Past, present, future: the ethics and governance of big biobanks conference

UK Biobank Ethics and Governance Council

3-5 November 2014
Wellcome Trust, 215 Euston Road, London NW1 2BE

Contents

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Design: Jag Matharu, Thin Air Productions Ltd

Photography: Wellcome Images

Printed on Revive 50:50 Silk, a recycled paper containing 50% recovered waste and 50% virgin fibre.

TAP2655/19-03-15/V6B

Executive Summary

Introduction

UK Biobank contains a wealth of biosamples and information provided by more than 500,000 participants. Having opened for access in 2012, the resource is supporting a diverse range of health-related research intended to improve the prevention, diagnosis and treatment of illness and the promotion of health throughout society. Already a valuable resource for the international research community, UK Biobank continues its work and its ambition to enhance the data in order to make the resource all the more valuable, for example through major new initiatives to analyse biochemical and genetic markers in all participants and through an imaging sub-study.

While UK Biobank is not unique in terms of its scientific design, it is unusual in terms of its scale, detail and long-term nature. For this reason, and in parallel with the development of the scientific plans, full consideration was given to the ethical standards and the model of governance under which the project should operate. This work resulted in the publication of an Ethics and Governance Framework (EGF) for UK Biobank which lays out explicitly the organisation's commitments to participants, the public and other stakeholders[1]. In adopting this approach the project aimed to create trust, recognising this as a key element to the success of UK Biobank in terms of giving people the confidence to agree to participate and in maintaining their confidence and participation in the long term.

The Ethics and Governance Council (EGC) was set up in 2004 by the principal funders of UK Biobank (the Medical Research Council and the Wellcome Trust) to advise on revisions to the EGF and, more generally, to advise on the interests of research participants and the general public in relation to UK Biobank. It is the job of the EGC to see that the guidelines in the EGF are followed to safeguard participants and researchers and to monitor and report publicly on the project's conformity with the EGF commitments. The EGC's work is to a large degree, and necessarily, influenced by the developments of UK Biobank. Further, its role is performed against a changing communication, technology and social background for all the stakeholders and one which cannot be predicted. Indeed, it is precisely for these reasons that the EGC was established by its funders as a necessary part of such a long-term and ambitious project as UK Biobank.

1 The UK Biobank Ethics and Governance Framework (Version 3.0, October 2007) is available at www.ukbiobank.ac.uk/resources

Purpose of the conference

The idea that the EGC should hold a major international conference sprang from the sense that, after ten years of working alongside UK Biobank, the Council was in a position to share its experience of biobank governance as well as to elaborate its thinking in relation to the substantive issues faced by the project.

A successful evening public lecture (given by Professor Alastair Campbell on the topic 'Biobanks – can ethics keep pace with the science?') served as a curtain-raiser for the two-day international conference on 'Past, present, future: the ethics and governance of big biobanks'.

The conference served more than one purpose. It facilitated an exchange of views about the way to govern biobanks and, in particular, about the articulation of the EGC's role as a 'critical friend' of UK Biobank. It prompted discussion about a number of difficult ethical issues already encountered by the project as well as identifying some upcoming challenges in the ethics and governance of big biobanks. And, last but not least, the conference represented the EGC's first step towards more active engagement with a wider stakeholder community (reflecting the interests of a broad cross-section of people responsible for the management of biobanks and big population studies, and people and organisations concerned with the ethics and governance of such studies).

Session topics

The conference sessions included: an overview of the governance of UK Biobank; governing access; engaging participants; feedback of results; genomic data and governance; follow-up through health and related records and data sharing. There were also sessions dedicated to hearing about the experience of other cohort studies and to discussing how experiences can be shared in the future, drawing on established and emerging international initiatives.

Reflecting the experience of a range of relevant studies, speakers were drawn from the Taiwan Biobank Ethics and Governance Council, the Estonian Genome Center, the ALSPAC Ethics and Law Committee, UK10K, the 1958 Birth Cohort, the Framingham Heart Study and the Deciphering Developmental Disorders project. In addition, we were joined by speakers representing the Public Population Project in Genomics and Society, the Global Alliance for Genomics and Health, the International Society for Biological and Environmental Repositories,

the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI)-ERIC, ELSI 2.0, the Expert Advisory Group on Data Access and the Nuffield Council on Bioethics. With additional and vital input from UK Biobank colleagues, this created a rich mix of experience; sessions raised not only broad questions relating to governance but also gave a practical insight on how issues are being addressed 'on the ground'.

During the registration process, delegates were invited to put forward what they considered to be the main current and upcoming challenges in biobank ethics and governance. Not only did this provide a list of comments to draw on during the discussion but it also gave the EGC an opportunity to see whether its own current agenda reflects the range of issues raised by a broad community of colleagues. The issues fell into the following themes:

- The need for responsive and enduring governance and consent frameworks.
- Participant and public trust, engagement and perceptions.
- Privacy, data protection and confidentiality.
- Feedback polices.
- Access policies.
- Governance of genomic data.
- Re-consent.
- Funding, management and impact.

