Chapter 7
Ethical Challenges for Biobanks: Two Sides of the Coin

Kirsi Vähäkangas, Suchetana De, and Pierre Hainaut

Abstract The many ethical challenges in biobanking include management of biobanks with quality issues and benefit sharing, consent issues related to autonomy of the donors, data storage, and privacy as well as the sources and use of samples and data. Thus, one side of the coin is the many potential health benefits, such as biomarkers for clinical purposes, which makes the development of biobanks containing human samples with linkable health data ethically justifiable. The other side of the coin is the ethical costs in the form of potential loss of autonomy depending on the consent practice, unknown or even unlawful use of tissues, and their future use in ways unacceptable to people. People, in general, are interested in genetic data and willing to donate samples and data to scientific research. It is important to cherish research integrity and listen to people's opinions to retain trust. In addition to public discussion, education of both scientists and lay people, and advanced legislation are important for the ethically good long-term development for the biobanking field.

Keywords Biobanks—biorepositories—ethics—GDPR · Informed consent · Incidental findings · Dynamic consent · Biospecimen sources—autonomy—communication · Training

7.1 Introduction

Biobanks or biorepositories with human samples and related clinical data are essential starting points for modern biomedical research to pursue the etiology, molecular basis, and potential biomarkers of diseases and their treatment. Thus, the creation of

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biobanks is ethically justifiable. Biobanks can be disease-based, cohort biobanks (e.g., birth cohorts) as well as population biobanks and vary greatly in size, from a few hundred samples to massive ones with millions of samples [1]. A global listing of biobanks can be found at the web pages of SpecimenCentral.com which is a volunteer mediator between biobanks and scientists trying to locate proper samples for their research. In any case, the more the better applies both to the quantity of sample-data pairs giving opportunity to good statistics, as well as to the quality of samples and data for proper laboratory (high-throughput) analysis to combine with health data.

Society expects great benefits from the biobanking field, not only for the health of people but also for value creation and financial benefits [1, 2]. On the other hand, biobanks contribute to the constitution of databases of health-related personal information which, if improperly used, may cause discrimination and threaten the autonomy of persons. These benefits and risks may be mutually discrepant, forcing an ethically loaded choice within the society. For such choices to be generally understood, education is needed, and for them to be fair, general discussion based on real understanding through the education is a necessity [3]. It is, indeed, an ethical issue whether people have a real possibility to affect who decides, and how such decisions are being made. Especially, minority groups and ethnocultural communities may vary in their perception of various societal processes and would need their voice to be heard about biobanking of tissues and health data [4]. Legislation naturally is the starting point for proper conduct in society. However, although abiding by the laws is fundamental, it is often not sufficient in itself to address the broad range of issues for good research ethics, especially in the fast-developing Big Science in which biobanks play a major role [5].

Many ethical issues related to biobanks have been identified in the literature (Table 7.1; e.g., [2, 5–7]). In addition to the much discussed and obvious donor-related issues, such as informed consent, privacy, and ownership of samples, actually all aspects of biobanks have an element of ethics in the considerations whether the conduct and decisions are right or wrong, and from whose perspective. Thus, if understood widely, the ethical aspects of biobanking also include the source and use of samples, social consequences, and information of donors and communities on the development of biobanks. In this vision, all actions involved in the biobanking workflow, including the management and quality issues, have implications for ethics in addition to the protection of donors and their rights. In the literature, the most discussed ethical concerns related to biobanks and genetic research include informed consent, secondary use of genomic data and samples, de-identification and reidentification, access to the samples and data, maintenance of privacy and confidentiality, withdrawal of consent, governance, national and international collaboration, the return of results, particularly about incidental findings, as well as quality control and economic issues [1, 8–10]. Further novel ethical aspects are emerging, accelerated by the development of Artificial Intelligence and Big Data science, which makes it possible to interpolate multiple datasets to extract information that has not been explicitly identified at the onset of the project. These emerging aspects require both rigor, adaptability and creativity in applying principles of ethics to biobanking,

Table 7.1 Ethical issues of health research related to biobanks

Topic of concern	Recognized significant points	Further considerations
Source of samples	• Clinical samples • Donated samples	• Transparency of the source
Consent	• Type of consent • Understanding the consent • Autonomy • Voluntary decision-making • Ability to withdraw	• No consent • Opt-in or opt-out policy • Discontinued awareness in long-term studies
Quality issues	• Sample collection • Handling and storage conditions	• Standard operating procedure • Training of personnel
Storage and privacy	• Anonymization/coding • Retracing to donor/specific ethnic group • Access to the information • Electronic health records	• Discrimination • Stigmatization
Ownership of samples and data	• Use • Distribution	• Custodianship • Independent advisory board to decide access to and distribution of specimens • Country-specific laws on specimens
Conflicts of interest	• Economic gains of scientists	• Commercial use of donated samples
Use of samples	• Primarily research	• Consent for further use
Management of results	• Planning for disclosure • Planning for storage and future use of the result	• Incidental/secondary findings
Communication	• Education of stakeholders • Interaction between various stakeholders	• Background knowledge of different stakeholders • Different means of communication

as well as the capacity to anticipate fears and expectations as well as to react to new developments and concerns in the evolving biobanking field.

7.2 What are Biobanks?

There is no consensus on the definition of a biobank, and different authorities define a biobank in different ways and having certain common elements (Table 7.2, Fig. 7.1). Biobanks have been defined as a collection of tissue/samples and data in most of the definitions. Quite remarkably, current definitions, e.g., by MesH, ISBER, and Wikipedia refer only to storage of biological samples and do not include the associated personal and health information [15]. Although expressed in only part of the definitions, distribution of samples for various research purposes is an implicit assumption in the definitions. Where expressed the wording varies, e.g.,

Table 7.2 Definitions of biobanks—what are the essential elements?

