BRIEFINGS IN BIOINFORMATICS. VOL 9. NO 1. 14–24
Advance Access publication October 23, 2007
doi:10.1093/bib/bbm050

Biobanking for Europe

Martin Yuille, Gert-Jan van Ommen, Christian Bréchot, Anne Cambon-Thomsen, Georges Dagher, Ulf Landegren, Jan-Eric Litton, Markus Pasterk, Leena Peltonen, Mike Taussig, H-Erich Wichmann and Kurt Zatloukal

Submitted: 24th April 2007; Received (in revised form): 23rd September 2007

Abstract

Biobanks are well-organized resources comprising biological samples and associated information that are accessible to scientific investigation. Across Europe, millions of samples with related data are held in different types of collections. While individual collections can be well organized and accessible, the resources are subject to fragmentation, insecurity of funding and incompleteness. To address these issues, a Biobanking and BioMolecular Resources Infrastructure (BBMRI) is to be developed across Europe, thereby implementing a European 'roadmap' for research infrastructures that was developed by a forum of EU member states and that has been received by the European Commission. In this review, we describe the work involved in preparing for the construction of BBMRI in a European and global context.

Keywords: *epidemiology; pathology; genetics; biobanks; databases; ethics; funding*

INTRODUCTION

Understanding the molecular and environmental basis of human diseases, in order to improve diagnosis and treatment is a top priority jointly for society and for biomedical researchers. This implies that funders and researchers need to combine to improve this understanding as rapidly and efficiently as possible. The pre-condition for such an improvement is the efficient organization of the resources that are the objects of study. This has been recognized by the world's major economies, which, via the Organisation for Economic Cooperation and Development (OECD), have stated [1] that 'biological resource centres are an essential part of the infrastructure underpinning life sciences and biotechnology . . . essential for R&D in the life sciences . . . and human health'. OECD goes further and specifies [2] that these centres need to be networked: 'a global network . . . is a critical element of the infrastructure'.

Where efficient organization of resources has been implemented, rapid progress has been achieved. A recent example [3] is the identification of moderate genetic susceptibility factors in seven chronic diseases. A total of 17 000 cases and controls were collated from multiple sources through the Wellcome Trust Case Control Consortium. The authors identified a need for further, yet larger studies. They also identified issues connected with inconsistent sample quality: different sources of samples showed differing degrees of 'missingness' (i.e. the percentage of failed tests in a set of single nucleotide polymorphism tests). The Cancer Genome Atlas Project has recognized this as a serious issue in tissue banking [4]. These issues of size and quality can only be addressed in a timely and

Corresponding author. Martin Yuille, The University of Manchester, School of Translational Medicine, CIGMR Oxford Road, Manchester M13 9PT, UK. Tel: +44 (0)161 275 5622; Fax: +44 (0)161 275 1617; E-mail: Martin.Yuille@manchester.ac.uk

Martin Yuille is with UK DNA Banking Network, CIGMR, The University of Manchester, UK.
Gert-Jan van Ommen is with the CMSB-Department of Human Genetics, LUMC, The Netherlands.
Christian Bréchot is with the Institut National pour la Santé et la recherché Médicale, Paris, France.
Anne Cambon-Thomsen is with UMR Inserm, Université Paul Sabatier - Toulouse III, U 558, Toulouse, France.
Georges Dagher is working with the INSERM-Tolbiac, Paris, France.
Ulf Landegren is with the Department of Genetics and Pathology, Uppsala University SE-751 85 Uppsala, Sweden.
Jan-Eric Litton is with Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.
Markus Pasterk is working with the International Agency for Research on Cancer, Lyon, France.
Leena Peltonen is with the National Public Health Institute, Biomedicum Helsinki, Finland.
Mike Taussig is with the The Babraham Institute, Cambridge CB22 3AT, UK.
H-Erich Wichmann is working with the GSF- Institute of Epidemiology, Munich, Germany.
Kurt Zatloukal is working with the Institute of Pathology, Medical University of Graz, Graz, Austria.

© The Author 2007. Published by Oxford University Press. For Permissions, please email: journals.permissions@oxfordjournals.org

cost-effective fashion through the application of advanced logistics.

The word 'biobank' is a little over a decade old [5] and has recently been defined by OECD [6] as 'a collection of biological material and the associated data and information stored in an organized system for a population or a large subset of a population'. Millions of samples with related data are held in different types of collections across Europe including at major biobanking facilities in at least six EU states. There are significant ongoing efforts in several European countries to run biobanks using international standards (e.g. ISO 9001, OECD Good Practices) and to implement access policies. However, while individual collections can be well organized and accessible, this is not always the case. There remains a need to harmonize between them and to ensure the longevity of the resources through appropriate funding mechanisms.

The European Commission and representatives of individual EU member states have recognized the need to address these issues. We outline here medium-term plans for the mobilization and rational development of Europe's biobanking resources. Issues connected with biomolecular resources are beyond the scope of this article.

