinical entities at the same level, to a growing demand for providing personalized medicine that, besides predicting which medical treatments will be safe and effective for a given patient, will also provide indications for patients to whom treatment could be useless, or worst, harmful. This new "vision" has given birth to a deeper research in the "omics" field (proteomics, peptidomics, lipidomics, metabolomics, trascriptomics) in order to identify more promising tools for risk assessment, identification and validation of new diagnostic biomarkers, drug targets or improvement of tailored treatment strategies (Figure 1) (1). This passage from an empirical medicine to a molecular one has, therefore, emphasized the importance of biomarker discovery.

Furthermore, understanding the genetic, cellular and molecular basis of many diseases has greatly improved thanks to the introduction of new biotechnologies, that promote the implementation of biomarker discovery studies designed to identify new biomarkers that predict, in a personalized way, the evolution of the disease, the lack of response to a given drug treatment, or the possible occurrence of side-effects. In addition, the integration of computerized data derived from studies of biomarker discovery has helped defining new algorithms for the definition of risk to be applied in a customized clinical approach that, ultimately, would allow the prompt application of treatment protocols optimized for each individual patient and an economically more rationale use of drugs (2).

In order for biomarkers to be clinically approved, they should be confirmed and validated on a large number of specimens and should be reproducible, specific, and sensitive (3). Once validated, they can provide valuable information about screening, follow-up, and prediction of response to treatment (4). In an accurate analysis of the major pitfalls in the translation from biomarker discovery to clinical utility, Drucker has identified three areas of potential intervention, the possibility to make different selections before initiating the discovery phase, the adoption of biomarker characterisation/validation strategies, and the robustness of analysis techniques used in clinical trials (2).

Biological Banks and Biospecimen Science

Given the potential applications of biomarker discovery studies to the pharmaceutical, biotechnological and bioinformatics fields, one can understand the great interest of biomedical research in Biological Banks. Indeed, technological advances in various fields of human research has allowed for designing research projects involving a large amount of biological samples from high numbers of well-stratified individuals affected, carriers, or predisposed to genetic or environmental diseases, or from those exhibiting variable response to drugs, possibly in comparison with matched control groups. Consequently, sample availability has assumed a crucial role in the field of biomedical research, at the point that many research activities are seriously invalidated by the heterogeneous quality of the human specimens used (5, 6). At present, in fact, the heterogeneity in the quality of collected biomaterials is often significant, at a point that many researchers feel that it may contribute to irreproducible results, impeding the development of more effective therapeutics and diagnostics (7, 8). This issue was extensively discussed at the 2nd Annual Biospecimen Research Symposium organized by the Biorepository and Biospecimen Research Branch (BBRR, formerly Office of Biorepository and Biospecimen Research) of the Cancer Diagnosis Program at the National Institutes of Health, USA on March 2009, during which the results of a survey carried-out among researchers were reported, showing that a substantial proportion of them feels that sample quantity/quality was defective, thus limiting their scope of work (Figure 2) (http://biospecimens.cancer.gov/meeting/brnsymposium/2009/).

In this context, Biological Banks, defined in the Oviedo Convention as "operational units that provide a service for the storage and management of biological material and associated clinical data, in accordance with a good laboratory practice, privacy law and ethics guidelines", are an important font of resources even after many years of collection. These facilities, also thanks to the implementation of standard operating procedures (SOPs), harmonization of the available information, together with the development of processes of data integration, are well-suited to the growing demand for biological samples homogeneous for pathology, clinical features and collection and storage procedures, to be included in research protocols.

Among the goals pursued by a Biological Bank, the following should be highlighted:

- To encourage scientific research for the identification of pathophysiological mechanisms.
- To provide an adequate number of biological samples for studies of biomarker discovery for the identification of new predictive, diagnostic and/or prognostic biomarkers, potentially transferable to clinical applications, up to innovative treatments such as "targeted therapy".