Definitions[a]	Unique element in the definition	References
A biobank is a systematic collection of biological specimens and health information from participants		[11]
Biobanks are repositories of biological samples with accompanying linked data		[12]
A biobank is a biorepository that accepts, processes, stores, and distributes biospecimens and associated data for use in research and clinical care	Use for clinical care	[13]
Biobanks are comprehensive and well-organized collections of human biological samples and associated clinical and research data	Well-organized	[14]
Biobank is an organized collection of human biological material and associated information stored for one or more research purposes		P^3G
Collections, repositories, and distribution centers of all types of human biological samples, such as blood, tissues, cells or DNA, and/or related data such as associated clinical and research data, as well as biomolecular resources, including model and microorganisms that might contribute to the understanding of the physiology and diseases of humans	Biomolecular resources, including model and microorganisms that might contribute to the understanding of the physiology and diseases of humans	BBMRI-ERIC
Facilities that collect, store, and distribute tissues—e.g., cell lines, microorganisms, blood, sperm, milk, breast tissue, for use by others. Other uses may include transplantation and comparison of diseased tissues in the identification of cancer	Uses may include transplantation	MeSH
A material entity consisting of storage facilities for specimens (DNA, blood, tissue) derived from humans and information related to these specimens		German ethics council
An entity that receives, stores, processes, and/or disseminates specimens, as needed. It encompasses the physical location as well as full range of activities associated with its operation	"Full range of activities" not defined	ISBER

P^3G Public Population Project in Genomics and Society, *BBMRI-ERIC* Biobanking and BioMolecular resources Research Infrastructure-European Research Infrastructure Consortium, *MeSH* Medical subject headings, *ISBER* International Society for Biological and Environmental Repositories

[a]Direct quotations from the articles or from the organization website

"distributes" and "for use by others." Some of the definitions include also the processing of the samples ([13], ISBER (www.isber.org)). Potential commercial aspects of biobanks are not mentioned in the definitions. However, these aspects have major implications for biobanking. Beyond the potential of biobanking to support R&D and value creation, biobanking is in itself costly and financial sustainability is one of the major issues in biobanking [16–18].

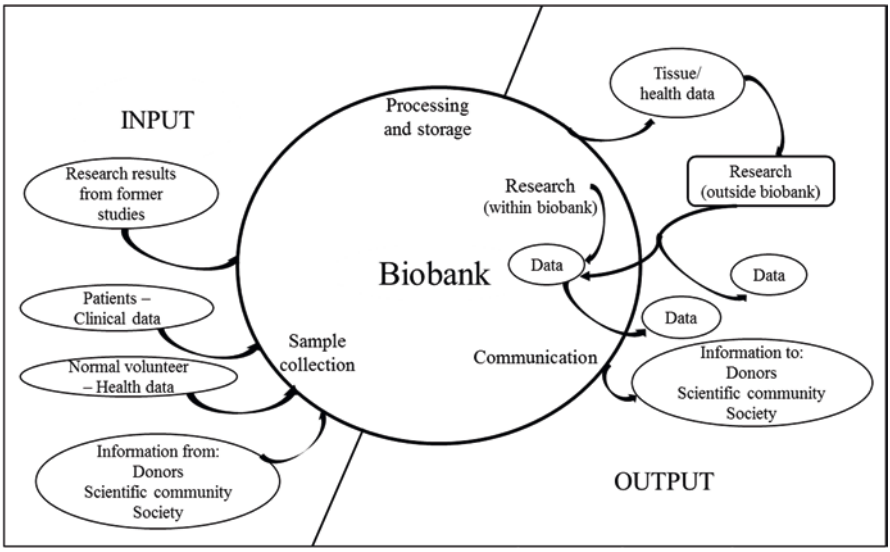

Fig. 7.1 Elements of biobank functions

Samples are physically stored in biobank facilities (repositories). This is easier for people to understand than the storage of data, which nowadays is usually made through structured electronic databases using formats that make it possible to interconnect them with each other. The weight of electronic datasets in the biobanking process is such that it is now common to conceptualize the biobanking field as a complex machinery to support the conversion of biological data into digital data through massively parallel methods such as genomics, proteomics, and metabolomics. There are different storage concepts for electronic data, none of which is fully secure, neither as to the security of data or security of privacy. Only computers not connected to the internet can be seen as relatively safe from hackers. So-called clouds, the term giving a false image of something almost out-of-reach, are just large central computers managed by some organization which probably has full access to any data in the "clouds" they manage. Protection systems, in the form of host- or network-based systems are meant to protect data from intrusion but are always, in principle, breachable. Although privacy may be overvalued, it still cannot be ethically acceptable to give people a wrong idea of the level of security of their identity linked to health data.

The various aspects of how a biobank operates are not regulated by any single legislation across Europe. However, the Council of Europe and the European Union have recommendations and regulations that are of direct relevance for biobank activities [19]. The recommendation for research on biological materials of human origin by the Council of Europe (2006) has undergone revision into the recommendation CM/Rec(2016)6 of the Committee of Ministers to member States on research on biological materials of human origin [20]. The scope of the Recommendation includes obtaining and storage of biological material of human origin for future

research purposes and use of such materials for purposes other than for which they were obtained. This is however only a recommendation and not binding legislation and hence dependent on specific legislation of the Member States for its implementation.

Another relevant piece of European regulation on biobank activities is the General Data Protection Regulation (GDPR), which was applicable as of May 25, 2018 in all member states to harmonize data privacy laws across Europe. The GDPR originates from Directive 95/46 (European Parliament & European Council 1995) of European data protection law [9, 19, 21]. Being a Directive instead of a Regulation, the Member States needed to adopt it in their national law. However, a reform to the data protection rule was proposed by the European Commission in January 2012, with the release of a draft Data Protection Regulation that led to the current GDPR (Regulation (EU) 2016/- OJ L 119, 04.05.2016; cor. OJ L 127, 23.5.2018). The GDPR promotes a uniform law among the Member States. Its primary aims are to give control to individuals over their personal data and to simplify the regulatory environment for international business by unifying the regulation within the EU [22]. The GDPR also provides a regulatory framework addressing the transfer of personal data outside the EU. The GDPR is not applicable for data which are not processed and which are not identifiable. In contrast, the Recommendation CM/Rec(2016)6 considers both "identifiable" and "non-identifiable biological materials."

At the national level, only a few EU Member States have existing legislative acts specific for biobanks, such as the legislation in Iceland, Hungary, Norway, Sweden, and more recently, Finland. In other Member States, the regulatory framework for biobanks is based on the recommendations of official national bodies, formulated in reference to national laws on research on human tissues or genetic research. [23–25]. In Finland, the Biobank Act [Act 688/2012] came into force on September 1, 2013. The Act involves biobanks for all purposes, not only for biomedical research, and all samples and data in the biobanks whether identifiable or unidentifiable [24]. Until the rolling-out of the GDPR, the Directive 95/46/EC has allowed certain flexibility to the Member States in adopting it in their national law thereby leading to substantial differences among the national laws. The deployment of the GDPR now requires that Member States adapt their regulatory framework for biobanks, in particular, to take into account the specific responsibilities carried out by data controllers (including the requirement to employ a Data Protection Officer (DPO) and the so-called portability of personal data (the right for persons to obtain and carry a copy of their personal data collected by a controller in a standard format).