Background

The European Strategy Forum on Research Infrastructures (ESFRI) comprises representatives of EU Member States and Associated States and a representative of the European Commission. Its role is to support a coherent approach to policy-making on research infrastructures. In 2006, its Roadmap for pan-European research infrastructure development across the sciences was published (http://cordis.europa.eu/esfri/roadmap.htm) and then formally received by the Commission. ESFRI's decision to include infrastructure to underpin research in the life sciences is significant because it indicates that there is, for the first time, a general recognition that the scale of life science research endeavours has increased to a point where separate research groups need to pool resources.

Six priority biological and medical research infrastructures were proposed costing €1.6 billion. This article focuses on plans for a European Biobanking and Biomolecular Resources Infrastructure (BBMRI) (www.biobanks.eu). The other five European infrastructures are for translational research (www.eatris.eu); mouse resources (www.infrafrontier.eu); clinical research (www.ecrin.org); structural biology (www.instruct-fp7.eu) and bioinformatics (www.elixir-europe.org).

In all cases, the development of these infrastructures requires preparatory work. This is designed to bring each plan to the point where funding from various sources (national sources, the Commission, other EU funds and the private sector) will have been agreed by all parties.

For biological resource management, the ESFRI roadmap proposes 'a pan-European and broadly accessible network of existing and *de novo* biobanks and biomolecular resources' (ftp://ftp.cordis.europa.eu/pub/esfri/docs/esfri-roadmap-report-26092006_en.pdf). ESFRI, comprising Profs G.J.B. van Ommen (U Leiden NL); M. Osborn (Max Planck Institute for Biophysical Chemistry, Göttingen, DE); E. Vuorio (U Turku, FI) with advice from an expert group, had argued that, following the rapid progress of genomic research in humans and their ancestors, biomedical and health research has expanded from the study of rare monogenic diseases to common, multi-factorial diseases. However, most complex diseases are elusive as they do not root in single defects, but are caused by a large number of small, often additive effects from genetic predisposition, lifestyle and the environment. Discovery will depend critically on the study of large collections of well-documented, up-to-date epidemiological, clinical and biological information and accompanying material from large numbers of patients and healthy persons.

The ESFRI report foresaw a project aiming to build a coordinated, large scale European research infrastructure of already existing and *de novo* collections of biomedically relevant, quality-assessed samples (with the possibility to link to related clinical and epidemiological information), to enhance therapy and prevention of common and rare diseases, including cancer. In this area of unique European strength, said ESFRI, valuable and irreplaceable national collections typically suffer from underutilization due to fragmentation. Major synergism, gain of statistical power and economy of scale will be achieved by interlinking, standardizing and harmonizing—sometimes even just cross-referencing—a large variety of well-qualified, up-to date, existing and *de novo* national resources.

BIOBANKING AND BIOMOLECULAR RESOURCES INFRASTRUCTURE

Overview

In order to construct a pan-European BBMRI, the European Commission has determined that a preparatory phase is needed. To plan this phase, a group of researchers decided to approach colleagues throughout the EU to determine their interest in BBMRI. This approach has resulted in the involvement of 19 countries, with 50 institutions agreeing to participate and 134 associated organizations (see Supplementary Table 1). Expressions of interest continue to be received. It is notable that 23 major European institutions and research organizations (ministries of health or of research, research institutes, funding organizations) are co-applicants and active participants.

BBMRI will build on existing sample collections, resources, technologies and expertise, which will be specifically complemented with innovative components and will be properly embedded into European scientific, ethical, legal and societal frameworks. Sustainability will be achieved by appropriate funding and financing solutions.

BBMRI will provide:

- Biobanks of different formats (based on collections of DNA, tissue, cells, blood and other body fluids, together with pertinent medical, environmental, life-style and follow-up data).
- Population cohorts (prospective, isolated and twin cohorts).
- Clinical case/control cohorts including disease-focused cohorts.
- Biomolecular resources (comprising antibody and affinity binder collections, ORF clone collections, siRNA libraries, proteins, cellular resources, etc.).
- Enabling technologies and high-throughput analysis platforms and molecular tools to probe gene, protein and metabolite activities.
- Harmonized standards for sample management.
- Harmonized databases and biocomputing infrastructure.
- Ethical, legal and societal guidance and platform.

BBMRI will give European scientists, industry and, eventually EU (ageing) citizens distinct advantages, such as

- Broad and unified access to catalogued information on biological samples and collected data, which is presently difficult due to different data structures and incompatible regulations for their access and exchange in different countries.
- Improved reliability and reduced ambiguity in comparing and interpreting results by guaranteeing a common set of standards and harmonization guidelines in sample preservation and analysis, which reflect the state-of-the-art in the field.
- A setting to establish an open-source (code) based federated database structure that can guarantee the same standard of data quality in annotation, while protecting donors' privacy.
- Access to a Europe-wide data and sample set, thus providing data with better statistical power or permitting the investigation of rare or highly diverse diseases, such as cancer.
- Capacity to develop prospective collections meeting the needs of particular research projects or clinical trials, based on Europe-wide networking of biobanks meeting compatible quality standards.
- Compliance with ethical and legal requirements.
- Sound governance system building on input by all stakeholders.

