Personal medicine—the new banking crisis

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As the healthcare industry moves from a twentieth century approach of providing treatments of last resort to a future of individualized medicine, biobanks will play a pivotal role in this transition. Yet at the cutting edge of biobanking research are new ethical, social and policy challenges beyond those familiar to basic biomedical research.

An unusually productive collaboration among academic, nonprofit and managed care researchers has produced the largest DNA biobank in the United States, and with it, historic milestones for speed, number of samples and a database with extensive ethnic diversity. The project, Kaiser's Research Program on Genes, Environment and Health (RPGEH), a trifecta of genetic, environmental and medical information, aims to address long-standing criticisms of biobank utility by identifying meaningful links between the many factors contributing to health outcomes[1] (**Box 1**). The hope is that this is just the first of many efforts where biobanks will play an essential role in the transition to personalized medicine by linking biological data to electronic medical records. To stay relevant, biobanks will need to enable pharmaceutical and diagnostics researchers to do longitudinal biomarker studies and develop downstream screening and diagnostic approaches. The promise of individualized medicine will depend in large part upon the ability of physicians to evaluate a patient's cellular and genomic traits alongside medical history, and interrogate the data appropriately (**Box 2**).

However, this kind of data sharing complicates the obligations and expectations of all users and owners, including scientists, research sponsors, companies, publishers and science policy makers. Uncharted complexities exist involving informed consent, patient confidentiality, management of incidental findings, and practical issues medical interfacing and commercialization. As biobanking initiatives and the research they facilitate expand in unprecedented ways, what practical, social, ethical and economic implications lie ahead?

Box 1 The Kaiser biobank

In 2011, academic, nonprofit and managed care researchers joined forces in an innovative collaboration to produce the largest DNA biobank in the United States. To date, Kaiser's biobank has achieved milestones for ethnic diversity and yielded tantalizing clues into the aging process and diseases such as multiple sclerosis. In just 15 months, the group genotyped 100,000 saliva and blood samples from patients of Kaiser Permanente. Collected from 170,000 biospecimens from Kaiser patients, the milestone is a significant stride toward the goal of collecting 500,000 samples by 2012 (ref. 1).

Funded by an NIH Grand Opportunities award and the Robert Wood Johnson Foundation, the group used genome-wide genotyping on the patient samples. Kaiser members consented to have researchers access and use their medical records, but because the true clinical impact of the information is currently unknown, medical files will not be annotated with research results. Federal stimulus funds, a significant price drop in biochip technology, and throughput that quadrupled 2009 rates was providential for Kaiser and the University of California, San Francisco (UCSF) team. The massively parallel system relied on custom arrays fabricated by Affymetrix (Santa Clara, CA, USA). For each sample, the system genotyped 675,000 to 900,000 markers, comprising single-nucleotide and insertion-deletion polymorphisms[1].

During last October's American Society of Human Genetics meeting in Montreal, Kaiser researchers described how the bank would enable better ways to detect, treat and prevent disease. One such inroad is the development of ethnic-specific arrays for European, African, Asian and Latino ancestry, including patterns of disease in families. Another, involving UCSF's Elizabeth Blackburn, used variation in telomere length in the Kaiser samples, suggesting links between shorter telomere length and various age-related diseases and earlier mortality. RPGEH will compare gene data against the backdrop of environmental factors—such as air pollution, water quality and proximity to parks, grocery stores and healthy foods. Studies underway using RPGEH-generated data include: incidence of prostate cancer among African American men, a multi-ethnic study on bipolar disorder, and a pharmacogenetic study of response to metformin, a drug used to treat type 2 diabetes.

Advantages to self-contained projects such as the RPGEH, the VA's Million Veteran Program and Vanderbilt University's 75,000 sample DNA biobank is that the healthcare provider and biobank are part of the same organization. Yet this is only one of an array of biobanking models, fed by advances in technology and the promises of individualized medicine.

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Box 2 Personalized medicine: dream or reality?

Following the rapid progress in genomics research, biomedical health research has expanded from the study of rare monogenic diseases to common, multifactorial diseases. Innovative, high-throughput technologies are widely expected to enable a better dissection of these complex, causally heterogeneous diseases into more homogeneous subgroups, which is a requirement for the advancement of personalized medicine.

