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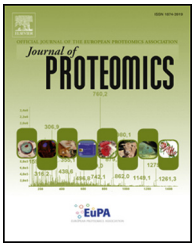

Review

Developments in biobanking workflow standardization providing sample integrity and stability☆

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ABSTRACT

Recommendations and outlines for standardization in biobanking processes are presented by a research team with long-term experience in clinical studies. These processes have important bearing on the use of samples in developing assays. These measurements are useful to document states of health and disease that are beneficial for academic research,

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Mass spectrometry
Diseases
Standardization

commercial healthcare, drug development industry and government regulating agencies. There is a need for increasing awareness within proteomic and genomic communities regarding the basic concepts of collecting, storing and utilizing clinical samples. Quality control and sample suitability for analysis need to be documented and validated to ensure data integrity and establish contexts for interpretation of results. Standardized methods in proteomics and genomics are required to be practiced throughout the community allowing datasets to be comparable and shared for analysis. For example, sample processing of thousands of clinical samples, performed in 384 high-density sample tube systems in a fully automated workflow, preserves sample content and is presented showing validation criteria. Large studies will be accompanied by biological and molecular information with corresponding clinical records from patients and healthy donors. These developments position biobanks of human patient samples as an increasingly recognized major asset in disease research, future drug development and within patient care.

Biological significance
The current manuscript is of major relevance to the proteomic and genomic fields, as it outlines the standardization aspects of biobanking and the requirements that are needed to run future clinical studies that will benefit the patients where OMICS science will play a major role. A global view of the field is given where best practice and conventional acceptances are presented along with ongoing large-scale biobanking projects. The authors represent broadly stakeholders that cover the academic, pharma, biotech and healthcare fields with extensive experience and deliveries. This contribution will be a milestone paper to the proteomic and genomic scientists to present data in the future that will have impact to the life science area.
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Contents

1. Introduction

The healthcare sector and the research community are in great need of diagnostic biomarkers that provide accurate indices of health status that can be used to assist clinical decision-making. The measurement of these biomarkers in accurate and reproducible quantitative indices further requires measures of standardization guaranteeing the quality control of the clinical samples providing these biomarkers.

It is also essential at this stage to insure that the technology platforms used to provide such biomarker measurements also are consistent in sensitivity and specificity irrespective of their global location. The measurement performed on an instrument in India should provide the same level of accuracy as an instrument in Sweden, United Kingdom or the United States.

Samples collected for clinical analysis are either used immediately or discarded or they are stored in biobanks for future use. The current methods of storage of samples are often different in different laboratories, hospital institutions, and government agencies. Consequently, one of the challenges encountered in biobanking activities has been the difficulty in inter-laboratory studies. Differences in experimental designs, protocols, as well as reagents and disposables used will impact on data quality and reproducibility. Standardization and best

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practice protocols have been proposed to address this problem [1]. Consequently, the strategic roles in biobanking are a matter at heart, where new directives and best practice with clear standardizations and procedures need to be applied.

Currently we have a situation where clinical samples are managed in biobanks spread throughout the world for biomedical research, both in the public and in the private sectors. A general concept is that each biobank follows its own protocols and in general implements its own quality criteria. This leads to a large variation on the way that the quality, integrity and performance of individual samples can vary extensively. A consequence of the current status is that experimental studies using these resources therefore lose statistical power and significance. An evaluation of the current tools at hand in biobanking and the resulting recommendations for improving this *status quo* is a very important first step in providing a best-case analysis that can be used as a model for improving current practice. It is likely that such evaluations will point out local recommendation linked to those local environments. Irrespective whether the enterprise of biobanking is being conducted on a small scale or on a large scale, the area of best practice in biobanking has many common elements that are universal to all biobanking activities. We envision that in the future, even the physical structure of sample storage will have common standard and integration with other areas of patient care [2]. Central to this thinking will be the development of consensus of standardized procedures and policy to guide future questions of the how, and where, and why samples will be utilized in providing benefit to the patient. Previously, Time magazine published an article on Ten Ideas Changing the World Right Now, where biobanking was highlighted as an important activity with important potential consequence for mankind [3].