Delegates

The conference registration was open to any interested parties and was advertised widely in the biobanking community. In total the event attracted 110 delegates from a broad range of countries and biobanks, including delegates from Iceland, Taiwan, the UK, Sweden, the United States of America, the Netherlands, Norway, Germany, Italy, Singapore, the Czech Republic, Japan, Canada, Austria, France, Estonia, Finland and Denmark.

Outcomes

The conference was valuable in several respects.

First, not only was the EGC able to share its experience but it was able to do so alongside inputs from UK Biobank (speaking directly to the project's progress and approach) and from the funders (speaking to the issue of feedback to participants). This served to crystallize the various ways in which the EGC functions as a 'critical friend' to UK Biobank.

Secondly, it was extremely valuable to learn about the experience of other cohort studies and to see what issues were raised by delegates. Several themes re-occurred throughout the discussion, including:

- Policies and procedures for feedback of health information to participants ('return of results').
- Participant and public engagement.
- Practical challenges in terms of linkage to health and health-related records.
- Access procedures and criteria for judging applications (including public interest considerations).
- Governance structures to support, and frameworks for, data sharing.
- Implications of the (draft) Data Protection Regulation.

Thirdly, it was an opportunity to bring together a wide range of people who have a real interest in big biobanks. The conference programme was designed for interactive discussion during the panel discussions as well as for informal networking during the breaks. Following the conference, colleagues have indicated that they had many interesting discussions during the breaks, and we have received comments from delegates who were comforted to know that their project is not the only cohort that is working through some difficult issues.

Next steps

We hope that this report will serve as a useful reminder for the conference attendees and an interesting account for colleagues who were unable to attend the event. While we have necessarily given only a brief summary of each session, videos of the full presentations are available on the EGC's website, www.egcukbiobank.org.uk, and via the links in this report.

Where do we go from here? The EGC is always open to contact from colleagues from the biobanking community and it will continue to publish Annual Reviews and its meeting Minutes. As part of an upcoming quinquennial funding review, the EGC has raised the question of whether it should, in future, take on a more outward-facing role and more systematically present itself as a lead node in a network of biobankers. This might involve an enhanced publishing programme or hosting subject specific workshops to promote collaboration. Without doubt, the conference was the EGC's first major exercise to engage with the broader biobanking community and, subject to the outcomes of the review, perhaps this can be seen as a stepping stone to a future more outward-facing role.

Public lecture 'Biobanks – can ethics keep pace with the science?'

Professor Alastair Campbell

Summary

The title of this lecture uses the metaphor of a race, suggesting that poor, unfit and ill-equipped ethics has little hope of keeping up with the dazzling pace of scientific advance, with its vast resources of talent and funding. Yet is this really an accurate picture? Three ethical challenges, provoked by the increasing success worldwide of biobanking, are considered: the nature of consent to participate in biobanking; the need to use the resource in ways that serve public interests rather than private profit; and the moral complexities of international data sharing. In each case major worries have been expressed that ethical values are being compromised in the name of scientific progress.

However, if we look at the vast literature on the ethics of biobanking we can see that such worries are not really justified. Not only has ethics kept pace with the science, it has in many ways foreseen the problems and offered creative solutions to them. Many scholars have forged new ways of discerning the ethical dimensions of the dramatic increase in data with potential research uses, provided by biobanks. These take us beyond narrow concepts of individual autonomy or of maximised social benefit, to richer accounts involving trust, generosity, social solidarity and world citizenry.

So, in fact, ethics is outpacing the science! Ethics is blazing a trail which science must follow, if it is genuinely to serve human ends.

View this presentation online:
https://youtu.be/WTR3qjrQU64

UK Biobank in 2014 and beyond

Professor Sir Michael Rawlins

UK Biobank was established in 2003 with recruitment taking place between 2006–2011 at 22 assessment centres. Over half a million participants were recruited.

The initial assessment involved baseline measurements (e.g. height, weight, blood pressure, lung function), the collection of blood, urine and saliva and an online questionnaire.

All participants are being followed-up through their health and related records; linkage has been made to death and cancer registries and inpatient and outpatient hospital episodes. Linkage to primary care records (including prescription data) is in progress.

A number of enhancements have and will be made.

- Complete: web-based assessment of diet (2014).
- In progress: a wrist-worn accelerometer mailed to all participants who agree to wear one (2013–2015); a standard panel of assays on samples from all participants (2014–2015); genotyping of all participants (2013–2015) and multiple imaging modalities (MRI, DEX scan) of 100,000 participants (2014–2016).
- Planned: cognitive function (repeat assessment of baseline measures and a broadening of cognitive phenotyping with new measures); occupational history and physical activity questionnaire.
- Under discussion: assaying a panel of infectious agents in the baseline sample and screening for cardiac arrhythmias.