If biobanking is ever to fulfill its promise of personalized medicine, data must be useful for clinical purposes and efficiently interlaced with healthcare systems. Several barriers stand in the translational pathway. Whereas flexibility in regulations will undoubtedly be needed lest biobank administrators become paralyzed by compliance efforts, regulation is important not only for ensuring data reliability but also for fostering public trust in biobanks. The costs associated with whole genome sequencing are declining, but clinically relevant data will be key to drive the field past research to clinical utility.

In the future, a family physician might routinely order a whole genome scan, or deploy algorithms that query pharmacogenetic or Mendelian carrier data, or interrogate genomic information. For banks aiming to store and acquire samples and provide clinical services, sales, marketing and training is essential to ensure the trust of healthcare providers. Michael Christman, president and CEO of Coriell Institute for Medical Research (Camden, NJ, USA), predicts as the costs of whole genome sequencing decline, genetic data repositories will need a custodian to handle audit trails and to guarantee confidentiality. "The raw data demands will be huge: a terabyte per individual, and gigabytes for consensus sequences. Physicians will need a trusted source of information."

Sample quality and certified extraction protocols are another place where biobanks can distinguish themselves. Généthon (Paris) is one of Europe's biggest tissue and cell repositories, with 300,000 samples collected from 80,000 people with 400 genetic disorders. The nonprofit, funded by a yearly telethon, uses standardized techniques, which adhere to the Organization for Economic Co-operation and Development recommendations, in collaborations with different research teams. Though the services activity of the bank is exclusively for research—not for diagnosis—tissue information, including over 2,000 cell lines, intercalate with medical records of patients with rheumatoid arthritis, epilepsy and other rare disorders. According to Généthon's director of DNA and cell banking, Safaa Saker-Delye, the biggest obstacle is the lack of interoperability between research and clinical databases. "This hampers the development of research requiring large number of patients," Saker-Delye maintains. "This is particularly true in genomics where association studies are thought to be one of the ways to identify genomic regions that contribute to the genetic risk of complex diseases such as diabetes, heart diseases or asthma."

Among biobankers, there is fretting that the $1,000 genome will be followed by the $1,000,000 interpretation. Biobanks cannot assist medicine unless there are reliable, efficient means to connect them to medical records. One solution posed by efforts such as Kaiser's RPGEH and the Veteran's Administration Million Veteran's Project rely on electronic medical records (EMR) to produce self-contained systems of integrated genomic and medical information. But conversion to EMRs is costly and time consuming. New projects, such as the US program initiated by President Obama, have been slow going with no definite end in sight. Kaiser's Cathy Schaefer, executive director of RPGEH at Kaiser's Division of Research, admits that the biggest challenge for the future of personalized medicine is not just genotyping but the link of genetic to medical data. When speaking about the sheer volume of data facing researchers generally, "we've outstripped our computational ability," says Schaefer. But, closed-loop projects like Kaiser's might lead to better health outcomes for multifactorial diseases and new disease taxonomies. The healthcare provider plans to reference genomic data against rates of blood pressure change, glucose metabolism, and a host of environmental and geographical factors. Schaefer, an epidemiologist, points out that 25–30% of Northern California residents are Kaiser members, and therefore, data from her cohort are representative, and compare favorably to samples retrieved from tertiary care settings or clinical trials."These aspects of the RPGEH make the available data very rich and useful for research," Schaefer states. Whereas single-nucleotide polymorphisms and genetic data are fairly straightforward to obtain, the informatics challenges of medical records are substantial. Diagnoses must be validated, laboratory data confirmed, and years of historical information in the EMR must be checked to ensure the clinical phenotypes can be linked reliably to the avalanche of biobanking information.

Biorepositories and shared databases

Defining the universe of biobanks will help in tackling this question. In general terms, biobanks are organized repositories of human biological material and associated data stored for research purposes. A recent survey shows that biobanks exist on every continent, even Antarctica[2] (**Fig. 1**). Beyond offering raw statistical power, biobanks facilitate studies of the structure and function of organs on microscopic and macroscopic levels, as well as cross-modality studies using materially different data (e.g., genome and protein interactions). Biobanked materials play a prominent role in research efforts aimed at identifying the key genes, proteins and signaling networks underlying disease, and at developing personalized therapies.