How BBMRI will work

Key components of BBMRI include comprehensive collections of biological samples from different (sub-) populations of Europe, which should be linked eventually with continuously updated data on the health status, life style and environmental exposure of the sample donors. This can only be achieved in a federated network of centres established in most, if not all, European Member States. This network is best described as a distributed hub structure (Figure 1). This structure will provide the flexibility needed to facilitate growth of the network with new members and partners and to allow adaptation to emerging needs. Data sharing will be enabled via federated database architecture with grid computing technology.

Biobanks, biomolecular resources and technology centres are members of BBMRI and connected to their specific hubs. Partners, who are not members, may be associated with members. In addition to domain-specific hubs, there are national coordinators

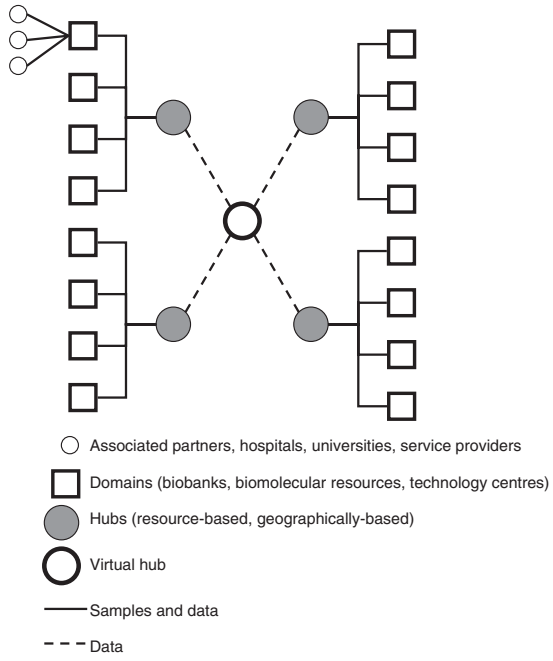

Figure 1: BBMRI—a distributed hub structure. The goal of BBMRI is to enable access by researchers to different sample types (with associated data) collected under different study designs. BBMRI will be a distributed hub structure in which the hubs coordinate activities, including collection, exchange and analysis of samples and data for the major domains. The biobanks, biomolecular resources and technology centres, which are members of BBMRI, are associated with their specific domain hub. A variety of public or private partners (e.g. universities, hospitals and companies), which provide biological samples, data, technologies or services, may be associated with certain BBMRI members. All domains will be linked to allow flow of data and samples.

to address issues specific for EU Member States, such as legislation or national funding systems.

BBMRI members represent the key providers of resources and technologies being leaders in the field and drivers of innovation and scientific excellence. Membership is non-exclusive but favours members that can link BBMRI to other national, European or global initiatives. Associated partners and subcontractors provide certain resources (services, data, samples and materials) to BBMRI. They may be a hospital or research institute or a ministry, government, research council or funding agency. Users may come from different fields of academia and industry. Access will be provided in the context of specific research projects and on the basis of secured funding.

BBMRI will integrate with several ongoing international activities, such as those pursued by P3G (Public Population Project in Genomics: a project to facilitate biobanking globally that was started by two European and a Canadian population genetics initiatives and that is growing rapidly worldwide), the Innovative Medicines Initiative of the European Commission Innovative Medicines Initiative, the OECD, and the UN World Health Organisation. To avoid duplication of guidelines, procedures and recommendations, BBMRI will exchange concepts and experience with these activities some of which are identified in Table 1.

BBMRI's preparatory work will address funding issues, needs in population-based and disease-based biobanks and related biocomputing issues. Ethical, legal and societal issues and biomolecular resources issues will also be addressed. Figure 2 shows the organogram for this work.

On funding issues, the major goal is to prepare documents required to ensure funding and financing of the implementation and operation of BBMRI. These will place special emphasis on the value generated for society and on the expected short-, mid-, and long-term return of investment to make possible long-term funding agreements. Funding and financing of BBMRI will need to embrace a variety of national and European funding schemes, financing through the health care system, income from industrial cooperation as well as contributions from patient organizations and private foundations.

Public consultation is an important aspect of the preparatory phase, since BBMRI will have an impact not only on researchers but also on the funding community, industry and on the general public. One component of the consultation process will be a Stakeholder Forum meeting.

The second phase of preparatory work will lead to the drafting of contracts. These will have been prepared with direct involvement of representatives of several European ministries and funding agencies. In order to achieve broad support, the drafts will then be discussed with ministries and funding agencies of European Member States that are not named BBMRI participants. There will be two types of contract: one to secure funding of construction and operation of BBMRI; the other to define the