The challenge at hand is to have the potential to build large standardized and high quality patient sample collections that offer information that can contribute as a critical factor for successfully developing new drug, and diagnostics developments. Biobanks will fill an important gap here that is strategic and key for future healthcare developments.

2. Economics and biobanking development

One should not underestimate the funding needed to build and preserve biorepositories [4]. Consequently, there is a need to further develop the value and treasure that biobanking holds. It is still a challenge for our healthcare society to develop, approve on the quality, standardize and organize modern units being built for future use. The demands on successful usage of biobank materials are many, especially in the area of novel drugs developed and introduced into the hospitals. The timeline for drug development in 2010 was 12.4 years for a drug to go from idea to the FDA. The budget needed to reach this in the pharma industry is $1.29 billion, on average. In the future, we need to be able to allocate and use biosample repositories to build knowledge and understanding of the molecular and environmental basis of human diseases. Our goal with standardization of biobanks and global initiatives in this field is to improve both diagnosis and treatment of disease in the world. Today there is a global trend in investing into biobanking developments with large resource investments. These developments are on one hand within the healthcare sector, and on the other hand in pharmaceutical companies. Considering that the pharma sector uses $127 billion (2010 for the top 500 companies), for drug development on average on a yearly basis, it's not an understatement that biobanks can easily be used to capitalize the value and to improve on the drug development efficiency. The research and healthcare societies will also need to support the development of integration systems that allow for search routines on sample collections, and types, as well as datasets that have been generated from these cohorts. At the end of the day, both the Chromosome-centric Human Proteome Project (C-HPP), as well as other global research activities are looking for tools that can bridge the data and deliverables that will be of major use in future drug development and patient care.

3. Ethical and legal aspects of biobanks

It is a given prerequisite that patient integrity needs to be protected in all circumstances of sample acquisition and eventual use. Most countries have such ethical laws in place that provide this protection. For biobanks in general, protecting the donor against research risks is a key responsibility. In Europe there is the biobank law that has a common basis in European countries and where each European Union member state has established their own national biobank law. There are global differences to the approvals needed for the establishment of biobanks, but in general there are international ethical guidelines [5]. The analysis of data must also be considered satisfactory by potential donors, since unless potential donors are adequately reassured, biobanking initiatives can be seriously compromised. The data generation in combination with clinical output from patient registries can be utilized in order to provide correlation and computational statistics discovering new phenotypes.

There is the risk that the patient data may fall into uses that are detrimental for the patient and society, so data protection is a key concern. In order to put this risk in perspective as far as hospital-based biobanks are concerned, fully identified patient data, that includes the personal, clinical as well as the laboratory data, is routinely only stored on protected hospital databases and servers that support their medical care. The standard routine procedure today is to de-identify individual samples with codes that can only be translated back to individual identities by the primary holders of the study permissions granted for samples to be acquired, stored, analyzed, and reported.

4. Guidelines and standardization

As of today, we are as yet still developing our understanding of how to best manage the collection, processing and storage of samples within biobanks. Each country based activity in biobanking seeks to establish its own ordered structure but in more or less an independent manner. As of today, there are no cross-border, internationally recognized guidelines from our governmental agencies on biobanking. There are many initiatives underway in Europe, North America and Asia that strive to find common standards and protocol processes rather than guidelines.

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The reasons for implementing a best practice type of operation are that the field of biobanking is immense in structure, expenses, and dedicated resources and incorporates so many different organizations and stake holders. There are unmet needs in developing standard practices in sample storage, record keeping, sample annotation, disease linkage and community/government oversight. The concept of protecting human subjects, including the collection and exchange of their samples and medical records has some level of protection under international law (Helsinki Accords, July–August, 1975) and several individual national initiates (*i.e.*, the Human Tissue Act in UK and the Act on Biobanks in Sweden). However the nature of medical care and academic medical research activities is to assemble varieties of samples from cohort studies for analysis in a variety of locations ranging from local clinics to national administered biobanks. The samples are investigated for the presence and levels of literally hundreds of different markers in hundreds to thousands of different clinical, academic, and commercial laboratories. Regardless of institution, the typical biobank workflow is illustrated in Fig. 1.