7.3 Management of Biobanks

In addition to the many guidelines on biobanking and its ethical aspects (Table 7.3), the literature also provides practical advice on how to establish and manage a biobank. Womack and Mager [18] list the key requirements: (1) Appropriate

Table 7.3 Organizations providing guidance and guidelines for biobanking including ethical issues

Name of the organizations	Main tasks	Websites	Relevant guidelines/ policies
Organisation for Economic Co-operation and Development (OECD)	International organization for economic development	www.oecd.org	Guidelines on Human Biobanks and Genetic Research Databases (2009)
United Nations Educational, Scientific and Cultural Organization (UNESCO)	International organization for culture and social development	www.unesco.org	1. International Declaration on Human Genetic Data (2003) 2. Universal Declaration on the Human Genome and Human Rights (1997)
Council for International Organizations of Medical Sciences (CIOMS)	International organization of biomedical scientific community also involved in developing ethical guidelines in biomedical research	www.cioms.ch	1. International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002) 2. International Ethical Guidelines for Epidemiological Studies (2008)
World Medical Association (WMA)	International organization of physicians	www.wma.net	Declaration on ethical considerations regarding health databases and biobanks[a]
Council of Europe (COE)	European continent's leading human rights organization	www.coe.int	Recommendation CM/ Rec(2016)6 of the Committee of Ministers to member States on research on biological materials of human origin
Biobanking and BioMolecular resources Research Infrastructure-European Research Infrastructure Consortium (BBMRI-ERIC)	European organization for biobanks	www.bbmri-eric.eu	Common Service ELSI
Public Population Project in Genomics and Society (P^3G)	International consortium for harmonizing the functions of biobanks for population health	www.p3g.org	P^3G charter of fundamental principles

(continued)

Table 7.3 (continued)

Name of the organizations	Main tasks	Websites	Relevant guidelines/ policies
International Society for Biological and Environmental Repositories (ISBER)	International organization for harmonization of biobank functions	www.isber.org	ISBER Best practices for repositories 3rd edition (Section L: legal and ethical issues for biospecimens)
Human Genome Organization (HUGO)	International organization of scientists involved in human genetics	www.hugo-international.org	Statement on Human Genomic Databases (2002)
Global Alliance for Genomics and Health (GA4GH)	International organization to create a common framework for the utilization of genomic and clinical data	www.genomicsandhealth.org	Regulatory and Ethics Working Group Work products
International Cancer Genome Consortium (ICGC)	International organization for collecting and cataloging genomic anomalies in some important cancers	www.icgc.org	Policies and guidelines on informed consent, access, and ethical oversight
US National Cancer Institute (NCI) Biorepositories and Biospecimen Research Branch (BBRB)	This is a branch of NCI (USA) providing tools for biobank functions	www.biospecimens.cancer.gov	NCI Best Practices for Biospecimen Resources

[a]A draft from the Work Group intended for open consultation after acceptance of the Executive Committee of the WMA, 18.3.2015

governance mechanisms including ethically relevant issues such as policies for consent, access and data privacy, and definitions of custodial roles and responsibilities, (2) Compliance with legal and regulatory requirements including ethical reviews and biosafety issues, also important from ethical point of view, (3) Assurance that materials are properly handled and stored, (4) Documenting the sources of human biological samples, (5) Quality control issues and accreditation, (6) Financial sustainability, and (7) Optimal usage of biobank assets, including potential use for other purposes than the ones originally planned. If a biobank company is sold or transferred to another data controller, mechanisms must be put into place to ensure that the purpose of the controller is in line with the original consent from the donors, who may have given their consent to certain type of biomedical research. Womack and Mager [18] advise that the "biobank should do everything within its powers to fulfil its contract with the subject." From an ethical point of view, sticking to the original contract with the donors would obviously be the right thing to do, but in a world driven by financial concerns this is probably just wishful thinking and binding legislation would be the only guarantee.

Organizations from different fields of interest have provided guidelines or policies which are relevant for biobank functions. Some of these organizations such as

OECD and UNESCO are large intergovernmental organizations which are not solely associated with biobanks. However, there are organizations whose primary focus is biobanks, such as ISBER and BBMRI-ERIC. Since the lack of uniform legislation regulating the functions of biobanks is well recognized, these organizations put forward guidelines for harmonizing the functioning of biobanks across Europe or internationally, thereby facilitating cross-border research which is expected to improve application of genetic and genomic research.

The more generalized guidelines such as the International Declaration on Human Genetic Data (2003) and Universal Declaration on the Human Genome and Human Rights (1997) by the UNESCO or, International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002) and International Ethical Guidelines for Epidemiological Studies (2008) by CIOMS have elements which can guide the functioning of biobanks. It is however noteworthy that participant-related issues including obtaining informed consent from the participant, withdrawal of consent, and protection of privacy and confidentiality have been covered in almost all the guidelines. Apart from that, access to the samples and data, storage of samples and data, ownership of samples, benefit sharing, international collaboration, qualification and training of the personnel, standardization of procedures, disposal of samples and data have been recurring topics among the different guidelines. In UNESCO's International Declaration on Human Genetic Data (2003) and Universal Declaration on the Human Genome and Human Rights (1997), the uniqueness and sensitivity of genetic data have been highlighted. The CIOMS' guidelines on biomedical research (2002) and on epidemiological studies (2008), deal also with research in countries or communities with limited resources and issues related to externally sponsored research. There are differences in opinions on the secondary use of the collected samples among different organizations. Biobank operation requires a controlled chain of procedures, from sample and data collection to processing and storage, as well as the distribution for the most useful research. The whole operation should be sustainable operationally (requiring high-level professionals to run the biobanks), ethically (with honesty and transparency, respect for all stakeholders and their opinions, and well-informed ethics boards being involved), and economically (importance of which is supported by the development of the field of *biobankonomics*) [5, 16–18, 26]. Harmonization among biobanks would enable larger and more useful studies including rare diseases. These are very big demands achievable only through a concerted effort by various international bodies. Many international organizations, either developed for the biobanking field, such as ISBER, or existing organizations which have expanded to include biobanking in their expertise such as NCI (National Cancer Institute), part of the National Institutes of Health in the USA, provide advice on the best practices for biobanks, including ethical aspects (Table 7.3). An important resource in this respect is the International Policy interoperability and data Access Clearinghouse (IPAC) developed by the Public Population Project in Genomics and Society (P^3G), a nonprofit international consortium headed at McGill University in Montreal, Canada. The IPAC aims at proposing a "one-stop" service for harmonizing international data and biospecimen exchanges service through normative tools and frameworks that respect the laws and regulations of each country while facilitating access (http://www.p3g.org/ipac).

