RÉSEAU EUROPÉEN **DE RECHERCHE TRANSLATIONNELLE ET D'INNOVATION EN ONCOLOGIE**

ONCONET SUDOE

SYNTHESIS REPORT ON TUMOR BIOBANKS AND DIAGNOSTIC PLATFORMS PRACTICES IN THE SUDOE AREA

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1. Background

Biobanks are an important compound of personalized medicine. They provide a platform for innovative biomedical research, playing an important role in discovery and development of new therapeutic drugs. Biobanks allow a multidisciplinary approach to the human health combining biological and medical approaches, as well as informative bioinformatics technologies, computation and modelling. The importance of biobanks has increased during the last decade, both in variety and capacity, going from small collections of samples to large-scale national or international repositories. Any single country, state, or society at the moment is not able to cover all issues involving the whole biobank problematic and thus Biobanks have an enormous innovative potential in the whole process of biomedical research in the twenty-first century from an international perspective.

The Organisation for Economic Co-Operation and Development (OECD) defines a biobank as a collection of biological material and the associated data and information stored in an organized system, for a population or a large subset of a population[1].

Biobanking has been identified as a key area to accelerate the discovery and development of new drugs, especially in oncology, and are key to provide resources for future investigations to understand the effects of genetic, environmental and lifestyle factors on human morbidity, mortality and health.
The aim of this report is to understand the role of biobanking in cancer research, the challenges faced and strategies to overcome these, for long term and sustainable research in the field of oncology.[2]

2. Biobanking Methodology

The availability of high-quality biological and environmental specimens for research purposes requires the development of standardized methods for collection, handling, storage, retrieval, and distribution. The International Society for Biological and Environmental Repositories (ISBER) is the leading global forum for the development, management, and operations of repositories. One of the key objectives for ISBER is to share successful strategies, policies, and procedures on providing fit-for-purpose specimens for research. We have found that many biobanks in the SUDOE area follow these recommendations.

Samples stored in the biobank may be transferred free of charge for biomedical research purposes for projects that have been scientifically approved. The request must contain

[1] OECD Creation and Governance of Human Genetic Research Databases, OECD. Paris. Glossary of Statistical Terms. 2006; available at http://stats.oecd.org/glossary/detail.asp?ID=7220. Accessed 15 Dec 2015.
[2] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4762166/#CR4

information about the project to be developed and the commitment of the center and/or of the requesting researchers not to use the samples for other purposes than that indicated.

The application is usually approved by a scientific committee external to the biobank, which will guarantee the quality and viability of the project and that of an ethical research committee, whose objective is the safeguarding of the welfare and rights of the participants in the project. The assignment of the sample may be accompanied by associated clinical information. In the event that this information is linked to a non-anonymized sample, the clinical information must comply with the provisions of personal data protection regulations (EU Directive 2016_680). In no case, the investigating personnel will have personal data that allow the identification of the donor. The biobank acts as a mediator between the health/care environment and the research environment. The biobank thus guarantees the confidentiality of the donor while facilitating access to relevant clinical information associated with the sample that allows greater efficiency when designing and analysing research data.

A key aspect of biobanking is related to ethics. Biobanks should protect the patient's identity and rights, and must apply codes or anonymization to ensure privacy. The three main factors of informed consent are adequate information, voluntariness, and competence. The participant should be informed of the objectives of the study, importance of their involvement to cancer research, potential risks involved and the chances of withdrawal at any time in the future.[3]

Also, analysis of cancer health inequities, however, requires more than the biological specimens. Also needed are the social data used to characterize and quantify the inequities.

There is a systematic process of data collection, processing and functioning of a biobank, as shown in Figure 1. The process involves different disciplines as bioinformatics, cytomics, genomics, proteomics, metabolomics, peptidomics, pharmacogenomics, tissomics and transcriptomics devoted to analyse and understand cancer prognosis and suggest treatment modalities.

