SECTION 2.

Role of biobanks in cancer research

The role of biobanks in biological research in general and their impact on medical, societal, and economic issues have been discussed in two reports from the Organisation for Economic Co-operation and Development (OECD) (OECD, 2007, 2009). The OECD publications address the importance, justification, and sustainability of developing biobanks for research. In 2014, the Biobanking and BioMolecular resources Research Infrastructure–European Research Infrastructure Consortium (BBMRI-ERIC), an umbrella organization for biobanking in Europe, was established to provide a focal point for biobanking activities in Europe and to provide fair access to quality-controlled human biological samples and associated data for cross-biobanking research (van Ommen et al., 2015; Mayrhofer et al., 2016).

2.1 Importance of biobanks

2.1.1 Biobanks are critical for cancer research

Human biological specimens have been used for many decades for translational purposes in cancer research, to investigate disease pathogenesis, to test scientific hypotheses, and to assess biomarkers identified in experimental studies. The advent of new technologies opens unprecedented opportunities to assess the status of the human genome and its expression, the complex networks of interactions between biomolecules, and the functional and clinical consequences of their alteration (NCI, 2016).

Therefore, studies on human specimens are also becoming critical for the process of discovering new mechanisms involved in causing cancer or in determining its progression, resistance or response to treatment, and clinical outcome (Riegman et al., 2006a).

Biobanks are the foundation of three rapidly expanding domains of biomedical science:

- molecular and genetic epidemiology (aimed at assessing the genetic and environmental basis of cancer causation in the general population as well as in families);
- molecular pathology (aimed at developing molecular-based classification and diagnostic procedures for cancers); and
- pharmacogenomics/pharmacoproteomics (aimed at understanding the correlation between an individual patient's genotype or phenotype and response to drug treatment).

2.1.2 Biobanks are important for developing personalized medicine and/or precision medicine

With conventional diagnostic methods, risk factors of importance, as well as the opportunity to prevent diseases that may emerge later, are often overlooked when the focus is on the symptoms manifested. Collecting and analysing biological specimens is a necessary procedure for pathology-based diagnosis and to enable patients to benefit from the applications of molecular and genetic cancer research.

Personalized medicine and precision medicine are transforming diagnosis in medicine and are leading towards patient-centred and multifaceted diagnostics (Hall et al., 2011).

Personalized medicine is an emerging practice of medicine that uses an individual's genetic and environmental profile to guide decisions made about the prevention, diagnosis, and treatment of disease. This concept has been refined and its scope expanded to include the approaches, decisions, and practices in medical facilities, resulting in the new term "precision medicine".

Precision medicine is defined by the United States National Institutes of Health (NIH) as "an approach to disease treatment and prevention that seeks to maximize effectiveness by taking into account individual variability in genes, environment, and lifestyle" (Precision Medicine Initiative Working Group, 2015). In precision medicine, genomic and epigenomic analyses with associated data can be used to define individual patterns of disease and susceptibility. Performing molecular-based assessments may become a systematic requirement at different stages of patient follow-up, potentially leading to better individual prevention, diagnosis, prognosis, treatment, and monitoring.

2.1.3 Biobanks have an impact on biotechnological and medical innovation

In the continuum from laboratory discovery to medical application, biobanks play a key role in life science research and development (R&D). Progress in medicine depends on innovation, development, and the translation of laboratory findings into clinical practice. Access to human biological specimens and associated data is often a prerequisite for such R&D advances.

Therefore, the development of high-quality biobanks with innovative research platforms has accelerated and facilitated this translational process. This is due mainly to technological advances and reductions in the cost of information technology (IT), used for data storage and for the assembly, evaluation, and analysis of large numbers of samples, as well as increases in analytic capabilities and the drastically reduced costs of DNA sequencing, with results available within a shorter time frame. Similar advances in mass spectrometry have drastically lowered the cost and expanded the ability to characterize proteins and the metabolites present in biological samples.

2.1.4 Importance of networking and exchanges between biobanks

Cancer is a burden faced by people across the globe. Occurrence and mortality rates vary in different parts of the world. In addition, studies of many rare forms of cancer are limited by the difficulty of recruiting a sufficient number of cases within any single collection centre, or even within one country.

Networking, or harmonizing, of biobanks can encourage the collection of higher-quality samples and data, enable larger research projects to take place, and reduce duplication of effort (Yuille et al., 2008; Harris et al., 2012). For cancer biobanks, networking can enable the study and classification of rare cancers; a cancer type is considered rare if fewer than 5 cases are diagnosed in a population of 10 000, and rare cancers make up at least 20% of new cancer cases (ESMO, 2010; van Ommen et al., 2015; Mayrhofer et al., 2016).