Issues under quality management include quality of the samples, quality management personnel, education of biobank personnel and scientists, standard operation procedures, audits or written periodic evaluations of the infrastructure, and accreditation and certification of the biobank [27]. One of the practical difficulties is retaining the quality of the samples in long-term storage. The more sensitive the molecule to be analyzed is, the more important are the storage conditions. Examples of very sensitive proteins include CYP-enzymes, which lose activity in freeze-thaw cycles [28]. Some molecules are naturally very fragile, such as RNA, while DNA can be stored long-term in many conditions. To ensure high quality and consistency of samples and their processing, a quality management system is mandatory [27]. Sample storage and processing related issues affecting the quality of the samples are, e.g., time of collection (diurnal variation), collection vessel, time from collection to processing, time from processing to freezing, temperature and length of storage, freeze-thaw cycles, and changes in SOPs over time. Naturally, all these should be carefully documented. Correct annotation of the samples requires special attention. Pellerin et al. [29] showed a 0.5% error rate among 403 DNA samples from 101 patients by analyzing four variable number of tandem repeats (VNTR). From the two mismatches found one was due to tissue mishandling and the other because of tissue mislabeling. They strongly recommend routine tissue genotyping as part of quality assurance.

Financial sustainability or biobankonomics is growing to a field in itself [1, 17]. Simeon-Dubach and Watson [1] have stressed the potential value of biobanks for all stakeholders, patients and tissue donors, funders as well as scientists. There are calculations on the start-up costs as well as the potential financial benefits, which show that the total benefits for the society would greatly outnumber the costs. The concrete products of biobanks can be in the form of publications and education, which may not bring in any immediate financial resources, but also patents and spin-off companies from the research, which can be financially evaluated. For these to materialize, more long-term investment than just for the biobank would be required. Companies are at the mercy of the world market and the possibility of people and society to pay for health. However, it is problematic if the same people try to pursue scientific truth and are responsible for the financial gain of a company. If scientists themselves stand to benefit financially from their own research there is a conflict of interest situation, which in worst case may steer the research towards less ethically sustainable practices. Examples of this have occurred in translational research for omics-based clinical biomarkers (see [5]).

7.4 The Issue of Consent

In the post-genomic era, two major changes are apparent in biomedical research: (1) the research involves minimal samples generally with less chance of physical harm to the participant and (2) the unforeseeable future use of the samples and data at the time of their collection [8, 21, 30]. The ethical concerns are aggravated by the

sensitive and unique nature of the genetic information—it involves not only the donor but all those genetically related to him or her, and may reveal genotypic characteristics which are not evident phenotypically. Genetic information, if not handled properly, has the potential to discriminate and stigmatize the donor or, in certain cases, create stress and anxiety. Thus, developments in biomedical research in the post-genomic era have led to wide discussions on recognizing the ethical concerns including the consent issue in the genetic research and genomics [5, 7–10, 31]. The biobank being one of the necessary infrastructures in carrying out this research therefore comes at the forefront of ethical considerations.

Initial recognition of the requirement of informed consent in research involving human subject is included in the Guidelines for Human Experimentation of 1931, developed in pre-Nazi Germany [32, 33]. These guidelines were the first to explicitly formulate the need for "full unambiguous and informed consent from test subjects [...], except in extreme extenuating circumstances." The Nuremberg Code (1948) following the trial of the Nazi doctors and later the Declaration of Helsinki (1964, see www.wma.net) further established the concept of protecting the research subject by prioritizing his or her well-being over the advancement of science and society and by clearly stressing the need for a formal informed consent. The Declaration of Helsinki represents a foundation for biomedical research and constitutes a cornerstone for many legal frameworks across the world [8, 34]. The concept of informed consent has two important aspects—autonomy and information. The purpose of informed consent is to provide the research subjects with adequate information about the research, including possible harms and benefits, before obtaining a voluntary, autonomous decision of participation from them. All in all, the ethical considerations in various existing guidelines and legislations are based on the idea of traditional research where the primary concern was physical harm to the research participant.

In biobanking, the unique challenge as compared to traditional research projects is that the exact destination and usage of the collected samples and data are not always known at the time of collection. Hence, the type of consent that is most suitable for biobanks has been a topic of wide discussion and is still debated in the literature. The types of consents mentioned in the literature for biomedical research are specific consent, and broader consent types such as sectoral consent, blanket consent, or open consent [21, 30, 35]. These have implications as to the amount of autonomy of the research participant (Fig. 7.2). In the current practice of biobanks, however, the most common type of consent in use is broad consent [35]. The main difference between specific consent and broad consent is the information, or lack of it, provided to the donor at the time of collection about the possible uses of the samples and data. Since informed consent is supposed to include detailed information of various aspects of the research including how the samples or data will be used, it can be argued that a broad consent which does not provide such information is not an informed consent at all [36]. Similarly, the use of a presumed consent with the provision to opt-out has also been debated intensely on the same grounds [37–40].