Accordingly, for the constitution of an efficient Biobank it is not only necessary that the biological material is collected, handled and stored in a technically appropriate manner, but that samples are also accompanied by a complete clinical documentation, archived through a computer support that allows for complete recovery of data in accordance with the protection of existing legislation on privacy of the donor subject. Such a tracking system translates into an immense value being able to allow data exchange process with consequent exponential beneficial effects for research (with a significant improvement in inter-

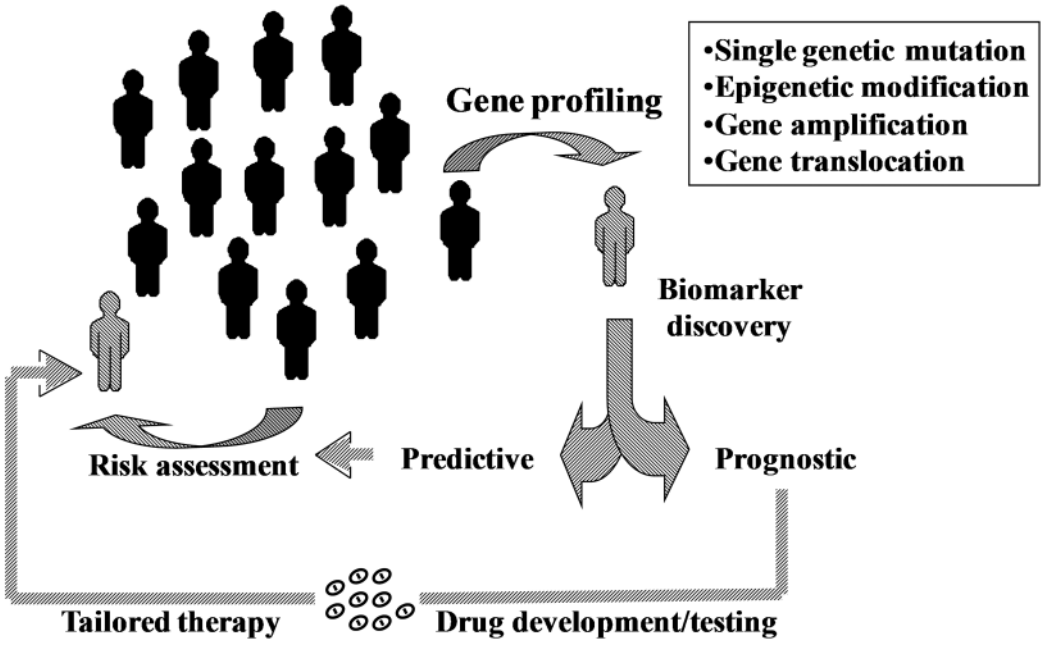

Figure 1. *From gene profiling to tailored therapy. Gene profiling allows patient pharmacogenomic evaluation and disease-specific molecular biomarker identification. A prognostic biomarker will help develop new therapy approaches later employed in populations of patients who are likely to respond to these treatments, and for whom the specific biomarker will have a predictive role.*

institute sample exchangeability), hospitals, industries, and, by extension, citizen health care. Biobanks are, thus, important resources whose value resides not only in the stored material, but also in the associated information that are made accessible for scientific investigation. Collecting samples and data, and hence storing them, allows not only to gain a large collection of cases for future studies, but also to follow-up the evolution of a given disease.

One example of clinical application of personalized medicine comes from the management of cancer patients, that represents a key area of care in Europe. Cancer, in fact, is a major cause of morbidity and mortality worldwide and, according to the latest estimates, the incidence and prevalence of malignant tumors are increasing in both sexes, boosted by the increasing aging population. Over the past two decades, the progress made with the introduction of new therapeutic approaches, better organization of services, increase investment in support services, and improvement of screening services and prevention, has resulted in an increase in survival and a reduction in mortality from cancer, and in increased costs of management for cancer patients. Indeed, it now appears evident that conventional therapeutic approaches based on the choice of chemotherapy on the basis of histopathological evaluation of the tumor is out-dated, in an era in which personalized oncology is based on a pharmacogenomic evaluation and on the way neoplastic cells respond to targeted chemotherapeutics (Figure 3) (9). Thus, research has focused on the cellular and molecular mechanisms of tumor development, growth and metastasis, which has led to the identification of new cancer-specific molecular targets (10-12), generally consisting of single genetic mutations, epigenetic modifications, or gene amplifications/translocations (13). The understanding over the molecular basis of cancer has allowed for significant improvement in assessing the etiopathogenetic mechanisms, identifying new biomarkers as determinants of outcome response rates, ensuring survival and safety (14, 15), predicting patient's failure to respond to drug treatment, or identifying and minimizing the occurrence of side-effects, through integration of the acquired genetic knowledge and knowledge on drug effects (reviewed in 9, 16, 17). Thus, it should be highly valuable to understand how gene mutations generate different clinical features with different behaviours concerning both their aggressiveness and response to treatment, in order to set-up the best tailored-therapy for each patient (18). Indeed, this will allow identification not only of patients who may benefit for a targeted-treatment, but also of patients for whom a pharmacogenomic-based therapy might be detrimental (Figure 3).