Networking implies a multidirectional flow of information, expertise, and biological materials between cancer centres and research institutions and requires the adoption of common technical standards for specimen collection, storage, and annotation, and for data collection and management. Biobanks have an important role in facilitating such exchanges and in providing logistics and infrastructure for multicentre research projects involving cancer centres, academic medical centres, and diagnostic and healthcare facilities. Biobank networks involved in the collection, processing, storage, and dissemination of biological specimens can range from small operations with single projects in research or university laboratories to large operations in hospital, academic, or commercial biobanks. National, regional, and international networks are also developing to provide resources from diverse populations. For example, the Low- and Middle-Income Countries (LMICs) Biobank and Cohort Building Network (BCNet), coordinated by the International Agency for Research on Cancer (IARC), has established a virtual catalogue to document the resources of its members.

The operational model and governance of networks depend on their focus and mission. One such model is the *federated* model, where the biobanks maintain their samples and

contribute to a common network project when necessary. Another model is the *project-based* model, where the biobanks collect samples for a specific project (Vaught et al., 2009).

Several factors can contribute to the success of a biobank network. They include:

- well-defined goals, effective coordination, and funding mechanisms;
- efficient communication between the relevant medical disciplines and the global scientific community;
- standard operating procedures (SOPs), compatible informatics systems, and harmonized informed consent and material transfer policies and procedures; and
- tools to enable de-identified, up-to-date follow-up and retrieval of information and clinical data on participants.

These tools are key to the success of biobank networks.

The European Prospective Investigation into Cancer and Nutrition (EPIC) study, a population-based study that was initiated in the 1990s and coordinated by IARC, is an example of an effective networked project. The project involved partners from 10 European countries and 23 EPIC centres, and each centre collected biospecimens and data. Blood samples and associated data, including lifestyle and dietary information, were collected at baseline. Blood samples from participants in eight out of the 10 European countries are kept in the IARC central biobank. For two Scandinavian countries, blood samples are kept locally.

Although EPIC has a central biobank for the baseline samples, the tissue samples from individuals who develop cancer are kept at the centre, and this forms the EPIC federated biobank.

The EPIC study has provided opportunities for researchers to investigate lifestyle and cause of death (Bergmann et al., 2013) as well as dietary intake in relation to mortality among people who develop different types of cancer, such as colorectal cancer (Aleksandrova et al., 2014) and prostate cancer (Rohrmann et al., 2013), and other diseases, such as ischaemic heart disease (Crowe et al., 2012).

2.1.4.1 Tools for effective networking

Several important tools have been developed in recent years for effective networking and resource sharing between biobanks. Some examples are the following (see also Section 3.8).

- The Minimum Information about Biobank Data Sharing model (MIABIS 1.0 and MIABIS 2.0). MIABIS 1.0 recommends the minimum data items and the format of the items required to enable the exchange of biological samples and data, and required to initiate collaborations between biobanks (Norlin et al., 2012). MIABIS 2.0 provides an ontology that represents the administrative entities and includes data about the biobanks where specific specimens of interest are stored; this ontology can be helpful to answer research-relevant questions, such as those about the scope and curation status of the specimens and the contact information for curators of biobanks (Brochhausen et al., 2013).
- The Sample PREanalytical Code (SPREC) (Lehmann et al., 2012) identifies and records the main pre-analytical factors that may have an impact on the quality of sampled clinical fluids and solid biospecimens and their simple derivatives during collection, processing, and storage. However, the SPREC tool may be less important with the release in 2015 of the European Committee for Standardization (CEN) norms (CEN/TS 16826, 16827, and 16835) (CEN, 2015) and with the new ISO 276 standards, which will become available within 2 years.
- The CEN norms deal with the standardization of the entire process of sample handling, from primary sample collection to analysis. They are based on studies undertaken to determine the important influencing factors. The Technical Specifications draw on the effort to codify and standardize the different steps in the pre-analytical phase.

2.1.4.2 Visibility and standardized citation schemes

Being part of an international network and contributing to a global catalogue of available resources, with the possibility of creating population-based biobanks, provides opportunities for biobanks to benefit from the experiences and tools developed for networks. Increased participation in research will result in an increase in the visibility of biobanks and their recognition as an important part of research infrastructure. These attributes can serve to augment the confidence of researchers and donors in the institutions and countries that the established resources are managed effectively and used optimally.

Recently, a programme of guidelines for reporting bioresource use and standardized citation schemes has been established to formally recognize the efforts involved in generating, maintaining, and sharing high-quality bioresources.