A multidisciplinary approach is employed with all aspects of disease prevention, prediction, therapy monitoring, optimisation, drug discoveries and drug development.[2]

[3] https://academic.oup.com/jncics/article/2/1/pky011/4994489

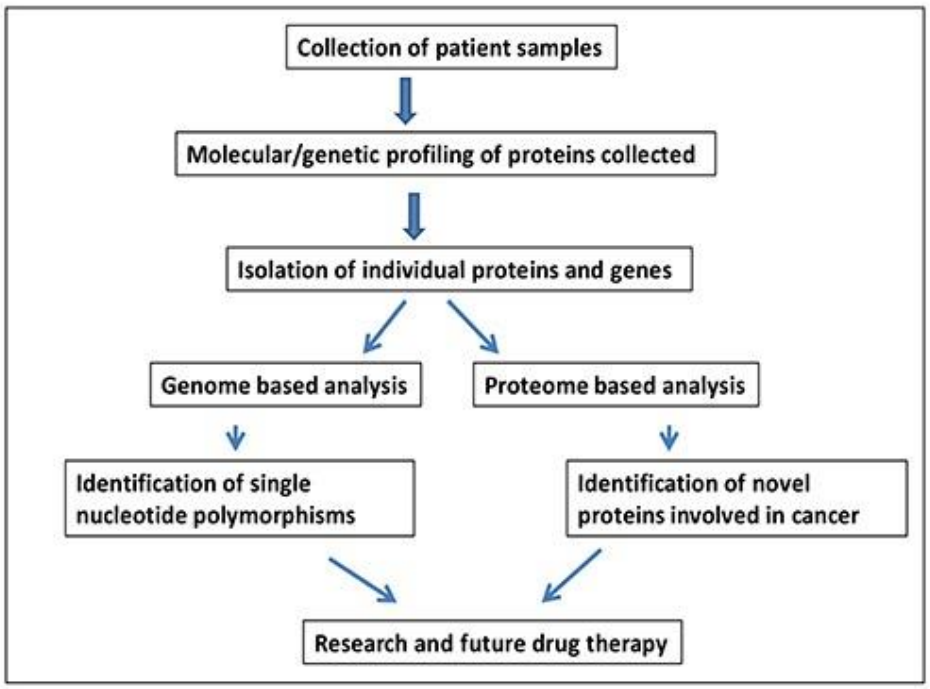

Figure 1: Functioning and purpose of a biobank (Patil, S. *et al., Oncol Rev*. 2018, 12(1): 357)

3. List biobanking results

This work package was intended to provide a guidance document reflecting the collective experience of the biobanks in the SUDOE area, according to a broad input received from repository professionals.

Results have been collected upon Onconet Sudoe partner members interactions with the hospitals in corresponding regions. We received answers from 16 biobanks: 14 in Spain and 2 in Portugal. French biobanks did not report any information.

The biobank locations and contact information are gathered in the Onconet Sudoe Interactive map available at the website http://resources.onconet-sudoe.eu/resources/c/biobank/. This is not a comprehensive listing of biobanks in each region. Actually almost all main hospitals treating oncology patients have their own biobank. However, the mentioned website shows biobanks providing information for this project.

Figure 2: Location of Biobanks according to the information provided ion the project's website http://resources.onconet-sudoe.eu/resources/c/biobank/.

Throughout this document, effective practices are presented for the management of specimen collections and repositories and the term "Best Practice" is used in cases where a level of operation is indicated that is above the basic recommended practice or more specifically designates the most effective practice.

4. Tumors Analyzed

Cancer is a leading cause of death worldwide, accounting for 18.1 million new cases and an estimated 9.6 million deaths in 2018, according to the World Health Organisation.[4] Europe accounts for 23.4% of the global cancer cases and 20.3% of the cancer deaths, although it has only 9.0% of the global population.

[4] https://www.who.int/cancer/PRGlobocanFinal.pdf

Cancer is a generic term for a large group of diseases that can affect any part of the body. Other terms used are malignant tumours and neoplasms.[5]

In 2018 the three main cancer types in terms of incidence were cancers of the lung (2.09 million cases), female breast (2.09 million cases), and colorectum (1.80 million cases), and were ranked within the top five in terms of mortality (See Figure 1)- Together, these three cancer types are responsible for one third of the cancer incidence and mortality burden worldwide. Other common cancers are prostate (1.28 million cases), skin cancer non-melanoma (1.04 million cases) and stomach (1.03 million cases). The most common causes of cancer death are cancers of lung (1.76 million deaths), colorectal (862,000 deaths), stomach (783.000 deaths), liver (782,000 deaths) and breast (627,000 deaths). See Table 1 for details.