In this light, the availability of a Biobank with SOPs diversified depending on the nature of test samples, will allow execution of specific studies for identifying molecular

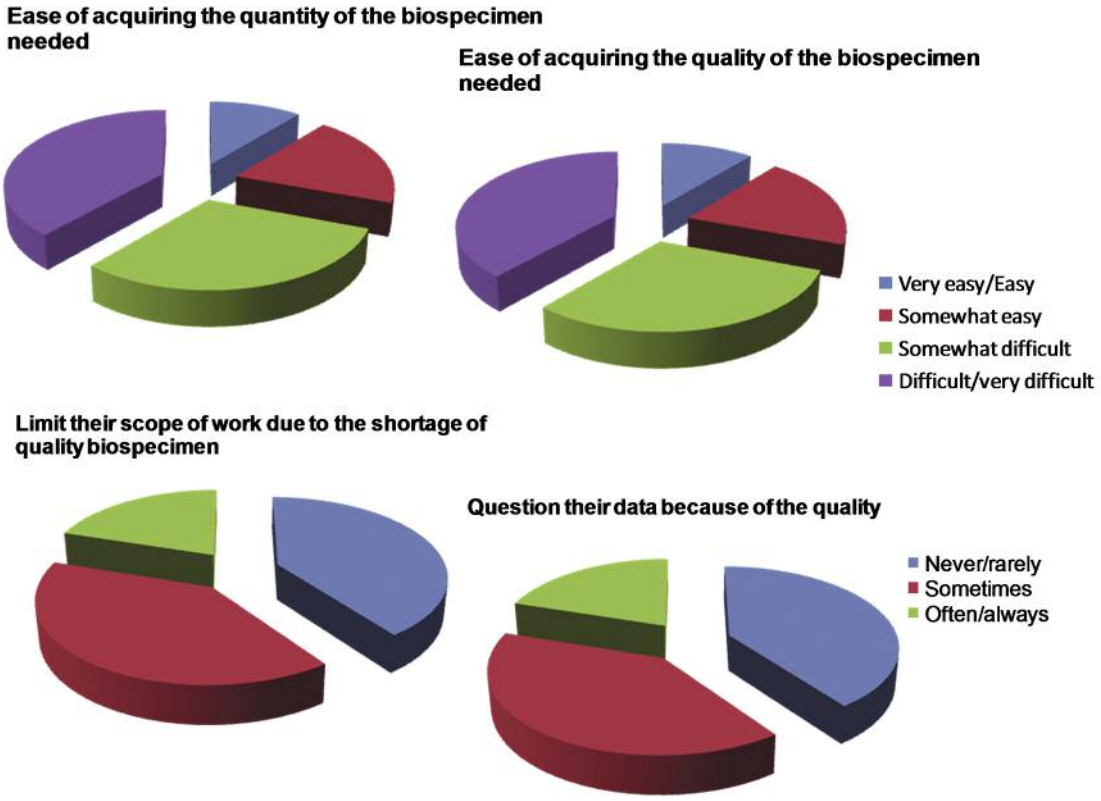

Figure 2. *Difficulties and consequences in acquiring the quantity of quality samples needed. Variability of collection, processing, storage, and annotation of the majority of human bio-specimens available for research, have been included in a survey directed to researchers. A lack of ease in acquiring the quantity of "quality" biospecimens needed emerged, as well as the the fact that many investigators question their data due to the shortage of quality samples used, which, thus, limits the scope of their work. Modified from Compton CC. The Cancer Human Biobank (CaHuB): (Advancing the Vision of Personalised Medicine. Available at: http://biospecimens.cancer.gov/ meeting/brnsymposium/2009/).*