Biobanks vary considerably in the particulars of what types of data they store and how this information is organized and accessed. Samples can include DNA, RNA, tissues, tumors, cells, blood or body fluids. Specialty collections feature biopsies of rare diseases and cancers, or specific anatomy such as eyes, bone and cartilage. Additionally, some biobanks use data derived from biomaterials, such as molecular analysis, microarrays and immunohistochemical techniques to reveal a mechanism of action or disease biomarker. Neuroscience biorepositories, for example, are especially rich and complex with records comprising any combination of microscopy images, single and multi-unit recording data, structural and functional magnetic resonance imaging, positron emission tomography, electroencephalography and magnetoencephalography.

Biobanks also differ in their organization. They can serve as part of a value chain, moving samples from primary sources to researchers. Alternatively, the scientific goals behind storage schemes can be quite specialized, as with the types, combinations and volumes of stored samples and data, and the technical requirements for storage and access. Geography plays a role in how samples are exchanged, as do the infrastructure for managing and maintaining the bank and the recovery strategies in the event of disaster. Conditions of privacy (descriptors, if any, of source individuals), procedures for anonymizing data, and the regulatory environment also bear on bank organization and access. Further, the governance of a biobank and funder expectations (public or private) shape the approach to intellectual property rights, the accessibility of bank information, distribution of the bank's resources and the eventual therapeutic use of its materials.

The market potential for biobanks is consid-

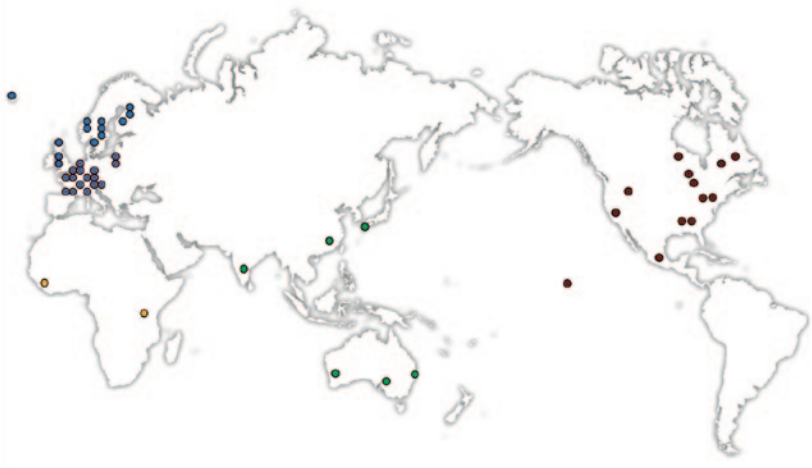

Figure 1 Biobanks around the world. A survey shows that biobanks exist on every continent, even Antarctica. Only national or institutional repositories are counted, so this graphical view is not meant to be comprehensive. (Reprinted with permission from ref. 2.)

erable. The sector, by one estimate, will grow 20–30% annually to over 2.25 billion by 2015 (ref. 3; **Fig. 2**). Today, many major biobanks are comprised of nonprofit, academic and national concerns. (**Tables 1** and **2**).

Practical challenges

Despite their differences, biobanks share common practical challenges. Logistics loom large. Acquiring samples poses the biggest variable cost, which is modulated by recruiting and contracting sites, properly obtaining donor consent, developing collection and shipping kits, and transporting materials to and from storage. Once at the bank, specimens need to be cared for properly, often in liquid nitrogen freezers. Cataloging, bioinformatics, laboratory management, inventory control and auditing must converge to ensure the integrity of complex data. Samples and their associated data must be tightly linked to retrieval and distribution systems for efficient, correct shipment after being requested by a researcher. Sample mix-ups could have disastrous consequences for firms developing diagnostic tests and the patients who would use them. Lack of standard operating procedures—or their careful enforcement—can cause data quality to deteriorate. For example, the National Cancer Institute's (NCI's) Cancer Genome Atlas project was launched on the assumption that its researchers could obtain quality tumor specimens provided by dozens of biobanks. NCI researchers instead found that only about 1% of the promised samples were usable, and biobankers often did not know what their inventories actually contained[4].