Table I: Guidelines, procedures and recommendations applicable to BBMRI

Title	Organisation	Link
Tissue banking for Biomedical Research	National Cancer Centre	http://www.bioethics-singapore.org/resources/pdf/AppendixB-Dr%20Kon.pdf
Biorepository Protocols	Australian Biospecimen Network (ABN)	http://www.abrn.net/pdf/ABN.SOPs.Review.Mar06.final.pdf
Biological Resource Centres: underpinning the future of life sciences and biotechnology	Organisation for Economic Co-operation and Development (OECD)	http://wdcm.nig.ac.jp/brc.pdf
OECD best practice guidelines for biological resource centres	Organisation for Economic Co-operation and Development (OECD)	http://www.wfcc.nig.ac.jp/Documents/OECD.pdf
European Human Frozen Tumor Tissue Bank TUBAFROST	The European Human Tumour Frozen Tissue Bank (TUBAFROST)	http://www.tubafrost.org
Common Minimal Standards for Biological Resource Centers	International Agency for Research on Cancer, World Health Organisation	http://www.iarc.fr/News/RecommendationsBRC.pdf
Human tissue and biological samples for use in research. Operational and ethical guidelines	Medical Research Council (MRC)	http://www.mrc.ac.uk/pdf-tissue.guide.fin.pdf
Best Practices for Repositories I: Collection, Storage, and Retrieval of Human Biological Materials for Research	International Society for Biological and Environmental Repositories (ISBER)	http://ehs.sph.berkeley.edu/Holland/Biorep/BestPractices2005.3.5.pdf
First-Generation Guidelines for NCI-Supported Biorepositories	National Cancer Institute (NCI)	http://biospecimens.cancer.gov/biorepositories/NCI.First.Generation.Biorepository.Full.Guidelines.pdf
Transport of infectious substances	World Health Organisation (WHO)	http://www.who.int/csr/resources/publications/biosafety/WHO.CDS.CSR.LYO.2005.22r%20.pdf
UN Recommendations on the Transport of Dangerous Goods. Model Regulations.	United Nations Economic Commission for Europe (UNECE)	http://www.unece.org/trans/danger/publi/unrec/rev13/13files.e.html
A Cold Greeting: an Introduction to Cryobiology	Biotech	http://www.bioteach.ubc.ca/Bioengineering/AColdGreeting/
Specimen Collection, Preparation, and Handling	Labcorp	http://www.labcorp.com/datasets/labcorp/html/frontm.group/frontm/section/speccol.htm

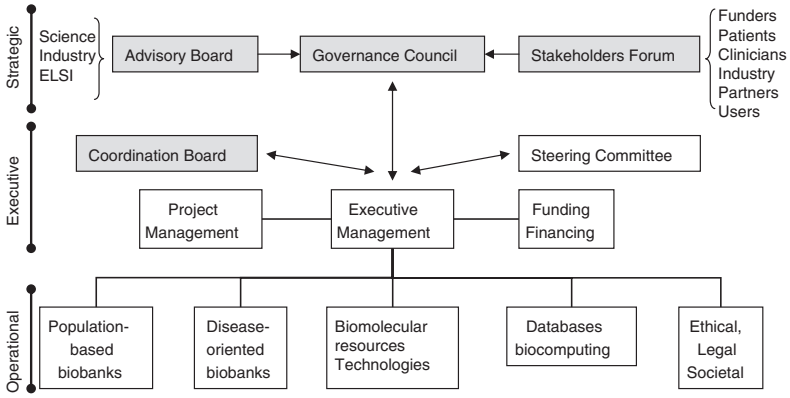

Figure 2: Organization of BBMRI's preparatory phase. The preparatory phase of BBMRI is organized, first, to achieve precise specification of the infrastructure by groups of participants (with expertise in population-based and disease-based biobanks, in biomolecular resources and technologies, in databases and biocomputing and in ethical legal and societal issues) and, second, to organize appropriate funding for the infrastructure. BBMRI participants work in each of the organizational entities shown above, according to their expertise. Entities that are shaded also receive contributions from other fields (as shown). The Governance Council receives contributions from participants and associated organization. The Coordination Board receives contributions from other related research infrastructures.

relationship of members, such as biobanks, resource or technology centres with BBMRI.

The flexible decentralized hub architecture of BBMRI will facilitate this fast-moving strategy. It will allow operations to start with a small number of members that represent the leading and most advanced European biobanks and resources. This architecture will also permit and facilitate inclusion of further members, in particular, those from new EU Member States. Moreover, this architecture is highly compatible with worldwide networking among OECD members and others in the Middle East, Asia, Latin America and Africa.

Population-based biobanks

Europe's national health care systems have facilitated collection of clinical samples and produced highly reliable health care records. Furthermore, Europe has strengths in epidemiological studies that have, over decades, accumulated data complemented often by biological samples. The diversity of European populations with well established but different histories is a beneficial feature for various research strategies. New biobanking initiatives have been launched and just like the older biobanks, they all rely on these strengths.

For maximal utilization of both old and new biobanks, the critical components of expertise need the integrated efforts of European epidemiologists, biobankers, clinicians, experts in different fields of laboratory medicine, molecular geneticists and experts in high-throughput 'omics' technologies, database and IT experts and statisticians. The single most critical element for epidemiological data harmonization is a suitable and flexible database structure that can handle both longitudinal and quantitative data, often collected over decades.

Before proceeding to database harmonization, web-based cataloguing of existing population biobanks and epidemiological data collections is needed. Such a cataloguing effort needs to be harmonized with global efforts such as that undertaken by P3G.