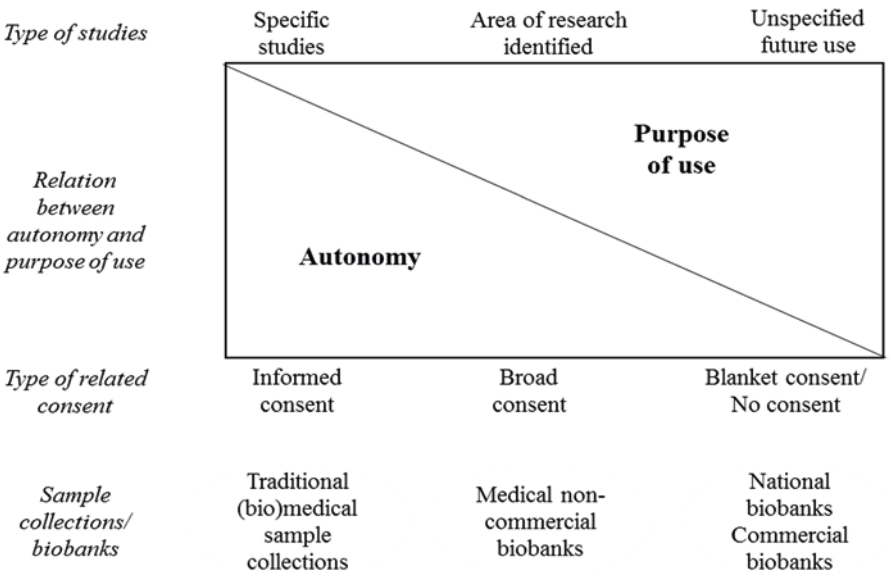

Fig. 7.2 Degree of autonomy in relation to other aspects of biobanking

Another consent type which is gaining support in the context of biobanks is the dynamic consent. Dynamic consent involves providing and updating information to the donors and putting them in control for the use of their samples or data, through a web-based platform, and has been argued to be more suited for biobanks compared to other consent types [41]. The term "dynamic consent" was coined by Jane Kaye of the University of Oxford in the course of the EnCoRe project (Ensuring Consent and Revocation), a joint academy-industry program developed in the UK between 2008 and 2012 to explore new mechanisms for empowering individuals with more control over any personal data they disclose, with the overall vision of making the consent "as reliable and easy as turning on a tap, and revoking that consent as reliable and easy as turning it off again." EnCoRe included research on the development of appropriate regulatory regimes, on IT system architectures, on consent management systems, and on the development and implementation of easy-to-use interfaces and has released publicly available deliverables on each of these aspects (https://www.hpl.hp.com/breweb/encoreproject/deliverables.html). An interesting idea emerged from the studies by Conley et al. [42], who concluded that the opinions of the research participants in biobank studies about their samples and the conditions of their use resembled a trade secret concept. Based on this, they propose a legal contract as the basis of the exchange of their DNA to compensation and/or information. This actually resembles the situation of the company 23andME which provides genetic information in exchange for a saliva sample (Box 7.1). When people feel that they are in the control and can decide for themselves, they seem to be very open to providing samples and data for research.

Criticisms of dynamic consent have argued that such an extensive form of participation is not necessary. A systematic analysis of the qualitative sociological literature on public and patient's perceptions towards consent concluded that "few people demanded recurrent, project-specific consent." Other criticisms have argued that dynamic consent may actually cause bias for recruiting study participants by repeatedly confronting them to the complexity of biomedical research and asking them again and again to formulate an "opinion." However, as public perceptions evolve over time, and as individuals become more and more aware of their rights and of the need to protect their personal data, the concept of dynamic consent is gaining traction, in particular, for prospective studies.

In the Data Protection Regulation [22], processing of special data including genetic and health data is only possible in certain cases as listed in Article 9 (2). The first point mentioned in this list (Article 9 (2) (a)) is to obtain a consent from the donor, followed by other situations (Article 9 (2) (b–j)) where processing of genetic data is possible even without the donor's consent. In this regard, Hallinan and Friedewald [21] have presented justifications for the absolute necessity of a consent from donors for biobanks, to uphold the ethical principle of autonomy in biomedical research and to maintain the fundamental rights of the person providing the data. The information to be provided to the sample donor when the data and samples are directly collected from the donor are listed in Article 13 of the Data Protection Regulation. Apart from other information, the purpose of processing, the period of storage, restrictions to processing, and the right to withdraw consent at any time are mentioned in the list. An important aspect in the consent issue is the fact that people have difficulties in understanding and remembering what they have consented to [43] stressing the quality of information given to participants as well as enough time to consider and discuss with other people [36].

With the development of Artificial Intelligence and the exponential growth of opportunities to aggregate health-related personal data with multiple other data sources, new mechanisms should be considered to ensure the rights of individuals to retain control over their personal data. Among such mechanisms, citizen-owned nonprofit data cooperatives may provide a basis for a democratically controlled and fair personal data ecosystem from which society at large may benefit. Cooperatives imply participatory forms of governance that set them aside from other forms of organizations such as foundations or shareholder-owned companies. A prototype for such a model is the Midata platform, a citizen-owned nonprofit cooperative founded in Switzerland in 2015 with the aim of acting as a trustee for data collection and guaranteeing the sovereignty of citizens over the use of their data. Within this model, individuals actively contribute to research as users of the platform by providing access to data sets and as cooperative members to control and develop the cooperative (https://www.midata.coop/en/home/).

7.5 Sources and Use of Tissues and Data

The multiple possible sources of tissue samples have different implications for the donor. Samples can be directly collected specifically to the biobank. However, the collection of samples can also be left-over tissue from surgery, or laboratory samples collected for medical tests, or from tissue biopsies, or from pathology archives. An interesting case is the company 23andME which retains samples and data from commercial genetic testing of customers (Box 7.1). Samples collected for biobanks are of different nature, from simple saliva samples from normal volunteers apparently with no health risk to the donor, as in the case of the kit sold by the 23andME company [44] to serial biopsies from tumor tissue with potential harm to the patient [45]. The risks of such biopsies include hemorrhage, infection, and needle-track

Box 7.1 The Case of 23andMe

The company 23andMe started off in 2006 as a genetic testing company providing direct-to-consumer testing [44]. In addition to selling tests to consumers, it developed a parallel business of selling tissues and data to scientific research. Consumers of the tests were asked to provide health information, access to their Internet behavior and requested to fill in an informed consent to use their left-over samples for research. The trust of genetic testing as a business opportunity was proven by the investments raised: by September 2012 the company had collected over 100 million US $, Google being the biggest investor. By 2016 their biobank contained DNA samples, related health data, and consent for further research from over four million people.

In practice, the company sells online kits to collect a saliva sample. The sample is shipped to the company and tested for two million whole genome SNPs, including SNPs associated with susceptibility to diseases. The customer receives a report through a personal web account. The rest of the sample is stored to be sold for public or private-supported research if the customer has signed a consent. Customers are attracted to this possibility by presenting it as a "full service" providing extra information. Of note, the extent of collected information goes far beyond self-reported health information, also including web behavior, no doubt interesting to advertising companies.

Future plans include consumer health service and a drug discovery program [80]. After a warning by FDA in 2013 about non-validated health-related genetic tests, the company is now collaborating with the FDA in developing health reports and getting them to the customers. In the meantime, the FDA has approved a genetic test for susceptibility to Bloom's syndrome. Drug discovery is a logical expansion of the business, from SNPs to sequencing and from known associations to new druggable target identification. In the words of the platform architect Arnab Chowdry: "having it in-house means that we get a bigger chunk of the value" (quote from [80]). According to Servick, people provide their data to 23andME willingly, being "almost addicted to participating in research."

seeding of the tumor, which are said to be extremely rare. Basik et al. [45], however, mention that safety data from cancer biopsies is scarce and the risks not fully understood. Despite these limitations, ethics review boards have generally considered favorably research projects involving serial tumor biopsies in clinical trials because the benefit to society outweighs the risk to an individual patient [45, 46]. Such thinking is not in line with the Declaration of Helsinki which states that society and scientific research should never be put above the safety of a patient. The source of samples naturally has a lot of implications for the contents of the informed consent, which needs to list potential risks to the donor. It is important to realize that sick patients may misunderstand sampling for research with sampling for clinical purposes (the so-called therapeutic misconception which is highly debated, e.g. [47]).