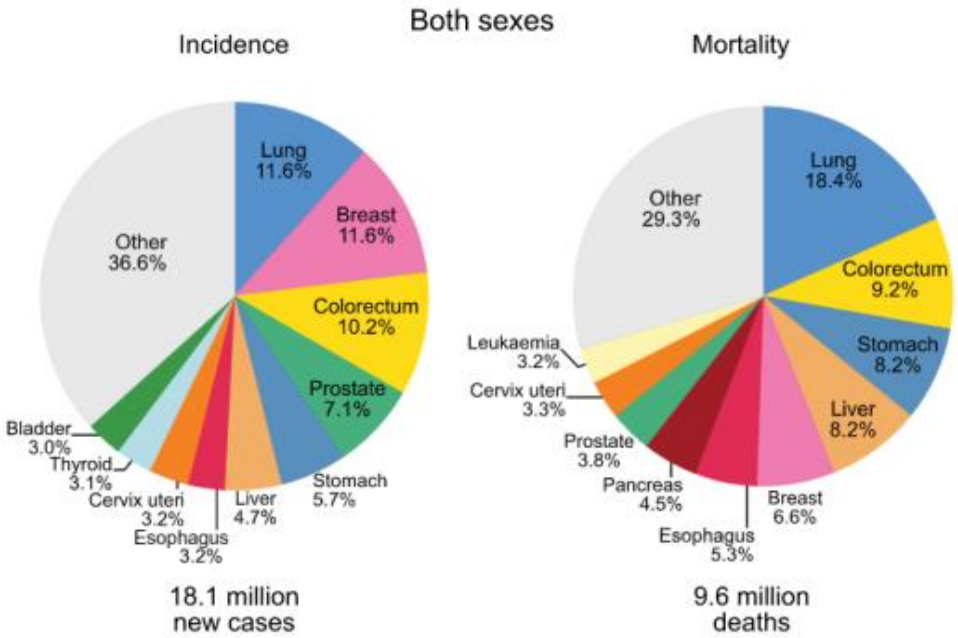

Figure 3. Distribution of cases and deaths by world area in 2018 for both sexes. https://onlinelibrary.wiley.com/doi/full/10.3322/caac.21492

[5] https://www.who.int/news-room/fact-sheets/detail/cancer

CANCER SITE	NO. OF NEW CASES (% OF ALL SITES)	NO. OF DEATHS (% OF ALL SITES)
Lung	2,093,876 (11.6)	1,761,007 (18.4)
Breast	2,088,849 (11.6)	626,679 (6.6)
Prostate	1,276,106 (7.1)	358,989 (3.8)
Colon	1,096,601 (6.1)	551,269 (5.8)
Nonmelanoma of skin	1,042,056 (5.8)	65,155 (0.7)
Stomach	1,033,701 (5.7)	782,685 (8.2)
Liver	841,080 (4.7)	781,631 (8.2)
Rectum	704,376 (3.9)	310,394 (3.2)
Esophagus	572,034 (3.2)	508,585 (5.3)
Cervix uteri	569,847 (3.2)	311,365 (3.3)
Thyroid	567,233 (3.1)	41,071 (0.4)
Bladder	549,393 (3.0)	199,922 (2.1)
Non-Hodgkin lymphoma	509,590 (2.8)	248,724 (2.6)
Pancreas	458,918 (2.5)	432,242 (4.5)
Leukemia	437,033 (2.4)	309,006 (3.2)
Kidney	403,262 (2.2)	175,098 (1.8)
Corpus uteri	382,069 (2.1)	89,929 (0.9)
Lip, oral cavity	354,864 (2.0)	177,384 (1.9)
Brain, nervous	296,851 (1.6)	241,037 (2.5)

Table 1: New cases and deaths for 36 cancers and all cancers combined in 2018

Table 1 shows the top cancer types for estimated cases and deaths worldwide for men and women combined.

For both sexes combined, lung cancer is the most commonly diagnosed cancer (11.6% of the total cases) and the leading cause of cancer death (18.4% of the total cancer deaths), closely followed by female breast cancer (11.6%), colorectal cancer (10.2%), and prostate cancer (7.1%) for incidence and colorectal cancer (9.2%), stomach cancer (8.2%), and liver cancer (8.2%) for mortality. By sex, lung cancer is the most commonly diagnosed cancer and the leading cause of cancer death in males, followed by prostate and colorectal cancer for incidence, and liver and stomach cancer for mortality.