Beyond daily functionality, a frontline question facing biobanks is how to best use the data to predict and treat disease. Though genome-wide association studies using materials from biobanks have identified hundreds of loci with genetic variants associated with certain traits, skepticism abounds about whether the small effect sizes seen in many of these studies can effectively predict disease or yield meaningful scientific insights. Critics say research relying on raw predictive power misses the clinical endgame; the usefulness of genetic information for prediction will depend not on herita-

Table 1 Major biobanks

Name	Sponsor	Services and scope
1000 Genomes Project	International	Genome sequencing of a large number of people around the globe to facilitate genome-wide association studies of disease.
Biobank Japan	Ministry of Education, Culture, Sports, Science, and Technology, Japan	Database for the advancement of personalized medicine.
Biobanking and Biomolecular Resources Research Infrastructure	Pan-Europe, European Commission	International consortium of existing and *de novo* biobanks and biomolecular resources, to serve as an interface between biological samples and data from patients and health populations to support biological and medical research.
BioVu	Vanderbilt University	Repository of DNA samples and de-identified health information from the Vanderbilt University Medical Center's electronic system.
CARTaGENE	University of Montreal	A repository of socio-demographic, health data and biological samples from 20,000 citizens of the province of Quebec in Canada.
Coriell Cell Repositories	Coriell Institute for Medical Research, United States	Repository of cell lines, DNA, tissue, plasma, serum, urine, cerebrospinal fluid and phenotypic data for use by Coriell scientists and researchers worldwide.
European Collection of Cell Cultures–UK	Health Protection Agency, Salisbury, UK	Cell culture collection for distribution to researchers; includes cell lines for 45 species, 50 tissue types, 300 human leukocyte antigen types, 450 monoclonal antibodies and at least 800 genetic disorders.
Généthon DNA and Cell Bank	Association Française contres les Myopathies, Evry, France	Largest DNA and cell bank in Europe for human and genetic disorders; established to prepare and distribute blood and DNA samples from patients with genetic diseases and their families for translational research.
International HapMap Project	Canada, China, Japan, Nigeria, UK, USA	International collaboration with the ultimate goal of developing a haplotype map of the human genome.
Kaiser Research Program on Genetics, Environment and Health	Kaiser Permanente Division of Research, California	Database of genetic (saliva and blood), behavioral and environmental data linked to electronic medical records to enable research on the genetic and environmental factors of disease.
Million Veterans Program	US Veterans Affairs	Large-scale database of genetic and health information for use in research on the prevention and treatment of diseases facing American veterans and nonveterans.
Swedish National Biobank Program	Swegene and Wallenberg Consortium North, Sweden	National program for the organization, promotion, education and quality assurance of Swedish biobanks.

bility but rather on how genetic information ultimately informs the cost-benefit analyses of existing clinical interventions. In addition to their much-anticipated potential for personalized medicine, these studies may help to uncover yet-unknown disease mechanisms.

Open source models such as the 1000 Genomes Project and the International HapMap Project, spurred by the US National Institutes of Health's (NIH's) data-sharing policy, promote collaborative projects and encourage data collection and sharing in publically available databases. But proprietary pressures to develop diagnostics and therapeutic products may offset open sourcing. Further, conflicting federal policies for data sharing send mixed messages to inventors. The NIH encourages patenting of diagnostic tools while discouraging the use of patents to prevent access to genome-wide association study data developed with NIH support. University patenting practices, competition among laboratories and the actions of commercial efforts may compromise creative commons–type models of biobanks.

The comprehensive electronic medical record itself is far from reality. Though President Barack Obama announced an ambitious initiative in 2009 to computerize the nation's healthcare records within five years, today less than 10% of American adults actually use them[5]. Integrating biological sampling data would add to the billions of dollars needed to integrate a system. It makes sense that efforts like the Kaiser genotyping project and the recently announced Veterans Affairs (VA) Million Veteran Program would link medical histories with biological samples. The VA has been keeping computerized health records for more than two decades, and Kaiser's efforts began more than 40 years and $4 billion ago.