Human tissue are invaluable resources both in research and in clinical medicine. It is no wonder then that tissue procurement for research has sometimes taken unethical turns, especially when stakes are high, health-wise and/or financially. The example of illegal organ trafficking in transplant business (Box 7.2) makes it clear

Box 7.2 Unethical Organ Trade

Improving organ transplantation practices since 1990 have led to increasing demands of transplantable organs. The business opportunity was immediately recognized by international criminal networks and illegal organ trade started to bloom. This was made possible by corrupt medical doctors and surgeons, public and private insurance companies paying costs of transplant operations abroad without checking the source of organs, and poverty among people willing to risk their health and life against donations, most of the time ignorant of the implications (see, e.g., [49, 90, 91]). In China, involuntary organ harvesting is forbidden by law but a 1984 regulation made it legal to remove organs from executed criminals with their prior consent or consent from relatives. It has been alleged that in 2006, 4000 executed prisoners provided thousands of kidneys and livers for mainly foreign patients [48]. The practice has been recognized by Chinese authorities and in 2007, China issued new regulation banning organ trade. Despite this, consistent media reports suggest that the practice still continues. In India, legal loopholes and poverty turned the country into a large market of kidney transplants. Poor people were often lured and forced by false promises to donate organs. Stricter regulations were put into place in 1994 but there is evidence that organized networks still evade these legal restrictions to continue organ trade. A survey in India showed that a significantly higher percentage of the sellers were under poverty line after the surgery than before, and up to a half were having health issues from the surgery [92]. Iran is the only country where organ trade is legal [92]. The trade is controlled by charity organizations with government support. Despite provided health insurance and heavy regulation to protect the donors, most of them, when asked afterwards would not do it again or recommend selling an organ.

(continued)

Box 7.2 (continued)

"Transplant tourism" (TT) consists of sick people from rich countries traveling to less developed countries in order to seek commercial transplantation opportunities. Efrat [93] compared the situation in two countries, Israel and Pakistan, both of which changed their legislation after the Declaration of Istanbul on Organ Trafficking and Transplant Tourism in 2008 [94]. In a few years in Israel, TT decreased significantly to one-fifth, while in Pakistan the changed legislation did not have a clear effect. Difficulties in cutting TT related to a large number of middlemen financially benefitting from organ trade. The fact that some countries do not release precise statistics makes monitoring the global situation impossible. From global ethical point of view, it is difficult to accept different local ethical standards for commercial organ transplantation [95] or regulated reimbursement model to increase living donations [90], as has been suggested as a solution to the lack of transplantable organs.

that criminal sources of tissue are difficult to eliminate and sometimes almost impossible to trace. Despite the internationally agreed Istanbul Declaration to stop organ trafficking [48], the practice remains underreported and has not stopped [49]. Concerns regarding "tissues for sale" are an important ethical issue, in particular, when biobanks are run as commercial, for-profit organizations. These concerns underscore the need for both public discussion of all aspects of biobanks and transparency about the sources of tissue.

Biobanks may be designed to serve different purposes, some of which are generally regarded as ethically good, such as the conservation of natural variations of species or the promotion of human health. However, within the medical field, opinions may vary regarding the acceptability of specific biobanking practices. For instance, there are different views on how to deal with genetic testing on fetuses and its implications. Testing for life-threatening genetic aberrations is probably acceptable to most people and justifies biobanking. The availability of both genetic tests and biobank infrastructure raises an ethical challenge in providing opportunities for extending testing to conditions that do not dramatically reduce the quality of life of the person (e.g., Down syndrome; [50]). In the study by Hill et al. [51] the parents pointed out two important points in prenatal genetic testing for single gene diseases: the accuracy of the test and the availability of genetic counseling in connection with the testing.

A particular ethical challenge arises when a biobank has to cease its activity and to face closure and dispersion of its contents. It is striking to note that many regulations and guidelines have been developed on how to build a biobank and that almost none address the difficult problem of biobank closure. Whether or not specimens and data should be simply disposed of and destroyed at the end of a specific program is a matter of debate, with arguments for both sides of the coin. When

decisions of retaining specimens are made, they must be transferred to another biobank and repurposed for other programs. There are no defined ethical guidelines regulating such decision processes. The problem is compounded when biobanks face unscheduled closure due to lack of funding, technical problems, or lack of appropriate governance. In such cases, a conservative approach would require that a biobank closure program be formally developed and submitted for approval by a relevant legal or institutional ethical review board. Biobanks should consider insuring themselves against the risk of unexpected closure in order to make sure they have sufficient resources to handle the ethical dispersion of their assets.

Finally, one should keep in mind that it is always possible to use tissues and data from biobanks for sinister purposes, as well. Recent history is rife with discrimination based on skin color, ethnicity, or, indeed, diseases. For instance, mentally incapacitated or ill, and patients with epilepsy were force-sterilized according to law until to the late 1960 in the USA and Europe, including Finland, a practice now regarded as totally unacceptable and criminal (see, e.g., [52, 53]). It is not farfetched to imagine that someone somewhere given the chance, e.g., by non-existing oversight of further use of the samples and data, would buy the material for purposes not generally acceptable. Examples include development of targeted biological weapons or discrimination based on ethnicity in the war zones.

7.6 Incidental Findings

In high-throughput genetic analysis such as genome wide sequencing (GWS) or whole exome/genome sequencing (WES) the amount of achieved information is staggering. Such studies are usually designed as exploratory endeavors attempting to find links between phenotypes or disease and genomic traits. In the course of such analyses, gene variants are found which are known or suspected to associate with conditions and diseases other than those under study [54, 55]. Such incidental or secondary findings (IF) create ethical issues that need to be considered in any biobank-based study [56–60]. It is recognized that biobanks should include in their policy a strategy for the documentation, management, and communication of incidental findings. Naturally, individual differences occur in opinions, even among professionals whether to whom and how to give information of genomic variations and their relationship with diseases or disease risk [61]. Arguments both for and against giving out the individual findings can be presented (Table 7.4). For these reasons, Viberg et al. [57] call for more empirical research before comprehensive policy for handling incidental findings in biobank research is adopted.