What makes UK Biobank special?

- Prospective: it can assess the full effects of a particular exposure (such as smoking) on all types of health outcome.
- Detailed: the wide range of questions, measures and samples at baseline allows good assessment of exposures.
- Big: inclusion of a large number of participants allows reliable assessment of the causes of a wide range of diseases.

Discussion

Amongst the points raised in discussion were:

- UK Biobank's 'no feedback' policy[2], the consents given by participants, and where participants claim to have a right to know.
- Where the lines between clinical and research relationships can become blurred.
- UK Biobank's enhancement work.
- Communications with participants and re-contact.

2 UK Biobank's policy is essentially 'no feedback' with the exception of (i) routine feedback of some standard measures taken at the assessment centre and (ii) feedback in the event that an incidental finding is made during the assessment centre visit (such as a possible melanoma).

View this presentation online:
https://youtu.be/wOqQHRnBJfo

Governance of UK Biobank: the EGF and the EGC

Chair and respondent: Professor Bartha Maria Knoppers

Drafting the Ethics and Governance Framework

Professor Alastair Campbell

An Interim Advisory Group was established in 2003 by UK Biobank's principal funders, the Wellcome Trust and the Medical Research Council (MRC). The Group met on four occasions; it debated the key ethics and governance issues relating to UK Biobank, decided on the structure of the Ethics and Governance Framework (EGF) and discussed iterative drafts. The Group's work was informed by a number of public consultation exercises.

Structure of the EGF:

- Relationship with participants: recruitment, consent and confidentiality.
- Relationship with research users: stewardship and access.
- Relationship with society: management and accountability (EGF), external governance, benefit sharing and closure.
- Implementation and revision.

Key features of the EGF:

- To be adopted by UK Biobank and then abided by.
- Open to subsequent revision.
- Publicly available.

Key issues discussed: the model of broad consent, commercial use of the resource, feedback to participants, withdrawal and the independence of the Ethics and Governance Council.

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https://youtu.be/leVZ5XbaaG8

The Ethics and Governance Council (EGC) as a 'critical friend'

Professor Graeme Laurie

The EGC was considered necessary because of the breadth of UK Biobank's purpose (broad consent), the long-term nature of the endeavour and given the limitations in existing mechanisms, e.g. monitoring research was not in a Research Ethics Committee's (REC) remit. The EGC is an additional safeguard and a foundation of trust, the trusted third party or 'critical friend'.

During UK Biobank's development its funders commissioned a number of consultations on trust and governance. Participants generally recommended that some form of oversight body should be established and in such a way that it can act independently of UK Biobank and the funders. In advising, reviewing and reporting on UK Biobank's activities, the EGC serves as a 'mirror' for UK Biobank, providing critical and constructive advice.

The EGC is an example of reflexive governance and accordingly has a responsive role and has acted in relation to unforeseen challenges, for example, (1) when it became apparent that UK Biobank was unable to uphold its commitment to destroy a participant's data under the 'no further use' withdrawal option, due to technical issues and (2) when the EGC received a letter asking whether UK Biobank could be a resource for cloning, which led to an opinion in *The Lancet* and an EGC letter in response.

Reflexivity can be described as 'a system of in-parallel development and partnership in governance typified by arrangements which facilitate mutual learning over time'. In relation to UK Biobank there is:

- An Ethics and Governance Framework (*integrity of purpose*).
- An Ethics and Governance Council (*independent critical friend*).
- In-parallel development of protocol and governance (*adaptive*).
- In-parallel engagement with the shifting landscape (*reflexive*).
- Engagement with participants and publics (*mutuality*).

View this presentation online:
https://youtu.be/guiU-Bj0vZY

Chair and respondent: Professor Bartha Maria Knoppers

Today's governance challenges for the EGC

Professor Roger Brownsword

The headline issues for 2011–2014 have been:

- Finalising the access process and developing the EGC's 'oversight' role and responsibilities.
- Responding to enhancements of the resource (e.g. the imaging pilot) and, in particular, engaging with issues of 'feedback' and 'incidental findings (IF)'.

How should the EGC relate to UK Biobank as a 'critical friend'?

- In the final analysis, it is for UK Biobank to adopt principles and practices that it is prepared to defend as ethically sound; the role of the EGC is to help UK Biobank to understand the issues, not to impose an EGC view (if it has one).
- The EGC should encourage UK Biobank to 'internalise' its ethical responsibilities.
- Flexibility is needed in finding the most effective ways of engaging in dialogue with UK Biobank – whether at Council, or in subgroups, or in *ad hoc* meetings, and so on.
- The EGC and UK Biobank share a common aspiration but the EGC has its own priorities (especially to protect participants) within the governance network.