Regulatory and ethical impact

Biobanks sit outside the purview of existing national regulatory bodies that oversee laboratory testing, human subject research, patient privacy assurance and drug approvals. For example, the Clinical Laboratory Improvement Amendments issued by the Centers for Medicare and Medicaid Services regulate laboratory testing, and the US Food and Drug Administration regulates safety standards for marketed drugs and devices, but these bodies oversee researchers and companies using biobank data to generate medical products, rather than upstream biobanking practices or testing for research only.

The Common Rule, a baseline standard of ethics to which nearly all US government-sponsored academic institutions hold their researchers, protects humans enrolled in clinical trials. However, the Common Rule exempts research on de-identified data, which suggests that research using anonymized biobank samples would not require human subject protections. Though donation and banking of human biologic materials requires consent and privacy protection for eventual research use, it is largely unregulated in these endeavors. Similarly, the Health Insurance Portability and Accountability Act (HIPAA) Standards for Privacy of Individually Identifiable Health Information provides legal protection for patients' identifiable personal health information. HIPAA ensures patient direction over the use of their information unless it is de-identified; however, as we discuss below, the process of de-identification is unregulated and problematic. Not all state privacy laws apply to research with genetic data, and it is unclear whether HIPPA standards apply to identifiable genetic and medical information. The promise of biobanking rests on its connection to medical information both during research and the eventual connection of the data to individual medical records. Re-identification can pose dilemmas for researchers and doctors in situations where donors may wish to be contacted in the future about research results.

There is intense debate about what constitutes proper informed consent, how to honor donors' wishes for the use of their materials, and whether researchers and professionals should contact patients with future medical information. Implicated in these debates are the related issues of control over future uses of data and disclosure of research results to patients. In April 2011, Arizona State University paid $700,000 to 41 members of the Havasupai Indian tribe of Arizona for the use of blood samples for genetic research without sufficient consent. The tribe members thought they had donated blood for diabetes research, but researchers also used samples to study the genetics of mental illness ancestry, violating the tribe's values. In this case, the researchers' broadly worded consent document stated that the collected samples would be used to "study the causes of medical/behavioral disorders," which the tribe found inadequate and deceitful[6].

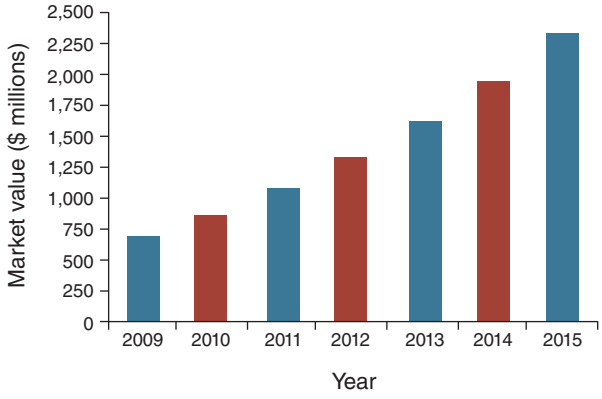

Figure 2 Global market value of the demand for human biospecimens and related services. (Reprinted with permission from ref. 3.)

Well-established concepts of informed consent require participants to be informed about the specific details of each proposed research project[7]. Kaiser gives plan members the option to participate in RPGEH research once they have reviewed and signed a consent form. Vanderbilt University's (Nashville, TN, USA) BioVu biobank, by contrast, represents one of the few repositories where consent is implied, and patients undergoing routine clinical testing must opt out of the database. Research on public perceptions have disclosed that the public wants continuing control and, at some level, consent. As such, an opt-out approach may not be an ideal solution, particularly given the noted controversies and existing legal norms. Because of the vast number of research participants involved in large-scale biobanking initiatives and the many projects that may be implicated, getting specific consent from each and every donor is, from a practical perspective, nearly impossible. Biobank researchers are left with two undesirable options, either the difficult task of attaining specific consent, or the ethically contentious practice of generalized consent.