Among females, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death, followed by colorectal and lung cancer for incidence, and vice versa for mortality; cervical cancer ranks fourth for both incidence and mortality. Overall, the top 10 cancer types account for over 65% of newly diagnosed cancer cases and deaths.

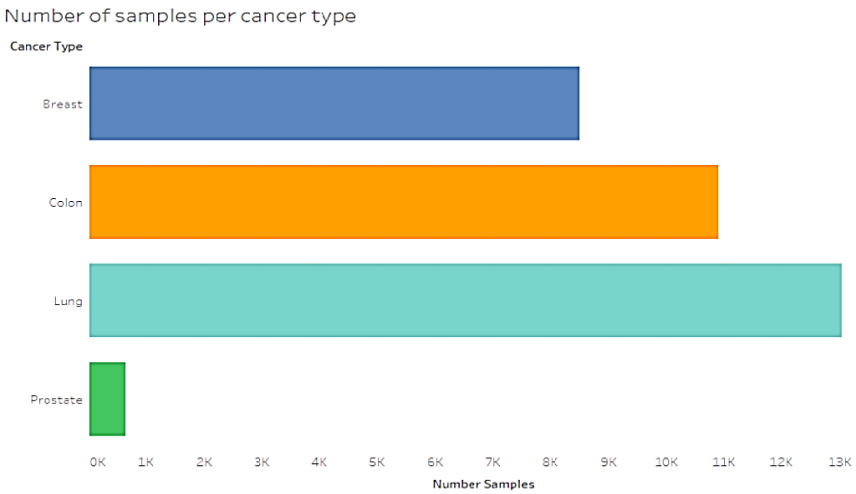

Figure 4: Number of samples per cancer type stored at the responding biobanks. A survey was performed to the biobanks with the aim to determine the number of samples. The sample volumes correlate with the most commonly diagnosed cancers.