What to focus on:

- The EGC has limited resources. It needs to focus on issues that are novel, significant, strategically important, and the like.
- Reactive: developing the IF protocol for the imaging pilot; responding to re-contact issues.
- Proactive: clarifying the issues involved in taking a position on feedback to participants.

What next for the EGC?

- Funders' quinquennial review in Spring 2015.
- Continuing responsibility to hold UK Biobank to account relative to the EGF and to safeguard the interests of participants and the public.
- Work with UK Biobank on major new questions of ethics and governance.
- Possibly adopt an enhanced outward-facing role sharing the experience of 'big biobanking'.

Discussion

The following key points were raised during the discussion:

- The generalizability of UK Biobank's governance model.
- The era of big data and biobank collaborations and what this means for governance.
- The potential impact of the (draft) Data Protection Regulation on biobanks.
- The opportunity for the EGC to take a more outward-facing role in future.
- The EGC's role as independent guardian of the EGF and the lines for reporting a concern.

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https://youtu.be/ix_AdTUsz9Y

View the discussion online:
https://youtu.be/-aJGYi9FZRk

Learning from the governance experience of others: case studies

Chair and respondent: Dr Jonathan Hewitt

Estonian Genome Center of Tartu University

Professor Andres Metspalu

The Estonian Genome Center (EstGC) is based at Tartu University. To date 52,000 participants (5% of the adult population of Estonia) have agreed to take part in the Estonian Genome Project, a prospective, longitudinal, population-based database which also contains health records and biological materials. The EstGC falls under Tartu University's Ethics Committee and has scientific collaboration e.g. FP7 project 'OPENGENE' with the University's Centre for Ethics.

The Estonian Human Genes Research Act (HGRA) came into force in January 2001 and, amongst other things, provides that:

- Gene donors have the right not to know their genetic data.
- Gene donors have the right to access personally their data stored in the Gene Bank.
- Gene donors do not have the right to access their genealogies.
- Gene donors shall not be charged for accessing their data stored in the Gene Bank.
- Gene donors have the right to genetic counselling upon accessing their data stored in the Gene Bank.

Public opinion and awareness of the Estonian Genome Project has been evaluated over the period 2001–2014; there has been an increase in awareness and in the percentage (close to 70%) of people in favour of the idea, although a recent survey found that around 30% of people were not aware of the initiative.

The Estonian Programme for Personal Medicine was approved for 2015–2018 involving strands on healthcare, research and development and commercialization. A pilot project for the R&D strand will involve sequencing of 5,000 individuals, use of the array-based genotyping on all participants of the Estonian Biobank and the development of analysis and decision support software. In time, and if the results of the Pilot Project are supporting it, a main project will offer these to everyone aged from 35–65 years old as a disease risk and drug response prediction test and in so doing create by 2022 an e-health database of circa 500,000 people with genotypes, electronic medical records, prescription data for use in research, medical practice and development.

Challenges and issues include:

- Awareness of health care managers, doctors and patients.
- New technologies and data empower patients to manage their own health.
- Ethical issues: the right to know and the right not to know; treatable and non-treatable conditions.
- Knowledge about associations between DNA variants and diseases is already useful in several cases, but is improving rapidly.
- Large workload to keep database of known risk markers updated.

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https://youtu.be/N2aa3N5LM-k

Taiwan Biobank Ethics and Governance Council

Professor Michael Tai

Taiwan Biobank aims to collect tissue and data from 300,000 persons in Taiwan aged 30–70 years old, including 100,000 patients diagnosed with various cancers. First announced in 2005, the biobank has been officially in operation since 2012 and to date has recruited more than 30,000 participants. The biobank is funded by the state through Academia Sinica.

The establishment and operations of Taiwan Biobank are regulated by legislation. It is a repository of tissues and information, but it is not allowed to directly carry out research unless approved by its Institutional Review Board (IRB) and the TBEGC (see below). Four subdivisions have been set up within the biobank: the medical genetic group, the ethical, legal and social implications (ELSI) group, the information technology group and the industrial application group.

The Taiwan Biobank Ethics and Governance Council (TBEGC) was established in 2006. It meets four times a year and has the following duties:

- To review the research protocols, and determine whether or not to release the tissue.
- To manage the data and information of the biobank and their utilities.
- To ensure the safety of collected information.
- To regulate/control the tissue usage and any cooperation with other tissue banks.
- To check the documents whenever any withdrawal takes place.
- To review any other issues TBEGC is given to govern.

The TBEGC established four subcommittees in 2014 to enhance its function: 1) information technology and management; 2) indigenous people and social legitimacy; 3) education and international relation and 4) ELSI.