Within the biobanking community, emerging consensus supports a participant-as-donor model of consent that is transparent about its lack of specificity and participants' lack of choice over the future use of their biologic contribution. Donors signing broad consents would essentially agree to unspecified and general use of their materials for research. This is the approach adopted by most population biobanks, such as UK Biobank (Adswood, Stockport, UK), Quebec's CARTeGENE and Swedish National Biobank Program (a consortium of ten biobanks from around the country). Outside the community's consensus,

however, national and international research ethics policies are not harmonized and little agreement exists in the general public or among law and ethics scholars. For example, a recent US focus group and survey study found a public that preferred a broad approach to consent over ones involving additional choices. But the preference was marginal, thus noting the lack of consensus on these issues. Indeed, as noted by the authors of the study: "54% of our survey and 42% of our focus group participants could be seen as preferring a control/choice-promoting model (e.g., categorical or study-specific consent) over a control/choice demoting model (e.g., broad consent)[8]."

At the heart of the debate is whether a broad consent can ever be truly informed and, therefore, satisfy well-established principles of consent. For some, adherence to some form of specific consent (that is, the provision of information about each project) remains essential. Others have suggested that because biobanks are for the public good, an altered consent process is both necessary and justified.

Although informed consent remains one of the most contested issues of biobank policy, other legal and ethical challenges also require careful attention. Clearly, there is a need for scrupulous protection of the rights and welfare of human subjects, especially children and individuals who are not legally competent to consent. Worries about confidentiality, especially when coupled with a novel consent process, have resulted in opposition to some public projects. The Icelandic case is illustrative. Starting in 1996 data were collected from most of the population to help identify human genes associated with common diseases. Consent was presumed by the government, rather than individually expressed in writing. This issue, together with concern about the commercialization of the information, led to the failure of a health sector database in Iceland. Whereas some argue for more transparency and more detailed informed consents, others wonder what uses might be permissible if donors did not expressly consent to them.

Internet access has heightened concerns about confidentiality. Though federal human subject protection law requires all identifying information be removed from data before sharing, true de-identification of medical records may be virtually impossible. For example, reconstructing a person's facial and cranial features from a brain image make old rules about identifying information a vexing problem[9].

On the other hand, there are undeniable benefits to sharing data, such as increasing statistical power and cost efficiency. But at the heart of biobanks—whether for genomic data, DNA, tissues, cells or other data forms and materials—is the entanglement of open science and the ownership of information. Genetics researchers report intentionally withholding data because of the sheer amount of work associated with sharing them and the wish to protect publication opportunities for themselves and other faculty[10]. Lack of clear national and international funding agency policies poses problems for scientists, as does perilously unstable funding. A regulatory patchwork of international policy makes data sharing across borders even more difficult (**Table 3**). For example, in the United States, federal government databases are not protected by copyright; in the European Union, they are.

In the absence of a standard paradigm for sharing data, comparison across studies may be difficult. Who will be responsible for converting data into standard formats, and how will the data be used? An investment in large-scale clinical research and sharing practices such as those promoted by the NIH's Roadmap for "Re-engineering the Clinical Research Enterprise" will yield a return once it enables a broad community of scientists, with proper coordination and integration of resources, to make progress[11]. In sum, the absence of such standards compromises comparisons across studies and may hinder innovation.

If a finding of potential clinical significance is detected during the course of a research project using biomaterials, what should researchers do? There are two general categories into which such findings fall: structural or functional incidental findings that are unrelated to the purpose of the study that may or may not have clinical significance, and results of a study that may be related to the purpose of the study but whose clinical meaningfulness is unknown. In 1999, the National Bioethics Advisory Commission recommended that findings be revealed to patients only if (i) they are scientifically valid and confirmed; (ii) they have significant implications for the subject's health; and (iii) a course of action to ameliorate or treat the concerns is readily available[12].

Overall, built-in processes for managing incidental findings have been recommended for most study designs and herein lie the more nuanced questions. Researchers might want to opt out of reporting to subjects, and, conversely, participants might want to opt out of being told. This becomes troublesome for a researcher if a finding is life threatening and disclosure violates the terms of the consent agreement. In the field of genetics, some have considered asking participants what kinds of results they would wish to receive. In neuroimaging, there is uncertainty about whether a physician qualified to read brain images should do so for all those acquired for research, for scans that are noted to be suspicious for an anomaly or not at all in order to preserve the separation of research and clinical medicine[13].