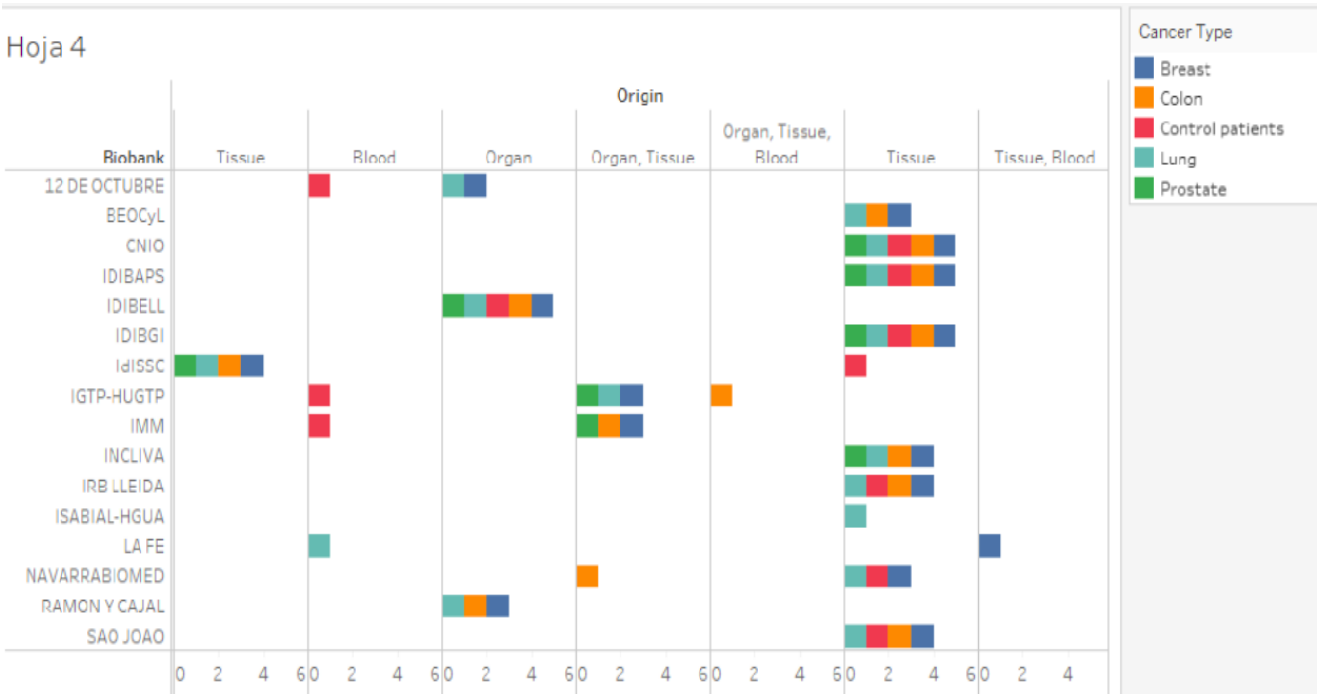

Figure 5: Origin of the samples by cancer type at the responding biobanks from this project.

5. Comparing biobanking practices

Collection procedures

A variety of protocols exists for the collection of different specimen types. The protocol chosen should be suited to the particular needs of the study, specimen types collected.

Sample extraction

	Sampling								
Sample Types	Aspirati	Biopsy	Biopsy, necropsy..	Biopsy, surgery t..	Biopsy, surgery t..	Blood	Blood draw	Surgery tissue	Surgery tissue, bl..
Tissue				■				·	
DNA, RNA, serum, plasma..	·								
DNA, RNA, Total blood, Pl..				▪					
DNA, Total blood, Serum							·		
EDTA Blood						·			
OCT, frozen tissue or, if n..		·							
Organ, Tissue, Cells, DNA,..				·					
Peripheral blood,..						·			
Peripheral blood, serum, ..									·
Plasma, serum, Mononucl..						·			
serum, plasma, total blood						·			
Tissue			■					▪	
Tissue total		·		▪				■	
Tissue Total, serum								·	
Tissue, DNA, RNA, serum, ..					·				
Tissue, plasma, serum, M..								▪	

Table 2: Different techniques for sampling applied at the biobanks responding the survey for this project.

Solid Tissues

The appropriate handling of tissues procured for research purposes can be facilitated by having a practicing pathologist supervise the actual procurement of the tissue; this is especially important to prevent the compromise of diagnostic specimens. Information from the pathologist on the characteristics of the biopsy or surgical material (e.g., percentage normal, percentage tumor, percentage necrosis, and/or percentage fibrosis) as determined by microscopic evaluation should be obtained on a per-specimen basis and recorded. It is well known that tissue specimens are heterogeneous with respect to the percent tumour, normal, necrosis, and fibrosis. Where possible, multiple sections or samples (aliquots) should be created.

Surgical Samples

Remnant clinical specimens may be collected from diagnostic surgical procedures. If not processed immediately, specimens should be placed in a clean or sterile container on wet ice (2 – 8°C) for transport from surgery to pathology or to the repository. It is also important to prevent cross-contamination, dehydration, and desiccation of tissues during transportation. Vacuum sealing, cooling of fresh tissues, or covering with sterile gauze moistened in biopreservation media is recommended if immediate fixation/stabilization cannot occur.

Blood

One of the primary decisions in storing blood samples is whether to collect anticoagulated (i.e., plasma, buffy coat, RBC) whole blood or coagulated (i.e., serum, clot) blood. When serum is collected without anticoagulant, the blood clot obtained after processing can be used as a source of DNA for genotyping and other DNA-related studies 19 . In similar fashion, blood collected with anticoagulant can yield a packed cell volume (containing both the buffy coat and RBC) to be used as a source of RNA, DNA, or viable cells.