The volumes of information concerning the description of these biomarkers exist for the most part in independent repositories that could be held on everything from personal computers to mega-servers. It is easy to imagine that more than a million gigabytes of such forms of information are present today and the volume of data is expanding exponentially due to modern on-line data generation from automatic analysis instrumentation. The challenge of these activities are many and have been recently reviewed in two seminal reviews published by the American Chemical Society in their affiliated journal, the Journal of Proteome Research [2,6].

5. Standards — human blood plasma and cerebrospinal fluid

Recently we reported on the development of a blood plasma reference material that is available as a global resource for proteomic and clinical research [7]. One of the objectives with providing a high quality global plasma reference is to standardize experimental laboratory studies that include quality aspects and continuity in biobanks. Large-scale science initiatives like C-HPP will for instance benefit as one scientific program when the entire human proteome is mapped and linked to human diseases. This is a heparin reference blood plasma standard, with a Control group defined as those with CRP (C-reactive protein) levels <3 mg/L as well as the Disease group with CRP ranges of >30 mg/L. We carefully pooled the hospital blood samples with both newborn children of 1–2 weeks, as well as youngsters, middle aged, and elderly patients at the ages of 65+. We made a full characterization of these reference blood plasma standards, providing more than 60 biomarker read-outs for each reference standard, respectively [7]. More than 10,000 reference sample vials are available for global use from our clinical unit in Lund, Sweden, stored and processed upon request by −80 °C robotic processing and FDA approved LIMS.

Cerebrospinal fluid (CSF) is another common biofluid, being used for diagnosing patients with neurodegenerative and neuroinflammatory diseases. Today the number of biomarkers in CSF is limited, but expected to grow in the near future, as the number of elderly patients develop CNS diseases. Recently consensus guidelines for CSF Biobanking for CNS Biomarker Studies were presented [8].

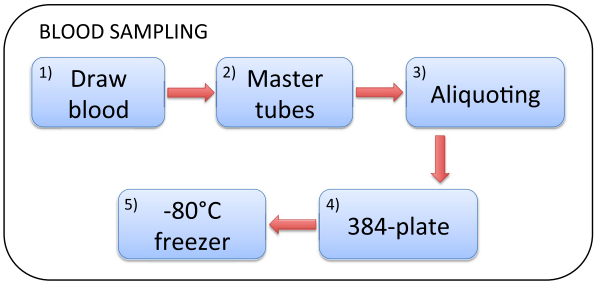

Fig. 1 – Illustration of the patient blood sampling and the proceeding workflow that the samples undergo from the clinic hospital and entering into the biobank.

6. Standardization of biobanks

The biobank archive with the sample collection therein must have a qualitative level that can meet a demand from the scientific community and the expert research teams, in order to be able to obtain the highest level of output data. It is mandatory to introduce standardization criteria that are documented in protocols and directives. These procedures can be implemented by a standard operation procedure (SOP), that guarantees the reproducible handling of clinical material. There are several different organizations that have presented best practice guidelines, such as ISBER (The International Society for Biological and Environmental Repositories, http://www.isber.org/), OBBR, IARC (International Agency for Research on Cancer, http://www.iarc.fr), OECD (Organisation for Economic Co-operation and Development, http://www.oecd.org) ABN (Australasian Biospecimen Network, http://www.abrn.net).

The SOP will be directed towards the experimental work that includes:

- standardization of clinical material sampling
- standardization of electronic records
- standardization of sample stability
- standardization of sample preparation
- standardization of storage
- standardization of analysis.

Following these standardization guidelines will offer measures of quality that are needed to ensure utilization of the sample sets in future healthcare settings. This will then serve as a unique resource in the development of new drugs and diagnostics, in addition to novel methodologies and the development of innovative technology platforms. The implementation will be directing the biobank society to use best practice needs, in order to use the patient cohort collections for future research.