In consequence, BBMRI will:

- Produce a document addressing the governance-related issues of European epidemiological data collections and epidemiological cohorts.
- Make a solid fiscal plan to guarantee the continuity of financing of systematic update of large cohorts with life-long clinical information and life-style/epidemiological data.
- Produce a plan to build an attractive research infrastructure for the post-genome studies of population cohorts linking the critical players in biobanking efforts to be able to recruit globally.
- Make an effort to establish solid standards for storage and harmonization of complex epidemiological data and for release policies of this data.
- Produce a solid plan for a flexible IT infrastructure to store and distribute the epidemiological and genetic data to investigators and prepare it for statistical analyses. The goal is to design a user friendly database structure that is flexible enough to accommodate complex data sets from different population cohorts and facilitate effortless slicing and dicing of complex epidemiological, clinical and 'omics' data. A code of conduct will be established for the use and development of such a database. This effort will be closely linked to the upgrading of European bioinformatics infrastructure (the ELIXIR plan).
- Produce a document describing the major needs and requirement for statistical and biocomputational analyses of the epidemiological data as a preparatory document for a statistical powerhouse of Europe. Such a centre, partially virtual and linking the key players of epidemiological statisticians, will greatly advance the utilization of large study cohorts.
- Contribute to European legislation and policy documents of data and sample release for large cohorts and population studies. This involves differences in national health care systems and data confidentiality legislations.
- Provide logistics standards and sample handling protocols for various platforms of expensive 'omics' technologies. Such platforms with high running costs and constant updating of large databases require intensified collaboration between academic institutes (and industry).

Disease-oriented biobank

Disease-oriented biobanking embraces a wide range of collection activities supporting diverse research purposes. Almost every major hospital in Europe supports collection of blood, DNA or tissues. Multicentre collections arise from clinical trials and genetic studies. Estimates of the number of European tissue banks exceed 200 including at least 70 major, internationally recognized initiatives. For blood and DNA the numbers are even larger. Many of are already organized within regional or national networks.

BBMRI will address the ongoing and future activities of disease-oriented biobanks building on previous and current work and on international guidelines. It will produce recommendations for the construction and operation of infrastructure and deal with questions of availability, quality criteria, rules of access, and incentives for participation.

In the first step, existing resources, technologies, standards and know-how will be integrated into the operational concept of BBMRI. An inventory will be prepared of existing biobanks and clinical sample collections in Europe that meet necessary quality standards. A web-based catalogue is envisaged that describes each resource and its terms of access.

Technical solutions and quality criteria for storage, retrieval and transfer of biological samples will be reviewed and an electronic manual of existing documents for biobanking methods is envisaged. This manual will include general considerations for laboratory infrastructure as well as Standard Operating Procedures covering all aspects of sample management.

There are several unresolved issues. Since common standards are missing until now, generic solutions must be developed, which propose ways to use existing clinical biobanks. BBMRI aims for harmonized standards, but integration of the existing individual biobanks may require flexible solutions. Realistically, different degrees of collaboration and access have to be provided and prototypes for access rules shall be developed. Further issues include:

- How to organize a review process to integrate existing resources?
- What criteria to use for selection of scientifically sound study protocols to facilitate access to and use of samples?
- How can competing interests of different groups in the same samples be met in a transparent and fair way?
- What fees are appropriate for academic and industrial users?

For new collections, standards are needed. These should be evidence based and properly considered requirements of novel analysis tools and platforms—from preparation of the sample to storage, retrieval and transfer.

To be successful with this initiative, solutions have to be found to motivate existing biobanks to make their resources available to others [7]. A system of incentives for providing biological samples within BBMRI will be developed. For instance, it might be attractive to provide incentives for contributors in the form of 'contribution points', which allow a ranking of resource providers who contributed to high quality publications and are preferred partners for joint research grants and qualify for success-dependent financial benefits.

The concept of a pilot network of biobank infrastructures will be developed that aims to provide a framework for training, testing and assessing proposed standards, and at developing networking/tissue and specimen transfer protocols.

For some countries, it might be helpful to develop a national structure for their biobanks and collections of biological samples, which then could serve as a national hub. This might address the varying requirements of biobanking-related national legislation and regulations.

Database harmonization and IT-infrastructure

The move towards a universal information infrastructure for biobanking in Europe is directly connected to the issues of semantic interoperability through standardized message formats and controlled terminologies. The information infrastructure has become a critical component in life-sciences research. The explosion of genotype data requires that data are properly loaded, accessed, managed, queried, analysed and shared. Longitudinal research over a long period of time, for generations of researchers, demands completely new methods and systems for gathering and storing genotype and phenotype information. The biobanks bring to the fore the problems concerning the need for standardized research data and a long-term storage strategy.