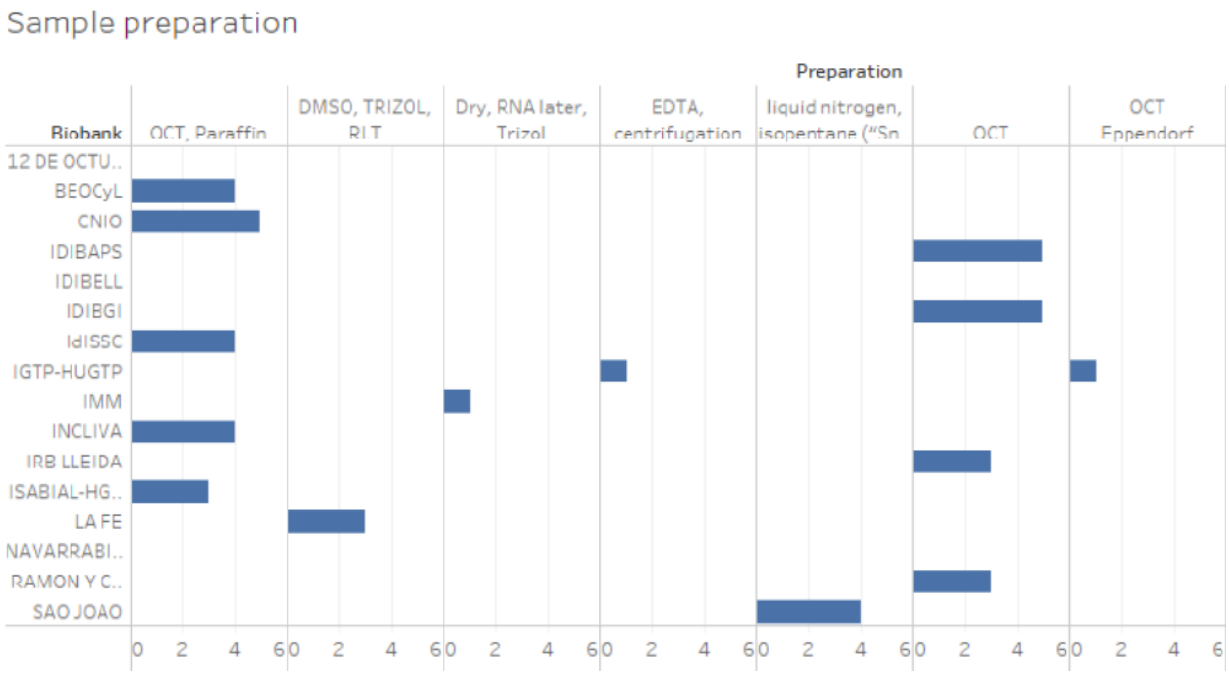

Figure 6: Sample preparation methods at the responding biobanks.

Conservation temperature

Most biobanks report -80º as the most usual temperature to store cancer samples. The variety of storage systems available for specimen collections continues to increase as technologies advance. Storage equipment selections should be based on the type of specimens and/or samples to be stored, the anticipated length of time the specimens will be stored, the intended use for the specimens, and the resources available for purchasing the equipment. Also important are the size and physical design of the repository and the number of specimens stored (as well as predictions for future growth in number of specimens stored).

The use of liquid nitrogen for long-term specimen preservation is optimal for the storage of some types of biological material and is also reported with temperatures of -196º. However, when considering storing in LN 2 vapor phase (≤ -150°C) vs. submersion in liquid phase (-196°C), vapor phase storage is preferred because it provides sufficiently low temperatures to maintain specimens below the Tg (Glass Transition Temperature; -132°C) while avoiding contamination issues and safety hazards inherent in liquid phasestorage. At temperatures below -132°C, the extreme cold arrests biological life and slows most chemical and physical reactions that cause specimens to deteriorate.