Improving the ways we accumulate and exploit samples will also depend upon integrated systems that allow for search routines on biobank repositories, as well as datasets that have

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been generated from these cohorts. The objective is to develop and integrate tools that can bridge the datasets of information held with each clinical sample with substantive deliverables that can be used to create future paradigms of health care and treatment modalities. There are organizational consortia that have the ambition to embrace this enormous challenge, such as Biobanking and Biomolecular Resources Research Infrastructure (BBMRI). The BBMRI was one of the first projects entering the European Research Infrastructure preparatory phase of the ESFRI roadmap funded by the European Commission in Europe (http://ec.europa.eu/research/infrastructures/pdf/esfristrategy_report_and_roadmap.pdf).

The proteomics field also lacks guidelines for standardized ways of working in the development and description of clinical biomarkers. Modes of such clinical operation are only in part being provided by the present application procedure for approval by central regulatory agencies such as the Food and Drug Administration (FDA) or European Medicines Agency (EMEA). However, there are ongoing biomarker projects, where the FDA in collaboration with the pharmaceutical industry is looking into standardization procedures for future use. The pharmagenomic field has clear remits of how to report data to the FDA (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126957.pdf). However, such a guideline is to be expected in a not too far future that will regulate the data quality and format required to be used in drug development and clinical biomarker and diagnostic developments. The proteomic field is, and will be closely associated to the use of high quality patient samples, and it is fair to state that the future success of proteomics is closely associated to a close collaboration with biobank structures and organizations.

These current clinical markers are often proteins, or other endogenous small molecules such as fatty acids, and metabolites. The biomarkers have been defined and globally accepted by Biomarker Definitions Working Group FDA — 1998, as: "*a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention*".

6.1. *The biobanking process*

Standardization of the procedures and parts that are needed for a biobank development of high quality is a real challenge that many clinical hospital groups have spent a lot of time around the last decades [9]. Modern biobanks differ in that they usually are collecting samples by automated processing with time stamp registration at each processing step. Time stamping provides not only overall tracking management that is of critical importance in documenting the life cycle of the sample within the biobank archive, but also quality control measures that provide evidence that all samples in a study have been equivalently handled and stored. The barcode indicator that is unique for each and every sample is the information code that is being scanned at each processing step that involves a transfer step of the sample tubes in the respective sample racks.

Examples of clinical sample barcodes are given in Fig. 2. Typically 1D barcodes are being used on patient samples that have been (primary tubes) in 2D barcode assignment.

The barcode itself is unique for each and every sample. The barcode will follow the sample throughout its lifetime, and is an important control element to ensure sample integrity. The importance of the barcode is central since it holds extensive information, not only of the patient details but also potentially on the specific study, the study parameters and the link to the time of sample processing. The barcode system and structure can be used freely in order to build a specific system and structure of the biobank. Systematizations can be built, or standard procedures can be provided, based on past experiences. The barcode use most often starts with registration of the study participant or the patient within the hospital. This has become a standard procedure with standard analytical coding for biospecimens. Defining the sample analytical code has been implemented in cancer epidemiological patient cohort samples [10].

The barcode is unique for each and every sample. That means that each of the barcode needs to be developed to have only one repeat within any given biobank.

This barcode is positioned on the side of the tube for 1D barcodes, and in the bottom of the tube for the 2D barcodes. The entire workflow of a biobank sample is more or less standardized and has a number of processing steps that are common and that in many hospitals has been developed to be a standardized procedure.

The value of the samples is dependent upon developing workflows that enable future use. These biobank sample-handling steps are illustrated in Fig. 2, where barcoded samples can be scanned and tracked from collection to analysis.