Two current initiatives aim to put in place standardized procedures for formally recognizing the contributions of biobanks in research through citations in scientific publications: the Citation of BioResources in Journal Articles (CoBRA) guidelines for the reporting of bioresource use in research articles (Bravo et al., 2015) and the Bioresource Research Impact Factor (BRIF), a standardized

citation scheme. Biobanks joining the BRIF citation scheme will have increased visibility and will benefit from participation in network projects (Cambon-Thomsen et al., 2011).

The formal recognition of the role of biobanks in scientific research will encourage sharing of biological resources and will increase the visibility of biobanks both nationally and internationally.

2.2 Issues in developing biobanks and using stored specimens

Developing and using the resources in a biobank requires the active involvement of many professionals and has ethical and legal implications. Section 3.1 is dedicated to putting these ethical, legal, and social issues (ELSI) into perspective. However, it is useful to highlight some of the key documents and principles that can guide decision-making when establishing a biobank. Key documents include the following:

- the WMA Declaration of Taipei on ethical considerations regarding health databases and biobanks (WMA, 2016);
- the WMA Declaration of Helsinki, which provides the general framework in which questions relating to medical research can be addressed (WMA, 2013);
- the more specific guidance issued by the OECD: *Guidelines on Human Biobanks and Genetic Research Databases* (OECD, 2009) and *Best Practice Guidelines for Biological Resource Centres* (OECD, 2007);
- best practice principles outlined by organizations such as the United States National Cancer Institute (NCI) (NCI, 2016) and ISBER (ISBER, 2012);
- guidance from the Global Alliance for Genomics and Health (GA4GH) (GA4GH, 2016) and the Public Population Project in Genomics and Society (P3G) (P3G, 2016); and
- European Union (EU) legislation, including the General Data Protection Regulation (European Commission, 2016).

Another useful approach derives rights and responsibilities from a set of four ethical principles guiding biomedical research: respect for autonomy, non-maleficence (to do no harm), beneficence (to do good), and justice (Beauchamp and Childress, 2013). Protecting the rights of individuals arising from these principles includes the development of appropriate methods to obtain informed consent from a potential participant and the development of research protocols that are fully compatible with the principles of beneficence, non-maleficence, and justice. The institutions and investigators that develop and manage biobanks also have a responsibility to protect personal data, ensure biological and environmental safety, and make collections accessible and available for reuse for research purposes under (the consented) defined conditions. Access requests should take into account the non-renewable nature of the specimens in setting priorities for scientific use, and the distribution of specimens for research should be governed by the use of clear and documented Material Transfer Agreements (MTAs). These rights and responsibilities are further defined and addressed in the remainder of this book.

2.3 Principles for sustainable biobanks

Developing a biobank is expensive. Added to the maintenance and running costs, this can place financial strain on underresourced institutions. These constraints are a significant obstacle to developing biobanks in low- or middle-income countries and for the long-term sustainability of biobanks worldwide. Overcoming these obstacles requires a significant concerted effort of national and international solidarity. The public sector (local and national governments and international bodies and organizations) has a responsibility to contribute to the funding of the basic infrastructure of biobanks, because of the important contribution of biobanking to research on global health and diseases. In contrast, the responsibility for the development and maintenance of sustainable and usable resources lies primarily with the institutions.

Institutions and the public sector should make provision for:

- infrastructure
- maintenance of infrastructure
- equipment
- running costs
- trained personnel
- data management systems
- quality management systems (QMSs)
- procedures to deal with ELSI.

In addition, users of the biobanking infrastructure facilities should contribute through cost reimbursement, for the financial and structural sustainability of biobanks. Thus, biobanks should establish user fees for access to human specimens, data, and services, to cover the costs of collecting, annotating, storing, retrieving, and processing the delivered biospecimens. However, human biospecimens should not under any circumstances be commercialized. Regardless of the role of industry in core funding, which is a matter of debate with serious implications, the legal responsibility and custodianship of the specimen collection and storage must remain within institutions. This is because people who agree to provide their samples donate to the institution and not to researchers or individuals, and the samples will remain in the primary institution after the research project ends or the researcher leaves the organization. To ensure continuity in the management of the samples, the institution should nominate another person who will assume primary responsibility for the samples.

In defining mechanisms for sustainability or stability, there is a need to develop safeguards for preservation of participant confidentiality and protection against improper use of human biospecimens and data. In addition, the stability of biobanks relies heavily on the value of the stored resources, in terms of their quality and scientific relevance and the use of the samples.

Financial forecasts have demonstrated that the actual costs associated with biobanking are significantly higher than recognized by researchers and funding bodies (Matharoo-Ball and Thomson, 2014). Cost recovery is essential for biobank sustainability and stability. Although each institution will have to decide on the cost-recovery model that will best serve its purposes, common elements to be considered include costs related to personnel, equipment, supplies, and service contracts.