Risks to participants arise if biobank samples are distributed beyond the remit of the original research. Uncovering anomalies of potentially unknown clinical significance or identifying a disease state or predisposition can involve psychological risks and potential intrinsic harm, violating donor privacy. Disclosure of sensitive information to third parties can result in discrimination. These protections are double edged: patients should know that anonymous use of tissue or data means they will never know specific information about findings related to their samples. There may be solutions that maintain privacy and give

Table 2 Key health organizations involved with biobanking

	Selected domains in which organizations are involved			
Organization/project	**Guidelines and tools creation**	**Networking and harmonization**	**Scientific discoveries**	**Biobanking**
International Agency for Research on Cancer http://www.iarc.fr/	X	X	X	X
National Cancer Institute http://www.cancer.gov/	X	X	X	X
Biobanking and Biomolecular Resources Research Infrastructure http://www.bbmri.eu/		X		X
International Society for Biological and Environmental Repositories http://www.isber.org/	X	X		
OnCore UK http://www.oncoreuk.org/index.html		X		X
Public Population Project in Genomics http://www.p3gobservatory.org/	X	X		

Source: Modified from P^3G

Table 3 Comparative review of international laws, guidelines and regulations on biobank-based research and consent requirements

Organization or country	Laws (L), guidelines (G) and regulations (R)	Model of informed consent[a]
World Health Organization	(G) Guideline for Obtaining Informed Consent for the Procurement and Use of Human Tissues, Cells and Fluids in Research (2003) (G) Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services (1997)	Specific informed consent Partially restricted consent Broad consent
Council for International Organizations of Medical Sciences	(G) International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002)	Specific informed consent
United Nations Educational, Scientific and Cultural Organization	(G) International Declaration on Human Genetic Data (2003)	Partially restricted consent
Human Genome Organization	(G) Statement on DNA Sampling: Access and Control (1998)	Broad consent
Council of Europe	(L) Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine (1997) (L) Treaty Series No. 195, Human Rights and Biomedicine. Protocol on Biomedical Research (2005) (G) Recommendation (2006) 4 on Research on Biological Materials of Human Origin (2006)	Specific informed consent
National Bioethics Advisory Commission	(G) Research Involving Human Biological Materials: Ethical Issues and Policy Guidance (1999)	Multi-layered consent
Australia	(G) National Statement on Ethical Conduct in Human Research (2007)	Specific informed consent Partially restricted consent Broad consent
Estonia	(L) Human Genes Research Act (2001)	Broad consent
France	(G) Ethical Issues Raised by Collections of Biological Materials and Associated Data: 'Biobanks', 'Biolibraries'—National Consultative Bioethics Committee for Health and Life Sciences (2003)	Specific informed consent
Germany	(G) Biobanks for Research—National Ethics Council Opinion (2004)	Broad consent
Italy	(G) Biobanks and Research on Human Biological Material—National Bioethics Committee Opinion (2006) (G) Guideline for Clinical Protocols of Genetic Research—Italian Society of Human Genetics (2006)	Partially restricted consent
	(G) Guideline for Clinical Protocols of Genetic Research—Italian Society of Human Genetics (2006)	Specific informed consent
	(G) Guideline for Genetic Biobanks—Telethon (2003)	Specific informed consent
	(G) Guideline for the Establishment and Accreditation of Biobanks (2006)	Specific informed consent
Japan	(G) Ethical Guidelines for Analytical Research on the Human Genome/Genes (2001)	Broad consent
Switzerland	(G) Biobanks: Obtainment, Preservation and Utilization of Human Biological Material (2006)	Broad consent Specific informed consent
Spain	(R) Royal Decree 411/1996, by which Activities Regarding the Use of Human Tissues are Regulated (1996)	Informed expressed consent
United Kingdom	(L) Human Tissue Act (2004) (G) Human Tissue and Biological Samples for Use in Research—Medical Research Council (2001)	Broad consent
The Netherlands	(L) Civil code, article 467 (1994) (G) Code for Proper Secondary Use of Human Tissue in The Netherlands (2002)	Informed expressed consent
Iceland	(L) Act on Biobanks No. 110 (2000)	Broad consent
Denmark	(L) Law on Biobanks No. 312 (2003)	Informed expressed consent
Sweden	(L) Law No. 297 (2005)	Specific informed consent
Norway	(L) Act on Biobanks (2003)	Informed expressed consent