Future challenges include:

- Planning of continuing education events for employees of recruitment stations and participating hospitals.
- Funding of the TBEGC: the TBEGC has no budget from the state and has to request special funding for any project, e.g. an international conference on biobanking has been proposed and approved by the TBEGC.
- The remit of the TBEGC – how much and how broadly can the TBEGC govern? Should the TBEGC ask questions regarding the general operation of the biobank, including finances, appointments etc.?
- Whether the TBEGC should review the research protocol of the biobank team (something that has been proposed by the ELSI group of the biobank team but was rejected by the IRB).

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https://youtu.be/w42I386lsOQ

ALSPAC Ethics and Law Committee

Professor Madeleine Murtagh

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a population-based birth cohort that initially recruited 14,000 pregnant women who had an expected date of delivery between April 1st 1991 – December 31st 1992. The Study has since expanded to involve four generations including the study mother and father/partner, grandparent, study 'children' and their partners and siblings and the study 'child's' offspring.

There are ongoing data collections and sub-studies:

- Annual questionnaire (including demographic and health information).
- Clinics – biosamples and imaging.
- Substudies including recall by genotype, qualitative studies and detailed phenotyping/exposure assessment.

The ALSPAC Ethics and Law Committee (ALEC) involves professionals and participants. It meets bi-monthly and receives input from the Original Cohort Advisory Panel. Established as an independent ethics committee from the outset, ALEC's remit is to:

- Offer ethical opinions – requests involving human tissue, imaging, patients of the NHS or prisoners go through the normal Research Ethics Committee (REC) process, although they go to an ALEC subcommittee first for input. ALEC is responsible for giving ethics approvals to any other research (e.g. questionnaires).
- Ensure sound ethical review of ALSPAC, in keeping with national and international law and policy.
- Oversee research ethics and integrity: principles and practices governing the conduct of ALSPAC.

Reflecting the changing relationship of science and society, ALEC is changing too:

- A considerable increase in the involvement of original cohort participants in the ALEC was established a year ago. In addition to attendance at the ALEC meeting, this group meets a week before the ALEC to consider documentation and other ethics issues to be considered at the ALEC meeting. Members of the group plan to write a paper about their experience of being part of the ALSPAC governance model.
- Involvement of participants in the governance of ALSPAC has a long history. Changes to the ALEC are an extension of this commitment to participant involvement.
- Involvement of participants from all ALSPAC generations has an invigorating positive effect on the work of the committee. Importantly, it ensures the alignment of science with participant and social values.
- ALEC's new terms of reference were recently finalised and require that in future half the committee will comprise professional members and half participant members.
- Co-governance – joint decision-making about ethics is being extended to the cohort as a whole: ÉCOUTER is a virtual engagement project using mind mapping to allow stakeholders to interact with the existing evidence (where this exists) on a topic of shared concern. There are plans to use ÉCOUTER and qualitative research to examine cohort participants' views. Planned topics include: commercialisation; return of results; recall by genotype and data sharing.

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Chair and respondent: Dr Jonathan Hewitt

Framingham Heart Study

Dr Daniel Levy

The Framingham Heart Study was initiated in the 1940s to address the emerging epidemic of, and limited epidemiological knowledge about, cardiovascular disease. The Study now involves three generations:

- The Original Cohort recruited in 1948 = 5209 participants.
- The Offspring Study recruited in 1972 = 5124 participants.
- The Third Generation Study recruited in 2002 = 4095 participants.

The Study's governance structure includes an Ethics Advisory Board. Summaries of the Board's opinions are communicated to participants through the Study's newsletters and participants are encouraged to address questions to the Board. The Board's remit is to:

- Consider complex questions posed by Study participants and investigators.
- Provide viewpoint of Study participants and the community.
- Advise the Executive Committee of the Framingham Heart Study.

Data and DNA (without any potentially identifying information) are available for access by Framingham researchers and other qualified researchers interested in the genetics of various diseases and health conditions. Participants were asked for their informed consent for genetic research, including the creation of cell lines; the vast majority of those asked gave consent.

The greatest challenge faced by the Study was in 2000 when the university affiliated with the Study decided to set up a for-profit company called Framingham Genomic Medicine to distribute the data and genetic information from Framingham Heart Study participants. The Study participants revolted when this was announced in the local newspaper. While these plans were abandoned, the Study subsequently sought consent to for-profit access resulting in 92% of the offspring cohort and 98% of the third generation cohort saying yes.

Discussion

Amongst the points raised in discussion were:

- Recruitment of ethnic groups.
- Study loyalty in generational cohorts resulting in high rates of consent.
- The benefits and challenges of participant engagement.

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https://youtu.be/_kSJ79w9N1Y

View the discussion online:
https://youtu.be/cd3lQA3NYUw

Feedback

Chair and respondent: Dr Jasper Bovenberg

Wellcome Trust and Medical Research Council Framework on feedback

Ms Katherine Littler

The mandate to create a Framework on feedback came from the research community; the following work informed its development:

- Literature review of the legal and ethical implications of incidental findings.
- Policy analysis.
- Assessment of the time and cost implications of feedback.
- Stakeholder workshops.
- Quantitative and qualitative research on public attitudes to health-related findings.