The models should be considered in the context of relationships between the users, funding agencies, academia, and universities, and possibly also industry partners. Contingency plans in case of unexpected incidents and inadequate supporting infrastructure, such as flood or fire disasters, interruption in electricity supply, and poor Internet connectivity, should be included in any model.

2.4 General considerations for establishing a biobank

Several factors must be taken into account when setting up and running a biobank. A detailed description of these requirements is provided in the *2012 Best Practices for Repositories: Collection, Storage, Retrieval, and Distribution of Biological Materials for Research*, developed by ISBER (ISBER, 2012). Some aspects of particular importance in setting up a biobank for cancer research are highlighted here.

2.4.1 Institutional commitment

Many factors contribute to the decision to establish and run a biobank. In practice, the process often starts with the willingness of medical doctors and scientists to develop a resource useful for diagnosis, prognosis, and research purposes. However, the establishment of a biobank must not rely only on individual action but also requires a clear commitment by the host institution, which also needs to ensure that collections are developed within appropriate legal, ethical, clinical, scientific, and technical guidelines, to provide historical continuity in specimen management and record-keeping. Finally, the biobank should ensure that the stored materials can be made available for research.

The purpose of the biobank must be clearly formulated and documented. In case of loss of funding or other adverse events that may prevent the institution from maintaining its commitment, it is the responsibility of the institution to take the necessary steps, depending on the applicable legal/ethical requirements. There may be an obligation to destroy the samples or to transfer the collected specimens and data to another institution that will take over the commitment for the long-term maintenance of the resources. There may be specific obligations related to such a transfer.

2.4.2 Ethical, legal, and social issues (ELSI) and governance

ELSI considers local, national, and international cultural, legal, social, and ethical norms. For example, the EU Data Protection Directive states that under EU law, personal data can be gathered legally only under strict conditions, for a legitimate purpose (European Commission, 1995). Furthermore, people or organizations that collect and manage personal information must protect it from misuse and must respect certain rights of the data owners, which are guaranteed by EU law.

However, there are conflicting data protection rules in different countries, which need to be observed during international exchanges. Therefore, common EU rules have been established to ensure that personal data have a high standard of protection everywhere in the EU. The EU Data Protection Directive also provides specific rules for the transfer of personal data outside the EU, to ensure the best possible protection of data when they are exported abroad.

ELSI and governance recommendations relating to governance structures, informed consent, data protection, return of results and incidental findings, and data and sample sharing are presented in Section 3.1.

An important governance issue to highlight when establishing and maintaining biobanks relates to public engagement programmes and the establishment of clear channels of communication with partners and stakeholders. Therefore, transparency in procedures and operations is critical, and clear descriptions of the roles and responsibilities of personnel should be communicated to partners and stakeholders. Given that participation is voluntary and that most biobanks operate on a non-economic basis, biobanks need public trust and support. It has become common practice for large-scale population biobanks to engage in consultation with the public and other stakeholders before the biobank is established (UK Biobank Ethics and Governance Council, 2015, 2016). Methods of communication could include, for example, consultation with community representatives, focus group meetings, workshops, interviews, public meetings, polls, and surveys. Public consultation is particularly important when ethnic or cultural minorities are approached to participate in biobank collections. Section 3.1 provides further information on transparency and

communication with key stakeholders, and Section 3.1.2.5 describes community engagement in relation to the consent process.

2.4.3 Biobank management and staffing

Biobanks should be adequately staffed, and the personnel selected for these tasks must be well qualified and have an appropriate level of specialized training. The biobank should be placed under the overall supervision of a biobank manager with sufficient training, experience, and seniority to fulfil the scope of the activities of the biobank. The manager is responsible for operations, including compliance with appropriate regulations, and has a critical role in receiving, processing, and responding to requests for access to stored specimens. The manager can act as a technical advisor to the access committee during the review of access applications.

Running a biobank requires dedicated staff members for specimen processing and storage and for data management. The job description, tasks, and reporting system of all supervisory and technical staff members must be documented. This is of particular importance in instances where biobank staff members also perform other tasks within the institution (e.g. pathology service or service activities in molecular biology). Staff members must have adequate educational backgrounds, experience, and training to ensure that assigned tasks are performed in accordance with the biobank's established procedures. Updated training should be conducted on a periodic basis for personnel, in accordance with applicable regulations and roles within the biobank.

Other personnel who are not necessarily staff members of biobanks but should be aware of the purpose and goals of obtaining high-quality bioresources are clinicians, researchers, technicians, nurses, surgeons, pathologists, and anaesthetists. The involvement of a pathologist in this process is crucial to ensure that patient care is not compromised (NCI, 2016).