A list of existing guidelines and laws outside the US on return of individual research results (IRRs) and IFs are given by Zawati and Knoppers [62]. Among the 15 documents, three are legal documents, the rest being guidelines and hence not legally binding. In spite of this, a lack of sufficient guidance in the literature for managing and returning IFs in genomic biobank research is noted by Wolf et al. [58] and Wolf [63]. Wolf et al. [58] report recommendations developed in an NIH-funded

Table 7.4 Arguments for and against delivery of incidental findings in biobank studies (based partly on [57]

	Considerations	Whose interest
Arguments for		
Disclosure is beneficial for individuals	Is the result analytically valid, clinically significant, and actionable	Participant, family, society
Disclosure promotes autonomy	Do the results have clear clinical use. Are they important to life decisions	Participant
Reciprocity requires disclosure	Participant gives a sample and gets information of his/her genetic status in return	Participant, scientist, research group
Return of incidental findings is in accordance with participant's wishes	Many or even most people want to receive individual genetic information	Participant
Arguments against		
Practical issues make disclosure unfeasible	Difficult to find a solution that fits all, risk of breaching confidentiality if all information of participants retained	Scientist, research group, participant
Disclosure can harm participants	Therapeutic misconception, potential anxiety, accidental delivery of wrong information	Participant, family, health care professionals
The relationship between scientist and participant does not create duty	Difference between a scientist and a clinical doctor	Scientist
Disclosure can harm research and prevent research from doing good	Beneficence in research is at collective level while in care at individual level	Research group, scientist, society

project, where they have identified biobank as the hub of a "biobank research system" that includes the primary research sites (collection sites) and the secondary research sites where biobank samples and associated data are processed and analyzed. The ten recommendations put forward by these authors highlight the central responsibility of the biobank itself in the management and return of IFs and IRRs. The differences in challenges between the preexisting and new biobanks in executing these recommendations have also been discussed, as well as the costs involved in returning IRRs and IFs [64].

A major question about IFs and IRRs is to determine which results and information should be returned to study participants [61, 65–68]. Wolf and coworkers [58] have categorized IFs into those which should be returned, could be returned, and should not be returned to the contributors (providers of samples and data). The IFs that should be returned are the analytically valid IFs of a serious health condition with substantial risk which are actionable and satisfy the applicable law (for example, verification from a CLIA certified laboratory). The IFs which could be returned are those which satisfy all the abovementioned criteria except being actionable but yet having "established and substantial risk of likely health or reproductive importance or personal utility […] likely to provide net benefit from the contributor's perspective." The IFs without personal utility or clinical significance are suggested not to be returned.

Very few original studies have addressed the perceptions of people about delivering individual genetic information to the donors of samples. Indeed, the wide variety of situations make it impossible to define a uniform approach. Aspects to consider include the situation of the individual (patient or non-patient volunteer), age and status (adult, fetus or child, non-autonomous persons), and clinical significance of the incidental finding (disease marker vs. risk for disease; childhood-onset vs. adult-onset disease; whether it is treatable or not). For a lay person, the notion of risk is often unclear and people may easily confuse an incidental disease with incidentally found risk for disease [57]. "Therapeutic misconception" is a term used by Appelbaum et al. [69] to describe the situation when people "fail[ed] to appreciate the distinction between the imperatives of clinical research and of ordinary treatment." Therapeutic misconception has been mentioned in the context of participant's expectations regarding the return of genomic IRRs and IFs [62, 70]. Townsend et al. [71] have reported that the general public and the parents of children with intellectual disabilities, who have undergone genetic testing with inconclusive results, were of the opinion that they should have a say in deciding what results should be disclosed to them. They regarded personal choice as more important than clinical relevance. A similar attitude was also observed in a study by Clift et al. [72], where patients and family members undergoing clinical genomic sequencing felt that they should be able to take part in the decision-making process about which results should be returned to them. In another study, a majority of lung and colorectal cancer patients stated their desire to be informed of all types of results, including genetic IFs [73]. On the other hand, genetic professionals often prefer to restrain the volume of data to be processed and to be selective on what and when to give to patients [74]. In the opinion of most genetic professionals, excessive data can be useless and stressful to the patient, in addition to requiring a lot of wasted resources. The authors point to knowledge in genetics as one of the potential reasons for such difference between the opinions of laypersons and professionals [75, 76].

From a biobanking perspective, the ethical challenges raised by IFs are important because the true significance of an IF may become apparent only several years after the completion of a research project. In this context, the biobank fulfills its role as a hub of a "biobank research system" by acting as a repository for information that patients and participants may feel of relevance to them. Although autonomy is encouraged legally and ethically, any decision of giving such information should be made after thorough consideration and understanding of the available information and not just mechanically exercising one's right.

7.7 Communication and Education

In recent years the development of high-throughput "omics" methodologies such as genomics, proteomics, or metabolomics, coupled with enhanced computing power and artificial intelligence, have propelled biomedical into a new era of "big data science." This new form of large-scale biology provides an unprecedented volume of

information on individual variations associated with health status, but also raises a number of ethical challenges (e.g., [5]). The aggregation of high-throughput data, made possible by linkable sample sets provided by biobanks, is essential for the development of clinical biomarkers and for drug development. Thus, it is no wonder that there is a lot of hype and enthusiasm on the role of biobanks in clinical research, both from the ethical perspective of advancing treatment and care, and from the ethically more complex perspective of making financial profit. This complex set-up makes communication and dialog mandatory between various stakeholders: (1) among scientists, (2) between scientists and participants providing tissues and data, (3) between scientists and investors either public or private, providing funding for research, and (4) between scientists, the public, decision-makers, and the society as a whole, who should ultimately exert the final say on these decisions. Successful communication between different stakeholders in biobanking requires education to understand the concepts and implications of large-scale biology, as well as the specific requirements of biobanking in this respect. Both nonprofessionals as tissue donors and participants in scientific projects to understand what they consent to, as well as people taking part in decision-making, e.g., when designing new legislation, need a sound understanding of biobanking issues and ethical challenges.

From the scientist's perspective, education and training are fundamental to correctly identify and duly address the various ethical challenges of biobanking and large-scale research in developing a research project. This has very practical implications, e.g., when submitting a protocol to an ethics committee or when preparing a grant application. Good communication between scientists is especially challenging in international multidisciplinary fields such as biobanking. Thus, it is important to know about the history and cultural differences to avoid past mistakes [3, 5]. Scientists themselves start to realize the importance and need of education in ethics [5, 36, 77] and the best ways of ethics teaching are actively investigated [78]. When stakes are high and scientific competition intense, multiple dangers arise, such as hastily-drawn or reductive translational studies on immature biomarkers, conflicts of interest between stakeholders (patients, researchers, industry), and temptation to cut corners in science, causing misconduct (e.g., [79]). Research integrity should be promoted by all means in the midst of enthusiasm. Although formal education in ethics of young scientists is required, the example by senior scientists through model learning is probably the most effective way [5]. No ethics teaching will sustain good scientific practice if research institutions, academia, and scientific journals do not create an appropriate context for research integrity and provide means to deal with scientific misconduct (as an example of recommendations on how to deal with research misconduct see www.tenk.fi).

Communication with the public is being made simple by easy access to the Internet. Both invitations to participate in research and biobanks and information distribution can be efficiently carried out through the internet. Although this possibility is already utilized in scientific research, there are limits: older people may not be computer literate or have a computer, and literacy or connection to the Internet is not self-evident in all parts of the world. An ethically relevant issue is also the behavior of people, which changes according to the situation and is more relaxed at

the computer than face-to-face. In fact, for some commercial companies, it has appeared very easy to get health data directly from people through Internet questionnaires [80].