6.2. *Assessing quality*

The establishment of new paradigms in mass spectrometry design, that allows rare analytes to be focused and identified, has heralded a new level of study in proteomics. This is especially important in the analysis of clinical samples, which represent complex mixtures of peptides, proteins, lipids and metabolites with broad dynamic ranges of expression. In this context, it is of utmost importance that studies providing quantitative indices of protein expression experiments are made with a qualitative experimental design using such high-end instrument platforms [11,12].

Researchers need better biomarkers of sample quality both to prevent expensive experiments on inappropriate material and to reduce artifacts, to find measures of RNA quality that work in paraffin-embedded tissue [9].

Many biobanking experts find that researchers give little thought to sample quality. An analysis of 125 biomarker discovery papers published in open-access journals between 2004 and 2009 found that more than half included no information about how specimens had been obtained, stored or processed [13].

Perhaps this is not surprising; biobanking practices have come under scrutiny only recently. The OBBR, established in 2005, released its first official set of best-practice guidelines in 2007, and last year released Biospecimen Reporting for Improved Study Quality to guide researchers on documenting how biospecimens are collected, processed and stored. The International Society of Biological and Environmental Repositories in Bethesda, Maryland, published its first edition of best practice in 2005, and a coding system — Standard PREanalytical Code — for describing what tissue had been collected and how in 2010.

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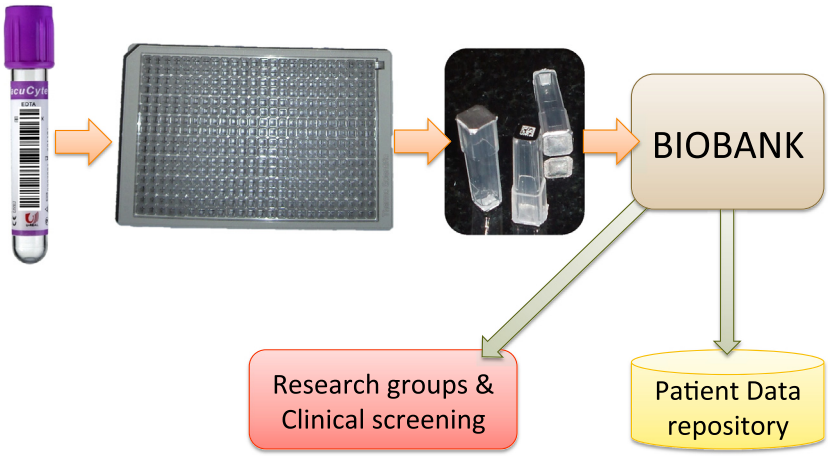

Fig. 2 – 1D and 2D barcode assignment that is unique for each and every sample and that will follow the sample throughout its lifetime.

6.3. *Blood samples*

Blood is the most commonly used patient sample type of all, and is used throughout the world for medical diagnosis and healthcare controls. Clinical chemistry units at hospitals have long standing experience in developing assays that utilize both plasma with various anti-coagulants such as EDTA, citrate and Li-heparin, as well as serum and whole blood. In some cases leucocytes (the buffy coat) are used for some clinical assays.

Millions of analysis are performed on a yearly basis in hospitals around the world with standardized protocols in a routine environment. These are part of the patient samples that are going to be stored for biobank preservation. The format of storage units is essential for the preservation and integrity of any given patient sample. Standard primary tubes ranging from 10 mL to 6, 7, and 2 mL are most commonly used for routine processing. Many of these tubes using screw cap sealing have been stored in the past. Nowadays, tube sizes of 500 μL and 900 μL, are in 96-tube formatted racks. High-density sample storage with small aliquot sample volumes is another practice that is gaining acceptance. For example, the use of 384 sampling tube formats containing 50–70 μL of blood fractions will typically result in hundreds of aliquoted fractions from a single 10-mL blood sample. We have presented standardized large-scale biosample solutions for small sample aliquoting, with a single-use biobank sample utilizing the 384-sample format. Long-term stability with respect to shipments within Europe was also included in this study, proven by a panel of biomarkers, quantified by the Clinical Chemistry unit at the Malmö University hospital. The current application is one strategy that enables us to have one-time use of samples. By many multiple replicates of the same sample makes it possible to maintain the quality of repeated analysis over decades, which is not the case if the sample goes through series of freeze–thaw cycles.