markers and genetic profiles for certain chronic disorders, *e.g.* cancer, that will help draw guidelines aimed at optimizing the risk/benefit of chemotherapy in cancer patients, with the ultimate goal of improving clinical outcomes and quality of life (QoL). Of particular note are the surveys conducted over the last three years by our working group, in order to: (i) identify biomolecular patterns that correlate to cancer development, to predictability of response of specific therapeutic approaches, as well as to the possibility of adverse events during treatment, in order to enhance both prognosis and QoL of patients (19-24); (ii) identify candidate genes predisposing to the onset of migraine, which could allow not only a molecular classification of various clinical forms of this highly disabling neurological disorder, but also a tailored-treatment and/or prophylactic approach (25, 26); (iii) investigate novel genetic variants involved in the pathophysiology of coronary microvascular dysfunction and ischemic heart disease, in order to design a customized clinical approach capable of improving patients' functional recovery (27, 28).

Sample Quality, a Mandatory Constraint

From the time of collection to storage and future analysis, the sample undergoes three major stages of processing: pre-analytical, analytical, and post-analytical. Unfortunately, the lack of adherence to guidelines and to standardized procedures in each of these equally important phases, has often rendered efforts to obtain reliable results in sample comparative analysis, useless and only few clinical biomarkers have proven useful and have been validated for routine clinical practice (29).

Moreover, using the right technology able to identify the proper resource for interpretation of the results is often complex, the current availability of biological material is insufficient and uneven among the various Research Centres, the existing storage areas are not always correctly handled, for organizational and/or financial reasons, and they often lack systems for control and monitoring. Inappropriate processing, handling and storage of blood samples may significantly affect the reliability of the material.

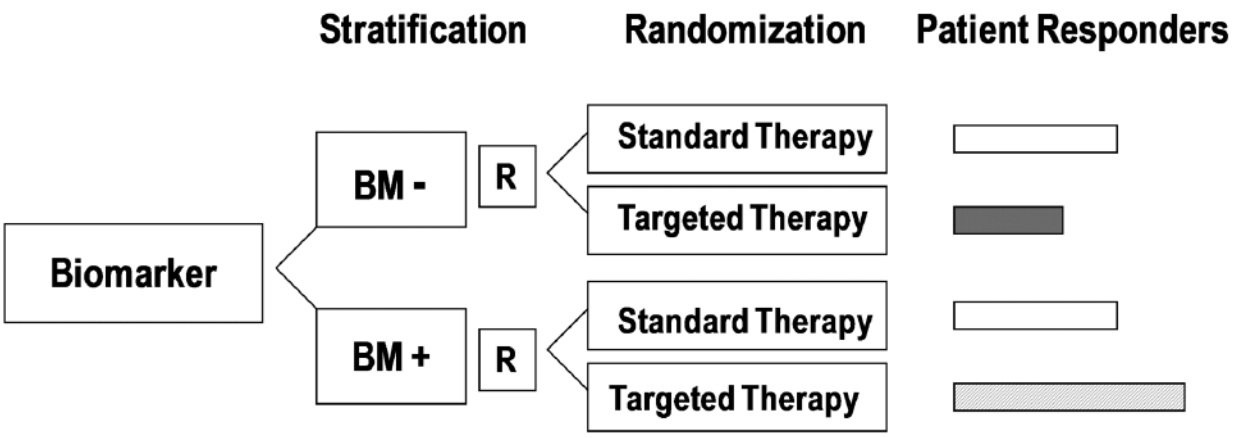

Figure 3. *Clinical outcome following stratification on the basis of presence of a predictive biomarker. The presence of a given biomarker will generate different clinical features with different behaviours concerning tumor aggressiveness and response to treatment that allow to set-up the best tailored-therapy for each patient. This pharmacogenomic-based approach will identify patients which may benefit for a targeted-treatment (dashed column), and those for whom it might be detrimental (filled column). For the latter, standard therapy (empty column) might still represent the best choice.*