The Framework was launched in March 2014. Its scope is:

- Incidental findings: 'a finding that has potential health or reproductive importance, which is discovered in the course of conducting research, but is beyond the aims of the study'.[3]
- Pertinent findings that relate to the aims of the study.
- All types of studies: imaging, genetics, physiological measurements.
- Findings with known clinical significance or relevance, not new research observations.
- Individual not aggregated findings.

The Framework applies to all human subject research that is funded by either the Wellcome Trust and/or the MRC and places the following expectations on researchers:

- Have a policy on whether or not health-related findings (HRFs) will be fed back to individuals that can be clearly articulated, and be able to demonstrate the reasoning behind their policy to research participants, funders and RECs.
- Include clear information on the study policy on the feedback of HRFs in the consent process.
- In cases where the policy is to provide individual feedback on HRFs, develop a robust, practical feedback pathway that is adequately resourced.

Re-consenting participants for follow-on research to an existing study are captured by the Framework. In such cases, the nature of the existing consent should be considered and the feasibility and costs of feedback are legitimate considerations. An example here is UK Biobank's imaging pilot, which provides an opportunity to build the evidence base on the implications of feedback.

3 Wolf *et al J Law Med Ethics* 2008; 36: 219

View the introduction online:
https://youtu.be/SbXutucXZ1g

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https://youtu.be/h3PB6ZV8NgI

Framingham Heart Study

Dr Daniel Levy

It has been the practice of the Framingham Heart Study (FHS) to report to participants potentially clinically actionable abnormal results from routine tests (e.g. blood pressure, blood glucose level). When recruitment of the Third Generation Cohort began in 2002, it was FHS policy that individual results of genetic analyses would not be returned to Study participants and this was made explicit in the consent form.

In 2006 a National Heart Lung and Blood Institute Working Group on 'Reporting Genetic Results in Research Studies' published[4] its findings that:

- There are conditions in which genetic results should be offered to research participants.
- The decision to report genetic results should not depend solely upon the discretion of the investigator, but should include a broader range of perspectives.
- Standard criteria/guidelines should be developed that include careful consideration of the risks and benefits to participants.
- Genetic results should be reported when the validity of the test is established; the associated risk for the disease is significant; the disease has important health implications and proven therapeutic or preventive interventions are available.

Participants were notified that FHS was considering notification mechanisms and recently, in anticipation of genome-wide genotyping, a genetic results consent clause was introduced into the Offspring and Third Generation exams. In response to the high rate of consent to notify (99.5%), the Executive Committee empanelled an expert committee to advise on a notification plan. After review of multiple genetic conditions potentially detectable from the Affymetrix 550K array data, 2 SNPs were deemed notifiable: HFE C282Y (hemochromatosis) and MEFV M694V (familial Mediterranean fever).

In preparation for notification, FHS prepared several documents for consideration by the Boston University Medical Campus IRB, including the draft participant notification letter, draft consent to notify personal physician, draft physician notification letter, draft newsletter article on plans to notify and information sheets relating to the two conditions. While the initial application to notify was rejected by the IRB, over time other initiatives and studies provided evidence that supported FHS's plan and notification is now given for these two conditions.

4 Bookman *et al Am J Med Genet* 2006; 140A:1033–1040

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https://youtu.be/W4yxZi19FxQ

Deciphering Developmental Disorders project

Dr Anna Middleton

The Deciphering Developmental Disorders (DDD) project aims to advance clinical genetic practice for children with developmental disorders by the systematic application of the latest microarray and sequencing methods. From the offset the project planned to look at pertinent findings only (i.e. those relating to developmental disorder) and not to opportunistically screen for, or report, incidental findings (IF). In order to explore this position, and to address the ethical challenges raised by these methods, the project conducted an online survey to assess:

- Attitudes towards searching for IFs.
- What factors influence attitudes?
- What processes do people want?

The survey has resulted in the largest empirical dataset of attitudes to feedback in the world. Seventy five countries are represented and 6944 people took part (4961 members of the public (of which 276 are UK Biobank participants), 607 genomic researchers, 533 genetic health professionals and 843 other health professionals).

Key messages from the survey are:

- People want data – when asked if IFs from genome studies should be made available the responses ranged from 72% yes from the genetic health professionals up to 91% yes from the public.
- Treatability is important – interest in feedback reduces as the data become less usable e.g. if a condition cannot be prevented.
- Attitudes are affected by professional background and genetic health professionals are the most conservative.
- Most people said researchers should not have to actively search for IFs – there is no expectation of information delivery at all costs.
- Policy in research does not need to obligate researchers to share incidental findings.