To focus on biological samples like blood, tissues and whole cells, competitive biobanking solutions are not sufficient: we need to organize the information about the samples, including registration of disease-related information, in order to investigate the properties of the organism as a whole and of the molecular and cellular makeup of the individual's tissues. The combined use of lifestyle surveys, associated biological samples and relevant registers will help us to identify possible links between genetic predisposition and disease. The successful and systematic collection of demographic and lifestyle data is central to the process of any epidemiological

or clinical study. An important purpose of biobank informatics is to identify the complete scope of information structures needed and to analyse how available nomenclature and coding systems can be used for storing and retrieving biobank information. Several controlled terminologies and coding systems may be used for organizing the information about biobanks. Some of them were originally created for other purposes and encompass only parts of the information needed for comprehensive coverage. If these data-management requirements can be met, the combined IT infrastructure will help each biobank to become be a supreme resource for epidemiological and clinical studies.

In biobank studies, traditionally, data have been collected into one centralized repository, a data warehouse, using strict data submission protocols. This creates a large amount of rigidity in the data-collection phase and also complicates the obligatory constant update of the warehouse information. In BBMRI, a complementary approach will be suggested where data is accessed on demand from participating centres, using direct database connections. This strategy offers flexible infrastructure for data sharing and collaboration between centres, providing the possibility to adapt the informatics infrastructure easily to different research needs. Each system has its own proprietary semantic structure, but is mapped to a logical data model that can be instantiated as a physical federated model or a canonical message model. Semantic interoperability is achieved within an enterprise via a hub-and-spoke topology, which reduces the redundancy and maintenance cost of point-to-point integration.

The post-genome era provides us with a broad spectrum of '-omics' technologies for collecting vast amounts of molecular information from biological samples, which have to be analysed in combination with clinical phenotype and collected lifestyle data of individuals. In spite of several large-scale projects and global achievements in standardization, these efforts have not yet been successfully unified. Inadequate standardization is a general problem that undermines full utilization of many biospecimens. Therefore, emphasis will be placed on providing best practice-based standard protocols for different types of sample and data collections, so that samples and data can be utilized well into the future. These protocols will be made public. Standardization of the whole sample handling process including the infrastructure required should lead to certification of BBMRI members.

Ethical, legal and societal framework

Biobanks and society are inseparable. Society needs biobanks because they can contribute greatly to health. But biobanks also need society in the form of generalized support, financial resources and the cooperation and trust of patients and healthy individuals. In democratic societies, science, and even more so 'big science' (such as BBMRI), cannot succeed without strong social and political support, social understanding and the resulting social legitimacy [8]. A considerable amount of work and many texts of different levels of binding force have been produced in the domain. A great heterogeneity has resulted and the efforts have been more on mapping the topics and the diversity than on constructing the foundations for a practical framework [9].

One formidable legal challenge for the establishment of the pan European BBMRI is how to navigate the complex set of laws and regulations governing biobanking in general and cross-border biobanking in the EU in particular. Specifically, it is vital that the broad and unified access to be provided to the data and samples collections of BBMRI partners and members is compliant with their laws and the content of the consent forms. To prepare for this, BBMRI will organize a bottom up, web based and regularly updated legal platform [10]. It will function under an administered and quality validated WIKI+ (Plus) format that will allow for authorization by a designated editorial board. This will be the basis for information tools to practically address the implementation of legal aspects in a harmonized way. Legal questions that will be addressed using the legal platform include the following. Does the realization of the BBMRI require the adoption of a specific legal framework? Should this framework be a specific piece of enabling legislation or could self-regulation suffice? Legal clarity is needed on the terms of participation, data protection, access and commercialization.

An analysis of the work already performed will be undertaken and a consultation mechanism towards implementation will be developed. Little has been done on developing incentives for sharing of resources [11] and so understanding the points of blockage will be a major goal.

Ethical questions that will be addressed include the following. How should 'harmonization' in ethics be interpreted? How does it differ from 'standardization'? To what extent is either practically feasible in ethics, from an ethical point of view? To what extent

is ethics in this area dependent on social context? What are the acceptable margins of deviation from standards in relation to BBMRI? What are the challenges in making BBMRI congruent with 'European values'? To what extent are ethical traditions in tension with new developments in this area?

Societal questions that will be addressed include the following. How should BBMRI address its social dimension? What do Europeans actually think about biobanks, seen as 'European level initiatives' and how they might perceive a large-scale initiative such as BBMRI? We know nothing about this crucial dimension of BBMRI. We want to begin to elucidate the relationship between the European citizenry and biobanks. This will be approached by constructing a methodology for assessing channels of information on biobanks on one hand and comparing various methods of consultation on the other hand.

What corresponds to BBMRI as a European infrastructure on the societal level? In the absence of a 'European society', we want to think in terms of varied 'European publics' and discuss possible strategies of BBMRI to interact with these various publics. Our basic assumption is that it will be crucial for BBMRI to interact openly and transparently with the European citizenry. Any other strategy would be conceived against the assembled wisdom of science and society studies on Europe conducted during the last decades. In order to achieve this goal, methods of consultation will be assessed [12, 13] and a strategy will be decided based on such experiences as a model of governance of BBMRI [14].

Furthermore, a survey needs to be done of the public perception of biobanks in Europe, including a study of the perception of larger collaborations like BBMRI. Also, an array of instruments—surveys, focus groups and citizen forums—must be established to assess the public perception of biobanks. Since the boundary between surveying public perception and engaging the public in a dialogue and exchange should be maximally permeable, strategies of citizen engagement and science communication should be part of BBMRI [15, 16]. The possibility that such a survey is performed by an institution that is independent of BBMRI will be considered and the choice will be reflected in the governance model. Connections to related projects in the different Framework Projects will be implemented.