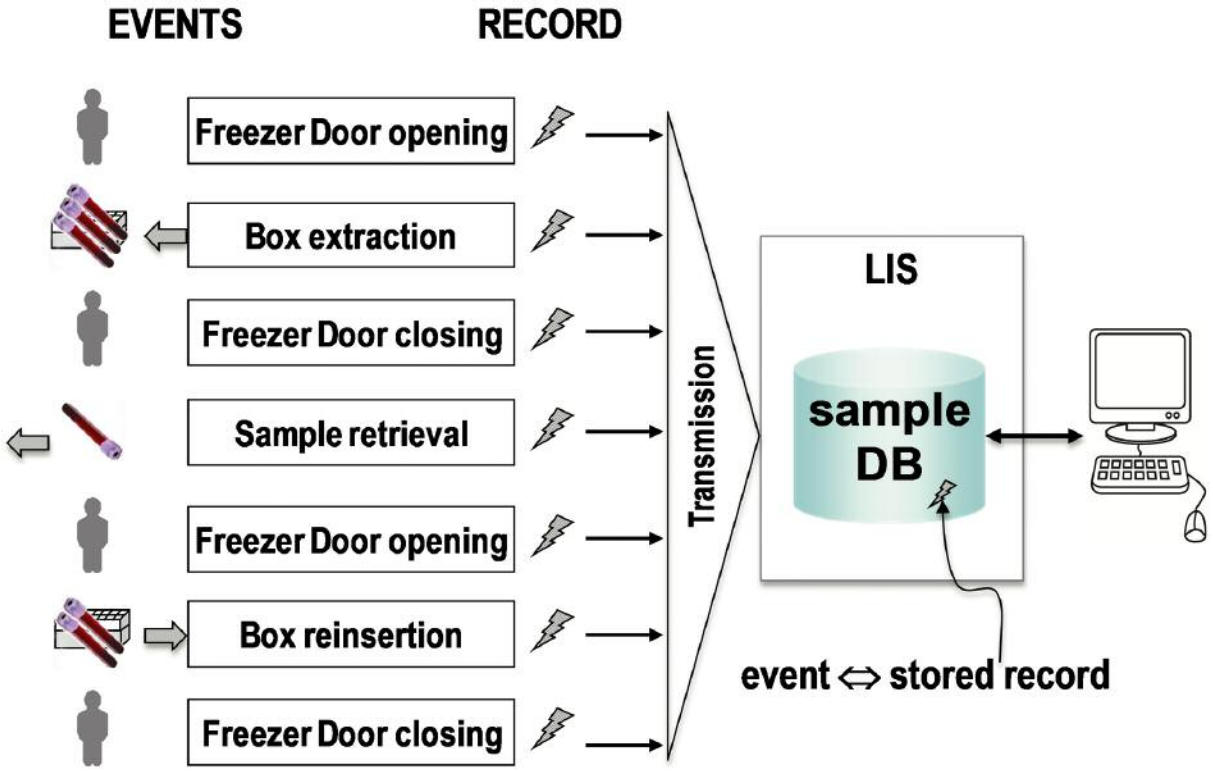

Figure 4. *Radio-frequency identification (RFID) technology to track sample storage conditions. RFID system employs a contactless passive transmission and the electronic information is written on a portable remote writer/reader device that allows multiple and contemporary readings of RFID supports. A time report is provided for every operation performed, which is recorded in session logs (operator identification, door opening/closing, rack insertion/extraction, sample insertion/retrieval) by means of a hand-held RFID reader. All data will be transmitted to Laboratory Information System (LIS) and will become part of the sample stored record (Modified from 54).*

The concept of "sample quality", already raised in several reports, could be rendered as "the ideal sample for a given purpose", and could thus be translated into “sample suitability”, and should last for the sample entire life-span. However, in a Biobank, once the "goodness" of a sample is ascertained, its “quality” depends almost entirely on pre-analytical variables related to the method of preservation of the sample itself. In particular, it is widely dependent on storage conditions and on the stability of freeze/thaw cycles (30).