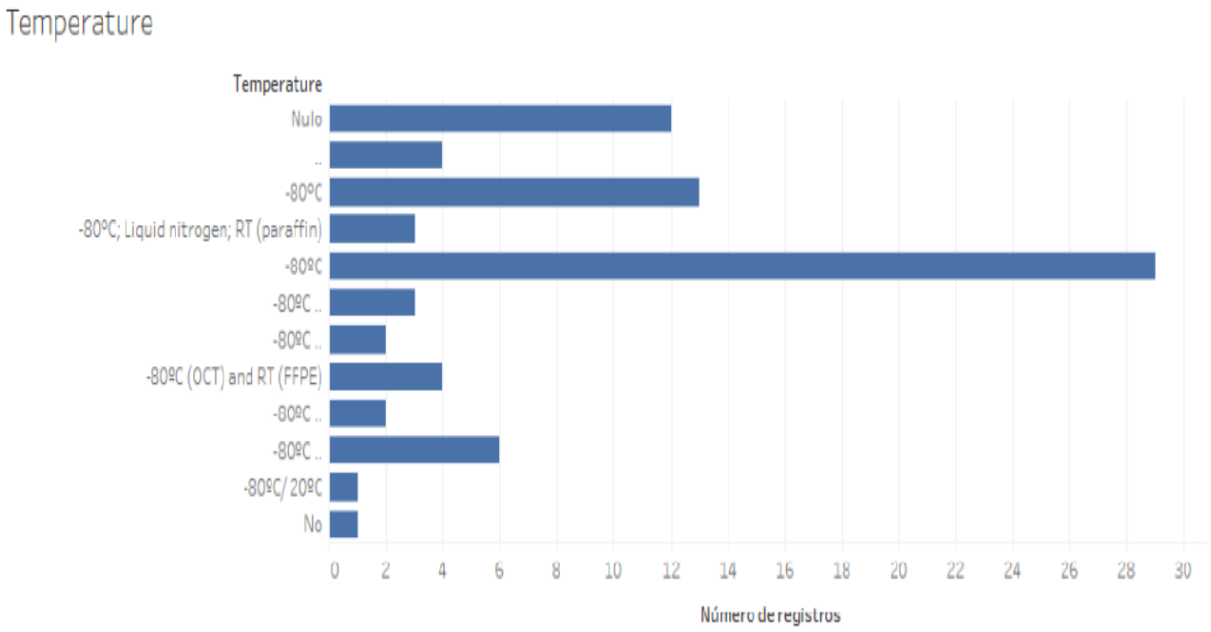

Figure 7. Temperature of storage for the samples in the biobanks consulted.

Formalin-fixed, paraffin-embedded (FFPE) tissues are usually stored at room temperature. Recent developments have allowed for the identification of biological storage matrices that allow for long-term maintenance of additional biological components at room temperature.

Best Practice: Temperature mapping should be performed to document and control the temperature distribution within a storage area upon installation and periodically at defined intervals.

Best Practice: FFPE blocks stored at room temperature (20 – 25°C) should be under controlled low humidity.

Best Practice: Specimen quality is maintained optimal when the FFPE blocks are stored at -20°C to 4°C. Repositories should validate the fitness-for-purpose of the paraffin they use to sub-zero temperatures.

6. How Regions compare to Scientific recommendations

Quality management

The purpose of a repository is to supply specimens and their associated data in a form that meets specific quality criteria and is provided in compliance with all necessary regulatory and statutory obligations. Therefore, aQMS that includes Quality Assurance (QA) and Quality Control (QC) programs should cover the full spectrum of a repository's operations. The implementation and maintenance of a QMS contributes to the long-term sustainability of repositories. These systems support the delivery of high-quality services to end-user communities and in doing so sustain the business, utility, and research viability of collections.

The sample collection and processing protocol should be underpinned by a study-wide quality program with the aim of producing samples and data that are fit for research purposes. This should include quality assurance (preventing errors and variability from occurring) and quality control procedures (detecting errors and variability if they occur) that should be built into the study design from the outset. Many biobanks in the SUDOE area are implementing quality schemes, such as ISO9001:2008/2015; these are suited to biobanks because they focus specifically on the quality of the samples and data. ISO accreditation also requires measurement of critical processes (for example, time from sample collection to ultra-low-temperature archiving) and continuous improvement efforts to optimize the performance of the organization.

7. Onconet Sudoe conclusions

Biobanks are diverse in their design and purpose; the idea of fully harmonizing historical and future biobanks is probably unaffordable and unfeasible. Rather than attempting to standardize biobanks to a uniform design, effort should be focused on designing and testing the sample collection protocol in a way that produces high-quality data and samples for research use. A full data audit trail should be generated on the sample collection process to allow collaborative use of samples and data across different biobanks. It is vital that quality programs are implemented to minimize the effect of introduced variability on the integrity of the samples and, where possible, consideration should be given to future proofing the collection. In this way sample biobanks should continue to provide valuable information well into the future and provide a long-term return on the initial investment in establishing the resource.

Biospecimen research: Where biobanking becomes science

A new line of thinking is emerging in biobanking: the need to identify and develop indicators (biomarkers) to show if a given sample has the quality to be used with a certain technique. Before using the sample, a simple test can show its quality and usability and if during the lifetime of the sample, it was kept in the appropriate conditions. Such biomarkers should allow researchers to compare analytical results from biologically identical samples, processed in different ways or stored for different periods of time.