The high-density biobank storage consideration is especially relevant to large cohort studies where samples can easily reach thousands in number. The capacity of biobank archives is directly related to parallel automated processing employing liquid handling instrumentations and high-density storage at −80 °C, respectively.

6.4. *Sample stability*

The samples stored in freezer storages will preserve the stability and integrity of processing steps the previous handling procedures included. Analytes that change in unpredictable ways due to improper sample handling, processing and storage are in most cases questionable for research purposes.

Tissues that are isolated during surgery, or even blood samples, drawn from the body, cells and molecules will undergo stresses that are unnatural in the body. For these reasons, both protein modifications such as phosphorylation and gene expressions will vary a lot as for instance cellular death occur. History of current or recent past medication use is another important factor to consider, and often is regulated by the inclusion and exclusion criteria of the biobank collections. Samples should be taken care of as soon as possible after isolation. For blood samples an overall time period of 2 h has been standardized in hospitals in Sweden to maintain molecular stability. The rule of thumb is that the breakdown and instability of the sample will increase over time. It is our experience in clinical laboratories, hospital departments and biobanks, that peed and good logistics are key to the generation of high quality biorepository samples. Another important sample processing variable is the storage temperatures, which are directly related to the stability of a sample. Traditionally, −20 °C has been most commonly used in the past for all type of samples. It is still sufficient and used for DNA samples, as DNA is a stable molecule.

However, ultra-low temperatures down to −80 °C is currently used by only one instrumental company, Liconic AG, as a standard product. At −80 °C, most biological activities, such as enzyme activity and metabolic degradation are considered to be nearly non-existing.

6.5. *Biobank storage*

The biobank storage is a central part, where the input and the output of the biobank freezer units need to be streamlined for the overall size and frequency and traffic that these study activities will have. As the number of samples collected in these automated freezer archives, will increase over time, it

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will demand for a plan that takes the sample numbers over time into consideration. A crucial part is to maintain stability of these large sample collections, where sample degradation is well known to occur even at low temperatures. The stability at a molecular level will compound size and structure related. DNA for instance is highly stable, whilst RNA is highly unstable. When it comes to proteins, peptides and metabolites, the stability spectra range from stable to meta-stable to unstable by published record where all variations can be observed. It is at this point where the standardization protocols are providing a tool to keep a reproducible quality of samples stored in any given biobank. Recent reports have presented outlines, guidelines, and recommendations of best practice, with regards to biorepository material type, in addition to the analysis of different molecular classes of clinical analytes [14].

The biobank infrastructure housing the frozen samples and the surveillance routines overseeing these facilities are also a matter of importance to ensure sample quality. It is not uncommon that power cuts and other irregular energy supply situations occur. These situations will lead to temperature shifts, which result in ambient temperature increases and consequent heating of the proteins within the sample. When the power is cut to a biobank freezer at −80 °C, then the temperature increase in the unopened storage will increase by about 1°/h. The solution to such unforeseen events is the maintenance of backup facilities of storage coupled with emergency power sources and/or availability to alternative forms of frozen storage containers, *i.e.*, liquid nitrogen.

7. Electronic systems for sample integrity

The electronic registry of the sample is a central part of biobank developments in order to safely preserve patient data. This registry can, or is usually integrated within the national healthcare system, which makes the value of the samples, and the resulting analysis data so much valuable. It allows for future follow-ups and evaluation of disease presentation, in addition to experience building on best practice in treatments of common diseases [15–18].