With regard to storage conditions, a sample can be considered stable if not altered by thermal, mechanical or chemical stress induced during freezing and thawing, stabilizer cytotoxicity, crystallization damage, repeated freeze/thaw damage and osmotic lysis. Indeed, proper storage ensures that sample degradation is minimized, in order to avoid that information inherent to samples can be seriously compromised by unsuitable preservation practices. It is estimated that about 10% frozen samples are unsuitable, due to extra-analytical phases, lack of standardized procedures, and specimen acquisition, handling and storage (31).

Temperature control during sample processing is essential and determines the suitability of the sample itself (32-34). Ideally, the storage of many aliquots of small volumes (35) should ensure a resource for a wide range of future scientific researches, and a temperature of -80˚C should be adopted in order to allow for soluble biomarkers to remain intact (4, 33, 36, 37). Alternatively, storage in liquid nitrogen may be required for certain very easily-degradable biomarkers (38, 39). Different storage conditions are required depending on the type of sample used and even of the biomarker under investigation (40). For instance, while isolated RNA must be stored at -80˚C (41, 42), isolated DNA, whose recovery significantly decreases at RT, can be stored at 4˚C for weeks, and kept at -80˚C for several years (43, 44). Conversely, live cells are stable at RT for up to 48 h but should be either cultured or cryopreserved in liquid nitrogen (45). However, the literature extensively reports that optimal storage conditions are different depending on the cell type and the preservation medium used (for review see 46). Furthermore, storage of serum at -20˚C is unsuitable for the vast majority of biomarker-based researches (34) and time-dependent decay has also been reported for many bodily fluids (38, 47, 48). Finally, some processing conditions negatively affect the sample status, such as out of range temperatures, multiple freeze-thaw cycles (30, 34), which may even occur during the time intervals between processing steps. The Biospecimen Reporting for the Improved Study Quality (BRISQ), has released recommendations for reporting data elements of human biospecimens (solid tissues and bodily fluids), expanding to the whole life-cycle of a sample (from collection to analysis) aimed at harmonizing the methods to trace information and facilitate effective inter- and intra-laboratory specimen sharing/use. (49). The importance of procedure setting-up and recording along the whole life cycle of biological specimens, allows to track the history of the sample itself and to detect, eventually, the evidence of decay and to rapidly identify artefacts during downstream sample assay (50, 51).

ICT Tools in Biobanking

The technical-scientific interest in bio-repositories includes, of course, more disciplines, concerning not only the health sector, but also the high-tech ICT. In fact, medicine and biology have the indispensable need to use IT tools for storage and characterization of the vast amount of data that modern biological research produces thanks to technological progress.

Following the recommendations published on the guidelines of the National Institutes of Health BBRR (52) foreseeing the need for more detailed information of samples used for research activities, a turning point has been represented by the development of the sample pre-analytical code (SPREC) labeling system (50). This system consists of a 7-digit code, in which each element corresponds to a punctual pre-analytical variable and contains a string of letters (different for each type of tissue) (53) that provides detailed information on all pre-analytical procedures that a single stored specimen encountered during its manipulation (53, 50).

Many Information and Communication Technology (ICT) tools have been proposed to offer comprehensive insight into the specimen features and to trace the procedures it has undergone. This is the case of system warehouses infrastructures, that have been designed to better integrate clinical and research data of samples stored in biological bank facilities, combining clinical data and research results. Examples of this technological tool are represented by the SPRECware (54), the ONCO-i2b2 (55) and the p-BioSPRE (p-medicine Biospecimen Search and Project Request Engine) (56) platforms, which have been set-up to find clinical data and all the information associated with pre-analytical encoding related to patient’s sample through query tool interfaces and to provide tools for biological specimens and related clinical data exchange.