Funding and financing

The increasingly large number of biobanks that now exist, provides a sound and pertinent infrastructural underpinning for a growing range of clinical research and genome epidemiology studies. However, biobanks are expensive to set up and maintain for long-term studies. Running costs for a case-based biobank are about €400 000 per year. More than €340 million have already been invested in biobanks operated by BBMRI participants and associated organizations. Lack of sustained funding has been identified as a major bottleneck in establishing long-term operation of resource centres for life sciences. This has a drastic impact on public health, for example, the development of prognostic biomarkers for common diseases, impact of environmental parameters. Furthermore, despite major investments in biobanks made in various EU member states, there is no pan-European coordination of efforts and no long-term funding schemes exist.

In order to develop a funding concept, the impact of harmonized organization of biobanks and improved coordination of existing funding schemes will be evaluated. It is anticipated that as a consequence of better coordination of funding, a significant contribution for the construction phase can be demonstrated even without the need for increasing the overall research expenditures. The reason for this is that current biobank projects often have to waste resources due to duplicated efforts, e.g. by independent development of IT-solutions or by independent implementation of, and therefore often different, standards and quality assurance measures. On the other hand, for full implementation of BBMRI and to secure long-term operation, increased investments into these key resources have to be made.

The long-term funding concepts will consider the whole spectrum of funding schemes including national, European and private funding organizations as well as financing solutions provided by the European Investment Bank. The funding concept will also include financing through income from cooperations with the pharmaceutical and biotech industry. Furthermore, financial contributions from academic users will contribute to the funding and financing concept. For academic users, agreements with Member States are foreseen, which follow examples already successfully applied in other types of research infrastructures.

Global integration

BMRI will follow a proactive global integration strategy to guarantee that solutions developed will be compatible with and provide a model for biological resource infrastructures worldwide. The strategy calls for close collaboration with global organizations listed subsequently.

Organisation for Economic Cooperation and Development (OECD): in 2001, OECD introduced [1] a new concept of repositories and providers of high quality biological materials and information: the Biological Resource Centre (BRC). In 2007, OECD declassified [17] best practice guidelines on BRCs, dealing with quality and biosecurity issues and providing specific guidelines for different types of resources. In 2008, OECD expects to propose how to create a global BRC network.

World Health Organization (WHO): this organization is increasingly interested in research aspects in general and defined in its 11th General Programme of Work, 2006–15 six core functions, out of one calls 'shaping the research agenda and stimulating the generation, translation and dissemination of valuable knowledge'. This is especially important for biobanks. Furthermore, the International Agency of Research on Cancer (IARC) in Lyon—a WHO agency—has published recommendations [18] that open the door to R&D repositories in medium- and low-income countries, which will be of increasing importance in the future. The IARC Cancer Control Forum—comprising national cancer institute directors globally—has prioritized the establishment of guidelines for BRCs.

Public Population Project in Genomics (P3G): this not-for-profit international consortium to promote collaboration between researchers in the field of population genomics. This platform has been launched, in order to provide the international population genomics community with the resources, tools and know-how to facilitate data management for improved methods of knowledge transfer and sharing, especially developing research tools for effective collaboration between biobanks.

DISCUSSION

We have described plans for the development of a research infrastructure for Europe that will serve the key resource needs of biomedical researchers seeking to identify factors important to the aetiology of human disease. Identification of these factors has become an important priority not only in the research agenda of biomedical research, but also in the societal agenda for science.

The plans for European biobanking that we have outlined underscore the widespread interest and enthusiasm for the plans among all the relevant scientific specialists. This interest and enthusiasm will need to be sustained not only by the specialists but also by the populations of Europe over a long time. This is because the development of infrastructure is incremental, because the benefits to human health can only start to arise after the infrastructure has been completed and because completion of the infrastructure will require debates and evolution of ethics and the law in numerous states.

BBMRI will require the mobilization of all relevant data at the same time as corresponding biological resources. Such mobilization has not yet been achieved fully by even a demonstration project. For example, within genetic epidemiology, there is no public place where one can view and search phenotype datasets, genotype datasets and sample availability data for a given disease or condition. Yet, this is essential to the design of further experiments on a given subset of samples. The reason for this is not scientific or technical. The reason is organizational viscosity—there is drag in the process of bringing together all the parties required to make an agreement and to fund that agreement. BBMRI will reduce that drag.