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https://youtu.be/jGz02hCrrPo

Chair and respondent: Dr Jasper Bovenberg

UK Biobank's policy and the role of the EGC

Dr Sheelagh McGuinness

UK Biobank has a general policy of 'no feedback' with exceptions:

- Some measures taken at the initial assessment visit were routinely fed back (the EGF explains that it would be 'impractical to hide results of some measures').
- The EGF also explains that 'even in this research context, there may be occasions when staff consider there to be a professional or ethical obligation to draw attention to abnormal measurements'. An example here might be a suspicious mole that is noticed by assessment centre staff or an abnormally high blood pressure reading. In such cases, participants were advised to see a clinician.

Justifications for this policy are that:

- It is a research rather than clinical setting (the assessment is not a 'health check').
- Time lapse/opportunity for appropriate counselling when it is not known what tests will be performed in the future.
- The value of feedback is uncertain and could cause harm (e.g. over treatment, insurance etc.).
- Anonymity (research will be conducted on coded data).

A subgroup of the EGC has undertaken a programme of work looking at whether UK Biobank's policy is still appropriate, with consideration being given to the policies of other biobanks and how the debate has evolved. While the literature contains a positive tone about feedback, the subgroup found that this relates to the need for researchers to consider, develop and make clear their policy on feedback; there was no sense that there was a gold standard that everyone should adhere to and no international consensus on what should and should not be fed back.

UK Biobank's imaging study will involve magnetic resonance imaging of the brain, heart and abdomen, low power X-ray imaging of bones and joints and ultrasound of neck arteries. The EGC and UK Biobank have worked together to discuss a range of issues associated with the pilot. Specifically, a small working group met regularly and discussed development of the feedback protocol, including the following themes:

- Existing approach to feedback in the EGF.
- Specific issues raised by imaging.
- Benefits to participants and the importance of engagement with participants; in particular attitudes and impact of feedback.
- Public good (particularly in facilitating research).

The imaging pilot will assess the feasibility and acceptability of the feedback protocol, with a view to informing the main phase protocol. The following will be evaluated:

- The proposed protocol for feedback of potentially serious findings that are identified by a radiographer and verified by a radiologist.
- The systematic review by radiologist of images from first 1,000 participants, as a means of assessing the proposed protocol.
- Attitudes and impact of feedback including an assessment of participants' attitudes to receiving feedback, assessment of the impact of receiving feedback on participants, their families and friends and assessment of the attitudes of radiographers, radiologists and general practitioners involved in the feedback process.

Discussion

The following points were raised during the discussion:

- Implications of the quality of a finding on a study's feedback policy (e.g. whether research or clinical grade).
- How attitudes to feedback change as more detailed explanations are provided. Both the DDD and Wellcome Trust/MRC surveys found that, as the nuances of the feedback debate were drawn out, initial support for broad feedback moved towards an emphasis on feedback of treatable findings.
- The transparency and communication of feedback and other policies to participants; including the need for clear information and the benefit of having different levels of information available for participants to choose between.
- Implications of feedback on insurance and the situation in the USA and UK with respect to insurance and genetic tests.
- The need for more evidence regarding the cost of feedback mechanisms.

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https://youtu.be/4rNxynPAM4E

View the discussion online:
https://youtu.be/Co6qLt-91xg

Genomic data and governance: case studies

Chair and respondent: Professor Mike Parker

UK10K

Dr Lucy Raymond

UK10K involves a UK-based population and aims to:

- Increase the depth of coverage of sequence at the genome level to identify intermediate frequency alleles between common and rare variants beyond that previously achieved for the 1,000 Genome Project.
- Better understand low frequency variants and rare disease.
- Identify high penetrant rare alleles that cause rare diseases.
- Make the data available to the research community.

There is a tension between the desire to make research data available to as wide a research community as possible and the fact that rare variants that cause rare disease are unique to an individual and thus make the individual readily identifiable. Also, there is a need to protect patient confidentiality within the clinical research setting where individuals have a specific disease and are being recruited once NHS provision is exhausted. UK10K's solution to this tension is a managed access system where data are made available to *bona fide* researchers. Minimum criteria for data access are that the researcher agrees not to try to identify the individual, they need to be generating peer review journal data and the principal investigator takes responsibility for data access and the management of the data on behalf of all staff. While the project cannot guarantee privacy, this mechanism can protect participants from exploitation.

The UK10K Ethical Governance Framework recognises two types of finding, those pertinent to the disease being studied (where there are often well-established management pathways for validation and communication to the patient and REC support for feedback) and those incidental to the study. While there was initial enthusiasm for reporting incidental findings (in addition to pertinent findings), in-depth discussion gave rise to less enthusiasm due to questions regarding:

- Competence to interpret the data.
- Which genes and more particularly which variants to report.
- What degree of validation was required.
- Evidence of penetrance of variance in an unaffected population.
- Duty to search out potentially hazardous variants.
- Resources to do this (e.g. financially), but mainly medical ignorance was the primary concern.