A comprehensive guideline, Model Requirements for the Management of Biological Repositories (BioReq), which, among the ICT requirements aimed at identifying the applicable tools to develop a Biobank information system, has reported a flow chart presenting the biological sample lifecycle processes from sample acquisition, through sample and data management, to sample destruction and distribution (57). In this light, a fine application of ICT to Biorepositories, is provided by radio-frequency identification (RFID) (54) or bluechiip® (58) technologies, which have been employed to ameliorate the tracking of the whole biospecimen chain of custody (54, 59-61).

RFID is a technology that that does not require bar code labelling, but uses communication *via* radio waves to

exchange data between a reader (interrogator) and an electronic tag attached to an object (label), for the purpose of identification and tracking (54). The cryotag uses a transmission contactless passive type and the electronic information is copied on a portable remote writer/reader device that allows multiple and contemporary readings of RFID supports and can associate a time record to every operation performed. Each operation concerning the insertion or retrieval of samples is recorded in session logs (including the identification of the operator and a sequence of operations, which may consist of inserting and/or extracting a rack or a single aliquot into/from a rack) by means of a hand-held RFID reader (54) (Figure 4). All data will then be transmitted to LIS and will become part of the sample stored record.

For its own features, RFID, radio waves, due to its low sensitivity to dirt, wrinkling, solvents, temperatures (59, 60), and pressure conditions (62), has proven an ideal tool to track the life cycle of samples between the end of the pre-analytical phase and the beginning of the analytical one, up to long-term storage (54). The Multidisciplinary Inter-institutional Biobank (BioBIM) of the IRCCS San Raffaele Pisana in Rome, Italy, has reported a pilot experience by collecting detailed reports encompassing the storage stages of biosamples, integrating data in the existing Laboratory Information System (LIS), and testing the durability of information at low temperatures, which resulted stable over a period of 5 years (Guadagni, F. Personal communication). One important feature of this technology is represented by the capability of RFID to read several transponders simultaneously, recognizing each individual sample, to contain kilobytes of data and to be potentially re-usable several times, since the transponder can be written-over an unlimited number of times. This, in addition to the possibility to place RFID tags on the cryovials, or on the wall of cryoplate/cryobox or, even, on the freezer door (63), allows to build-up a significant cost-effective policy.

The bluechiip® technology, in turn, is a passive wireless technology based on MEMS (micro electromechanical systems) equipped with a bluechiip® button ID device embedded into a Corning® 1.2-ml cryovial and the bluechiip® Matchbox® reader (56). In a pilot study conducted by the American Type Culture Collection (ATCC) to test bluechiip® efficiency against standard 1-D bar-code labelling systems, bluechiip® proved reliable when tested in extreme conditions (*i.e.* freeze/thaw centrifuge, snap-freezing, frost, autoclaving, microwave), in comparison to bar-code labels (56).

An essential feature of these IT devices – RFID or bluechiip® – is the possibility to implement solutions where the "events" are tracked autonomously, *i.e.* there could be no need of an explicit "reading" action performed by the involved operator. This opportunity reduces dramatically the possibility of human errors while simplifying the activities of operators who can focus on proper handling of samples.

Concluding Remarks

Based on these considerations, the implementation of a clinical database including clinical information of case studies relevant to cancer patients, associated with a Biobank able to collect biological samples from these individuals, represents an essential tool for evidence-based studies, in which the optimization of the SOPs and harmonization of the available information, together with the development process of data integration, could readily facilitate biomedical research. Of course, the availability of systems for monitoring storage conditions in bio-repositories, that ensure proper sample exchangeability among research facilities, will represent the starting point of future personalized medicine-based clinical trials, and will be of outmost importance in the evaluation of health needs of an increasing patient population and for planning of interventions aimed at social welfare prevention and improving the QoL of patients through the standardization of differentiated treatment programs. Additional advantages would be to better-define and develop a set of clinical/ diagnostic algorithms enabling for more accurate classification of the biological characteristics of each patient, accompanied by information predictive of clinical outcome and/or responsiveness to therapy. Ultimately, this will translate into obvious repercussions on the National Health Service and industry, with a consequent improvement in public health.

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