[a]Broad consent allows the use of biological specimens and related data in immediate research and in future investigations of any kind at any time. Partially restricted consent allows the use of biological specimens and related data in specific immediate research and in future investigations directly or indirectly associated with them. Multi-layered consent requires several options to be explained to the research subject in a detailed form. Specific informed consent allows the use of biological specimens and related data only in immediate research; forbids any future study that is not foreseen at the time of the original consent. (Reprinted with permission from ref. 16.)

information to patients. One idea would employ a third-party intermediary to contact patients in the future. Another model would provide a secure web-based consenting tool for patients to communicate with researchers in a dynamic but anonymous fashion over time. Recontacting patients and donors is always a wild card. Over time, families disperse. Public records might be inaccurate or lost. Individuals move and eventually pass away. Even when data have not been de-identified, recontacting participants from vulnerable populations, such as the mentally ill or homeless may be challenging. What investigators working on secondary research projects should do with genetic or other clinical information about a research participant with whom they have had no prior contact remains an open question. However, for those patients, donors and research subjects who consent to be contacted with future results, it is reasonable to suggest that biobanks accept this responsibility in whole or in part.

Another unresolved dilemma for stakeholders of biobanking initiatives is the degree to which research participants retain a legal claim on the tissue and information provided to a biobank. Like the practice of informed

consent, the issue of donor rights is both contested and unresolved despite being tackled in a number of American court decisions. To date, all legal verdicts have been hesitant to grant research participants a clear property claim on tissue donated for the purpose of research. For example, in the case of *Washington University v. Catalona*, it was concluded that individual tissue donors do not retain an ownership interest in their provided tissues and, as a result, cannot request that the specimens be sent to a particular research facility[14]. Though jurisprudence makes the idea of a property right doubtful, these decisions are context specific and far from definitive. Other legal principles governing research practice—such as those relating to human subjects' autonomy, the right to withdraw from research or unjust enrichment—may afford research participants a degree of ongoing interest in their donated samples and information. And research on public perceptions tells us that, in fact, most want this ongoing control[15].

Conclusions

Biobankers face an environment of uncertainty. Although common practices are starting to emerge within the biobanking community, disputes will inevitably be complicated by lack of consensus in the broader sociopolitical realm. Absence of clear oversight—both nationally and internationally—exacerbates existing practical and social issues and leaves biobanks with little standardized guidance on how to handle these formidable challenges.

Although each biobank has its own criteria for quality control and data protection, standardization across biobanks will optimize potential collaboration and bridge biobanking to commercial and clinical applications. Clear regulations will provide biobanks and the researchers who use them with standards for addressing practical, ethical and legal challenges by ensuring quality control of samples and ultimately will improve the protection of donor rights and their personal information.

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COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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Erratum: Personal medicine—the new banking crisis

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In the version of the article originally published, the citation in Figure 1 was given as ref. 14; it should be ref. 2. In Table 1, CARTaGENE was misspelled, and the descriptions in column 3 of this repository, BioVu's and the International HapMap were incorrect: CARTaGENE should be described as "a repository of socio-demographic, health data and biological samples from 20,000 citizens of the province of Quebec in Canada"; BioVu's description should read "Repository of DNA samples and de-identified health information from the Vanderbilt University Medical Center's electronic system"; and the International HapMap description should read "International collaboration with the ultimate goal of developing a haplotype map of the human genome." In addition, the amount of the Havasupai settlement was incorrectly stated to be $700 million. It should read $700,000. Finally, the work of Simon *et al.* (ref. 8) on biobank consent models was incorrectly described. The text should read, " For example, a recent US focus group and survey study found a public that preferred a broad approach to consent over ones involving additional choices. But the preference was marginal, thus noting the lack of consensus on these issues. Indeed, as noted by the authors of the study: '54% of our survey and 42% of our focus group participants could be seen as preferring a control/choice-promoting model (e.g., categorical or study-specific consent) over a control/choice demoting model (e.g., broad consent)[8]'." The errors have been corrected in the HTML and pdf versions of the article.