BBMRI will be a European network. Its biobanking focus is on human biosamples required to identify risk factors. As similar networks arise elsewhere in the world, BBMRI will support construction of a global biobanking network. However, European networks are also envisaged in other areas of biomedical science (Figure 3). EATRIS is a European network of new research centres translating basic discoveries into clinical interventions in major diseases. ECRIN is a European network of clinical research centres, clinical trials and biotherapy facilities for therapeutic innovations. In both these networks, human biosamples and data will be handled. It is evident that all three European networks—BBMRI, EATRIS and ECRIN—will generate greater scientific value, when the sample and data standards they adopt are identical or compatible and when there is data sharing between them. The upgrading of the European bioinformatics

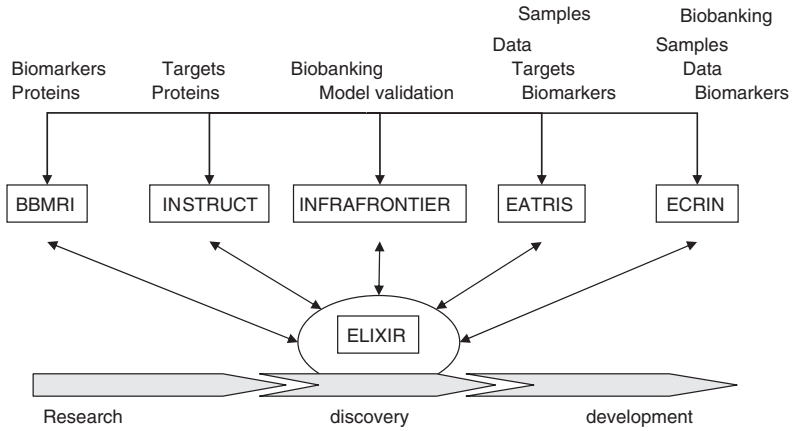

Figure 3: European biosample networks. BBMRI, EATRIS and ECRIN are infrastructures for management of human biosamples at different steps in the Research—Discovery—Development process. BBMRI, INSTRUCT and INFRAFRONTIER are infrastructures for management of biomolecular resources. The bioinformatics infrastructure ELIXIR will facilitate data sharing between these infrastructures.

infrastructure—ELIXIR—will facilitate this data sharing. This vision will take European biomedical science close to the OECD vision for the development of a global network of biological resource centres.

Acknowledgements

The development of plans we describe for biobanking and biomolecular resources infrastructure has involved a large number of people including those named in Supplementary Table 1. We wish in particular to name George Gaskell (London School of Economics, UK), Andres Metspalu (University of Tartu); Bill Ollier (University of Manchester); Jasper Bovenberg (NL); Thomas Meitinger (GSF, München-Neuherberg).

Key Points

- A Biobanking and BioMolecular Resources Infrastructure (BBMRI) is being developed across Europe, implementing a component of the European 'roadmap' for research infrastructures.
- The project will harmonize samples and data across the range of molecular epidemiological and pathological studies.
- The initiative brings together a wide range of experts in biomedicine, informatics and ethics and from the law and funding bodies.

SUPPLEMENTARY MATERIALS

Supplementary materials are available at *Briefings in Bioinformatics* Online.

References

1. OECD. *Biological Resource Centres: underpinning the future of life Sciences and Biotechnology*. Paris: OECD, 2001.
2. OECD. Towards A Global Biological Resource Centre Network. Paris: OECD, 2007. www.oecd.org/document/51/0,3343,en_2649_201185_33791027_1_1_1_1,00.html. (12 October 2007, date last accessed)
3. The Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 2007;**447**:661–678.
4. Waltz E. Pricey cancer genome project struggles with sample shortage. *Nat Med* 2007;**13**:391.
5. Loft S, Poulsen HE. Cancer risk and oxidative DNA damage in man. *J Mol Med* 1996;**74**:297–312.
6. Creation and Governance of Human Genetic Research Databases. OECD Publishing. 25 October 2006. ISBN-92-64-02852-8.
7. Bovenberg J. Whose tissue is it anyway? *Nat Biotechnol* 2005; **23**:929–33.
8. Cambon-Thomsen A. The social and ethical issues of post-genomic human biobanks. *Nature Rev Genet* 2004;**5**:866–73.
9. Chadwick R, Wilso S. Genomic databases as global public goods? *Res Publica* 2004;**10**:123–34.
10. Bovenberg JA. Legal pathways for cross-border research: building a legal platform for biomedical academia. *EurJ Hum Genet* 2007;**15**:522–4.
11. Cambon-Thomsen A. Assessing the impact of biobanks. *Nature Genet* 2003;**34**:25–6.
12. Burgess MM. Public consultation in ethics: an experiment in representative ethics. *J Bioeth Inq* 2004;**1**:4–13.
13. Godard B, Marshall J, Laberge C. Community engagement in genetic research: results of the first public consultation for the Quebec CARTaGENE project. *Community Genet* 2007; **10**:147–58.
14. Chadwick R. Bioethics and governance. *Bioethics* 2007;**21**:ii.
15. Gottweis H. Governing genomics in the 21st century: between risk and uncertainty. *New Genet Soc* 2005;**24**: 175–93.
16. Sanderson SC, Wardle J, Michie S. The effects of a genetic information leaflet on public attitudes towards genetic testing. *Public Underst Sci* 2005;**4**:213–24.
17. OCED. *Best Practice Guidelines on Biological Resource Centres*. Paris: OECD, 2007.
18. *International Network of Biological Resource Centres For Cancer Research: Recommendations on Common Minimal Technical Standards*. Lyon: IARC, 2006.