The unique code that each sample is provided will function as a "birth tag" throughout the lifetime of the sample. The code is followed and registered over time for each handling step that encounters the sample during its life time [19]. Once the sample tube is taken out from the biobank, the customer to where the shipment is made will be logged. The output address and the termination of sample surveillance end with this final step. Another aspect that is a key for the role that electronic systems hold for biobank samples is the ability of tracking. Clinical sample originating from the patient, whether blood, some other biofluid, or tissue, is the central part of all biobanking. The handling and preparation of these samples relay the biobank samples from clinical studies and will be annotated within various electronic systems, such as CAISIS, (http://biobank-suisse-ch.site-preview.net/wpProduction/?page_id=19), as well as a number of various laboratory intelligent management systems (LIMS). The structure of the LIMS is built in a hierarchical structure, so that the barcodes of the sample entities can be traced back to the sample origin. The LIMS structure starts with the study, followed by the patient group, and the patient as a unique entity. Next, the type of sample is given, often there are multiple samples taken from patients, like blood, tissue and urine as outlined in Fig. 3. In Sweden the healthcare system which is mostly based upon state hospitals, data management is handled in large e-health-like electronic structures with central databases. The advantage by these centralized LIMS and databases are that electronic capture of patient information is centralized and can be easily accessed. Within these databases, many patient

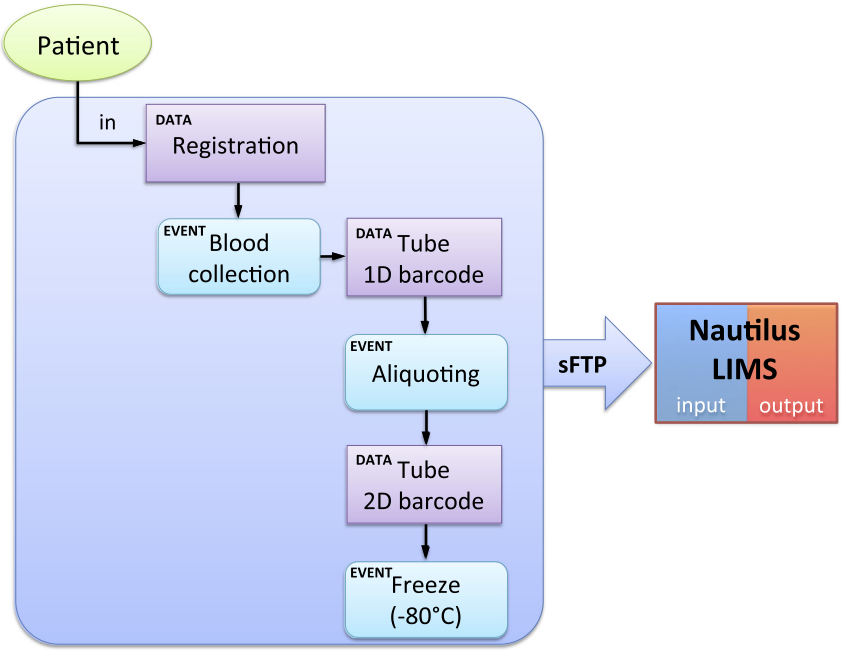

Fig. 3 – Laboratory intelligence management system operations and procedures.

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registries can be found, that provide healthcare wide information about; patient medical history, clinical data, birth registries, geographic locations of patients, death registries, *etc.*

8. Conclusions

Biobank repositories must be planned, managed and administered at a high level of professional organization. Operating a professional biobank requires not only the necessary equipment for storage but also a planned infrastructure. Biobank sustainability is dependent upon adequate staffing of managers and technicians for sample handling, clinical expertise in patient classification and clinical metadata associations, and administrators overseeing the legal, ethical, and consent questions that arise during the use of these samples in studies. More than 7000 rare diseases affect human mankind and less than 200 have available pharmacotherapy. These challenging healthcare issues will require large number of biobank samples with sufficient statistical power. Biobank organizations worldwide will need to cooperate and utilize these cohort sample resources to generate value in future science innovation that will translate value to the everyday life of the patient in the hospital.

A central role in the field of biobanking, increasing in global activity and investments, is the ultimate goal of improving efficiency within the healthcare sector [20]. Translating basic science to discover new and better treatments is an enormous challenge. Especially, we see the area of Personalized Medicines increasing, and it is not surprising that developing personalized medicine approaches now occupies much of the current development portfolio of the pharma industry. Unifying the different disciplines will aid in the fulfilling of the big picture that some of us call personalized medicine and systems biology.