Harmonisation of standards leads to scalability

The two most important aspects of a biobank are consistency and quality. The validity of the data generated by biobanked samples depends on their quality, which is, in turn, is dependent on the use of stringent standards in collecting these samples and delineating patient characteristics. A number of best practices and guidelines have been published over the last few years, such as the ISBER Best Practices 4th edition. At the end of 2018, the International Biobanking standard ISO 20387:2018 Biotechnology -- Biobanking -- General requirements for biobanking was published by the ISO TC276. For the first time, these documents are aligned, indeed, this development is expected to introduce a new level of harmonisation across the entire field. The expectation is that the introduction of these standards will allow for the scaling of the biobanking operations and the support of major research projects, both in academia and the pharmaceutical industry.

This document specifies general requirements for the competence, impartiality and consistent operation of biobanks including quality control requirements to ensure biological

material and data collections of appropriate quality. This document is applicable to all organizations performing biobanking, including biobanking of biological material from multicellular organisms (e.g. human, animal, fungus and plant) and microorganisms for research and development.

Biobank users, regulatory authorities, organizations and schemes using peer-assessment, accreditation bodies, and others can also use this document in confirming or recognizing the competence of biobanks. This document does not apply to biological material intended for food/feed production, laboratories undertaking analysis for food/feed production, and/or therapeutic use.[6]

8. References

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Standard Operating Procedures - Spanish Biobank Network. Available: http://www.redbiobancos.es/Publicaciones.aspx?i=34&p=131&g=

ISO 20387:2018 Biotechnology -- Biobanking -- General requirements for biobanking. Available: https://www.iso.org/standard/67888.html

ISO 8459:2009, Information and documentation — Bibliographic data element directory for use in data exchange and enquiry

ISO 9000:2015, Quality management systems — Fundamentals and vocabulary

ISO 9001, Quality management systems — Requirements

ISO 13485, Medical devices — Quality management systems — Requirements for regulatory purposes

ISO 15189:2012, Medical laboratories — Requirements for quality and competence

ISO 15378:2017, Primary packaging materials for medicinal products — Particular requirements for the application of ISO 9001:2015, with reference to good manufacturing practice (GMP)

[6] NOTE 1: International, national or regional regulations or requirements can also apply to specific topics covered in this document.
NOTE 2: For entities handling human materials procured and used for diagnostic and treatment purposes ISO 15189 and other clinical standards are intended to apply first and foremost.

ISO/1 EC 17000:2004, Conformity assessment — Vocabulary and general principles

ISO 0/1 EC 17020, Conformity assessment — Requirements for the operation of various types of bodies performing inspection

ISO/IEC 17021-1:2015, Conformity assessment — Requirements for bodies providing audit and certification of management systems — Part 1: Requirements

ISO/IEC 17025, General requirements for the competence of testing and calibration laboratories

ISO 17034, General requirements for the competence of reference material producers

ISO/IEC 17043:2010, Conformity assessment — General requirements for proficiency testing

ISO 17100:2015, Translation services — Requirements for translation services

ISO 17364:2013, Supply chain applications of RFID — Returnable transport items (RTts] and returnable packaging items (RPIs)

ISO 17511:2003, In vitro diagnostic medical devices — Measurement of quantities in biological samples — Metrological traceability of values assigned to calibrators and control materials

ISO 19011, Guidelines for auditing management systems

ISO 20166 (all parts), Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for formalin fixed and paraffin-embedded (FFPE) tissue

ISO 20184 (all parts), Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for frozen tissue

ISO 20186 (all parts), Molecular in vitro diagnostic examinations — Specifications for pre-examination processes for venous whole blood

lSO/TS20658,Med/ca/ laboratories — Requirements for collection, transport, receipt, and handling of samples

ISO/IEC 20944-1:2013, Information technology — Metadata Registries Interoperability and Bindings (MDR-IBJ — Part 1: Framework, common vocabulary, and common provisions for conformance

ISO 26000, Guidance on social responsibility

ISO 27799, Health informatics — Information security management in health using ISO/IEC27002 © ISO 201b All rights ha side adquindo por AURHN CONSULTORES S.P., S.L.P. el 2niy-i-8, Para pettier U (alizarin en un sisterna de red interne, deb era disponer de la correspodiente licencia de AENOR

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