Due to decreasing costs of genome sequencing, direct-to-consumer genetic testing (DTC-GT) is turning into a thriving business (for reviews see, e.g., [81, 82]). A flagship in this business is 23andMe, a US-based company ([44]; see Box 7.1) which has created a two-way business by selling genetic testing over the Internet and then asking for consent to retain the rest of the samples which are then sold further. Their biobank with matched samples and data is one of the largest existing. Thus, in this business model, the consumer (a healthy volunteer from the point of view of research) does not communicate with a doctor, nor with a scientist, but with a multinational commercial company. As pointed out by Zawati et al. [83], this is not unique to this company, and other DTC-GT companies often retain data from the analysis for future use.

When dealing with DTC-GT companies the privacy and autonomy of the consumers end when they fill out the health data sheet and sign the consent. They do not have any control over the purpose their samples are sold for. In the literature, the concerns on the adequacy of the consumer's consent and the transparency of the direct-to-consumer genetic testing companies have been expressed based on the data given in the company web pages, the only places where consumers can find information, often insufficient and even misleading [84], before making the decision whether to subject their DNA for testing [85]. Furthermore, many of the companies, based on their web pages, may not have clear policies as to testing of children, an issue where professional scientific researchers and organizations have made a significant effort creating guidelines [86].

The uniqueness of genetic data is well recognized in the literature and legislation. Unfortunately, the general public may not be aware of it and often lack the necessary knowledge to understand the future implications of sending their samples and personal information for such tests, and the information provided in many cases is not of sufficient help [84]. The absence of a health care professional to provide an overview of the process has led to this gap of knowledge and understanding which is being utilized by the DTC-GT companies for their commercial gains. The many ethical issues recognized in the literature regarding DTC-GT include misleading commercials, lack of reliability of tests, future use of the samples and data, what happens to the samples and data when these companies shut down, emotional impact to the customers on receiving the results, and tests for newborn or children. The bigger the company, the more share of the market it is able to buy and such a monopoly can be regarded even as a possible threat to democracy [44].

7.8 Conclusion

In biomedical research, good ethics is based on three basic ideas: honesty, respect, and professionalism. The generally accepted starting point is the value of human life. Even if these were self-evident in various functions of society, including

medical research, healthcare, and biobanking, a lot of developmental work and negotiations between stakeholders are needed in proper implementation of these principles. Multiple factors, such as the pursuit of personal or private interests, misuse of opportunities for financial gain and fame, carelessness in practical work, ignorance of proper rules of practice, or inappropriate use of biobanked tissues and data may compromise good ethical practice. Moreover, even when the intentions are good, quality pursued, and professional demands respected, there is always a possibility of human error. It is ethically important to admit this and make plans to deal with such flaws.

The basic dilemma of medical ethics lies in the difficulty to take into account both sides of the same coin. One side of the coin is the great expected health benefits from studies using human tissues. The other side is the ethical costs, in the form of potential harm for participants, loss of autonomy, unknown or even criminal use or sale of human tissue, and commercial use of tissues in a way unacceptable by people. The activities of biobanks actually place them precisely at the tipping point where the coin may flip towards one side or the other. In terms of ethical impact, biobanks have two characteristics that make them particularly important. First, they are durable (they generally exceed the lifetime of the projects they support and even the career of the scientist who has created them). This implies that biobanks are the most evident point of entry for secondary or tertiary usage of stored tissues, which can take place years if not decades after the initial tissue and data collection. Second, they operate at a critical junction in science, where biological data are processed and transformed into digital data. This particular role places biobanks with the specific responsibility of acting as custodian and caretaker for huge volumes of "data-to-be," the significance and impact of which is very difficult to predict. Despite these characteristics, biobanks are often merely considered just as technical infrastructure in the design and ethical approval of studies using human tissues. They are evaluated on the basis of their technical performance and compliance with recommended standards for specimen processing and storage. Their ethical responsibilities in setting up appropriate mechanisms and safeguards for long-term access and usage of tissues are rarely challenged. With the growing interoperability of multiple data sources, the ethical responsibilities of biobanks, both as data sources and custodians, will come under further scrutiny and will need to be addressed by appropriate regulation and legislation.

Ethics is about making balanced choices in particular in "grey zones" where regulation and legislation are underdeveloped or inexistent. As highlighted throughout this chapter, ethics for biobanks still contain many such "grey zones" and is therefore an important field for research and debate. Incidental/secondary findings, not explicitly targeted by initial research protocols but appearing as additional findings in large-scale molecular analyses, are unavoidable [87, 88]. Variants with no significance at the time of analysis may appear significant by time, which makes the accuracy of the analysis and proper documentation of the findings important. Strategy on whether and how to inform participants about secondary findings and what kind of support to give to those who find out or are told about a significant secondary finding should be in place beforehand.

Advancing this field of ethics for biobanks should be built on several pillars: (1) transparency enabled by education and public discussion, aimed at making participants, actors, and stakeholders knowledgeable about biobanking processes and ethical implications; (2) good governance, aiming at making participants an integral part of decision processes regarding tissue and data usage; (3) sound and fair funding and business models, ensuring the long-term viability of high-quality biobanks and protecting them against many forms of misuse that may stem from insufficient resources.

Human nature is somewhat irrational and unfortunately also susceptible to corruption. Institutions and organizations are not eternal and when they fail or die, their assets are often left to grabs according to market laws. When money becomes the main or the only driving force, many good principles may be forgotten or overruled. From a purely business point of view, quick, easy, and cheap access to data and tissue are the primary interest. From this point of view, regulations are often perceived as obstacles for innovation and value creation. However, from the point of view of respect for the participants and addressing the expectations of society as a whole, things look different. Fair regulation protects people and also provides a framework for good science oriented towards benefits for the people. Good societal ethics requires the protection of those less privileged and democratic decision systems to ensure the use of tissues and data in biobanks for generally acceptable purposes. Biobanks can be seen as giant telescopes for biomedical research, operating as large instruments that can be pointed towards unexplored areas of the deep universe of human biology. By transmuting the codes of Nature into digital data, biobanks operate at the very interface between Nature and Culture. We need a model where best practice from a technical viewpoint can make a harmonious match with the best practice from an ethical viewpoint [89]. This would not take away passion, intensity, and contradiction from the ethical scientific debate, but would outline a pragmatic road ahead for addressing the scientific and societal challenges and opportunities of "big data" research using human tissues.

Accepting the existence of issues and bringing them into awareness are the initial steps in establishing good ethical practices. In this chapter, we have pointed out the "grey zones" in biobanking and described the background for their existence. Such discussion, we hope, moves the biobanking field closer to building the best ethical practices.

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