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REFERENCES

[1] Betsou F, Barnes R, Burke T, Coppola D, Desouza Y, Eliason J, et al. Human biospecimen research: experimental protocol and quality control tools. Cancer Epidemiol Biomarkers Prev 2009;18:1017–25.

[2] Végvári Á, Rezeli M, Sihlbom C, Häkkinen J, Carlsohn E, Malm J, et al. Molecular microheterogeneity of prostate specific antigen in seminal fluid by mass spectrometry. Clin Biochem 2012;45:331–8.

[3] Park A. Ten ideas changing the world right now: biobanks. TIME; 2009.

[4] Hubel A, Aksan A, Skubiz APN, Wendt C, Zhong X. State of the art in preservation of fluid biospecimens. Biopreserv Biobank 2011;9:237–44.

[5] Lasso RA. The ethics of research biobanking. JAMA 2010;304:908–10.

[6] LaBaer J. Improving international research with clinical specimens: 5 achievable objectives. J Proteome Res 2012;11:5592–601.

[7] Malm J, Danmyr P, Nilsson R, Appelqvist R, Végvári Á, Marko-Varga G. Blood plasma reference material — a global resource for proteomic research. J Proteome Res 2013;12(7):3087–92.

[8] Teunissen CE, Tumani H, Bennett JL, Berven FS, Brundin L, Comabella M, et al. Consensus guidelines for CSF and blood biobanking for CNS biomarker studies; 2011.

[9] Baker M. Biorepositories: building better biobanks. Nature 2012;486:141–6.

[10] Betsou F, Lehmann S, Ashton G, Barnes M, Benson EE, Coppola D, et al. Standard preanalytical coding for biospecimens: defining the sample PREanalytical Code. Cancer Epidemiol Biomarkers Prev 2010;19:1004–11.

[11] Marko-Varga G, Végvári Á, Welinder C, Lindberg H, Rezeli M, Edula G, et al. Standardization and utilization of biobank resources in clinical protein science with examples of emerging applications. J Proteome Res 2012;11:5124–34.

[12] Marko-Varga G. Biobanking as the central tool for translational medicine. Clin Transl Med 2013;2:4.

[13] Simeon-Dubach D, Perren A. Better provenance for biobank samples. Nature 2011;475:454–5.

[14] Guerin JS, Murray DW, McGrath MM, Yuille MA, McPartlin JM, Doran PP. Molecular Medicine Ireland Guidelines for standardized biobanking. Biopreserv Biobank 2010;8:3–63.

[15] Végvári Á, Rezeli M, Döme B, Fehniger TE, Marko-Varga G. Translation science for targeted personalized medicine treatments. In: Sanders S, editor. Selected presentations from the 2011 Sino-American symposium on clinical and translational medicine. Washington DC: Science/AAAS; 2011. p. 36–7.

[16] Marko-Varga GA, Végvári Á, Fehniger TE. A protein shake-up. Public service review. European Union; 2011250–2.

[17] Kato H, Nishimura T, Hirano T, Nomura M, Tojo H, Fujii K, et al. A clinician view and experience of proteomic studies in the light of lung cancer in Japanese healthcare. J Proteome Res 2011;10:51–7.

[18] Kato H, Nishimura T, Ikeda N, Yamada T, Kondo T, Saijo N, et al. Developments for a growing Japanese patient population: facilitating new technologies for future health care. J Proteomics 2011;74:759–64.

[19] Kugler KG, Hackl WO, Mueller LA, Fiegl H, Graber A, Pfeiffer RM. The impact of sample storage time on estimates of association in biomarker discovery studies. J Clin Bioinform 2011;1:9.

[20] Master Z, Nelson E, Murdoch B, Caulfield T. Biobanks, consent and claims of consensus. Nat Methods 2012;9:885–8.

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