UK10K has a mechanism for feedback of clinically significant findings, i.e. those variants that contribute to the current disease state or alter the assessment of the future disease risk of the participant. The clinical validity of the research finding must be of equivalent robustness to information fed back from a clinical diagnostic test and the analytical validity of the research finding is established in an independent sample from the patient by a Clinical Pathology Accreditation (CPA)-accredited laboratory.

To date:

- >35 papers published by UK10K.
- Main area has been gene identification of new rare diseases.
- Many rare variants have been validated and reported back to participants.
- No IFs were fed back and participants did not ask for this information.
- There have been no requests by participants to access the data (e.g. no requests for their whole exome data).
- Data access requests have been modest although only recently become available.

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https://youtu.be/sjtDGaflKVA

1958 Birth Cohort

Professor Paul Burton

The 1958 Birth Cohort (BC) follows the lives of around 17,500 people born in England, Scotland and Wales in a single week in 1958. There have been a number of data collections over time and a biomedical survey was undertaken in 2002–2003 involving 9,377 participants, funded by the MRC. The primary objective of the survey was to obtain critical biomedical information via questionnaires, physical measures and biospecimen collection (blood, urine and saliva). Additional funding came from the Wellcome Trust to create a major DNA repository including transformed lymphocyte lines on a total of 7,526 subjects. This created the need for a data and biosample access mechanism.

In 2008–2009 direct funding was received from the MRC and Wellcome Trust to set up the infrastructure to provide streamlined access to data and biosamples. In the first instance this was through a one-off small grant, but in 2011 the data access infrastructure was fused with the bioresource infrastructure for a joint 42-month grant shared by Leicester University and Bristol University (in 2013 the full grant moved to Bristol). The ESRC, MRC and Wellcome Trust decided that it would be strategically efficient to use the resultant access committee to oversee access to the biomedical components of a series of national cohorts (including 1958, 1970, Millennium, Next Steps and UK Twins).

The Access Committee for the Centre for Longitudinal Studies Cohorts (ACCC) oversees access to: any applications involving biosamples; any requiring linkage of genotype and phenotype and challenging applications for phenotype or genotype alone. The following evaluation criteria are used to judge an application:

- Has the application been submitted by *bona fide* researchers?
- Does the application violate (or potentially violate) any of the ethical permissions granted to the study or any of the consent forms signed by the participants or their guardians? (Includes potential feedback of clinically relevant genomic findings?)
- Does the application run the risk of producing information that may allow individual cohort members to be identified?
- Does the application run a significant risk of upsetting or alienating cohort members or of reducing their willingness to remain as active participants in 1958BC-based research?
- Does the application address topics that fall within the acknowledged remit of the 1958BC project, as understood by participants?
- Does the application request access to an infinite resource (data or cell line DNA) or a finite resource (whole blood extracted DNA, blood, saliva and urine)?
- Assessment of science only for: finite resource; scientific issue impinging on another criterion; request for very large range of data and biosamples; application in practice impossible (technical review team).

The 1958BC has a number of strategic interactions, including with other data access committees. It has provided data and samples to a number of 'big biobanking' consortia and shares its experience with other major studies. In total 632 peer reviewed papers were generated from use of the resource between 2004–2013.

The major challenges in data access are:

- The multiple funders, studies and stakeholders.
- Resource demanding – the need for a streamlined process, robust security and ongoing horizon scanning and strategic discussion and planning to identify, predict and manage challenges.

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https://youtu.be/QiC22NEVv58

UK Biobank

Professor Sir Rory Collins

UK Biobank is centrally co-ordinating the assaying of many standard markers in the baseline samples from all 500,000 participants. The rationale for this approach is:

- Cost-effective way of increasing the usability of the resource for researchers, by providing data for (i) analyses related to many different disease outcomes and (ii) identification of subsets based on assay values.
- Conducting these assays in all of the participants at the same time should facilitate good quality control.
- Lower cost for conducting all of these assays at one time rather than in multiple retrievals and assays.
- Facilitates management of depletable samples.

Participants gave consent to 'Give blood, saliva and urine for long-term storage *and any testing (including obtaining genetic information and storing white blood cells so more DNA can be made)*'. This was on the understanding that 'none of my results will be given to me (except for some measurements during this visit)' and that 'even if you do consent to participate, you would be free to withdraw at any time later if you wished to do so'.[5]

All participants will be genotyped using a 820K bespoke UK Biobank Affymetrix genotyping chip. In addition, estimate ('impute') additional genotypes will be derived by combining measured genotypes with reference sequence data. Researchers can study associations of genotype data with biochemical risk factors and detailed phenotyping from the baseline assessment, along with health outcomes.

UK Biobank has kept participants informed about genetics studies; a newsletter was sent out drawing attention to the first genetic study (a study of lung disease) and UK Biobank's genotyping work, in addition to a video appearing on the project's website that describes the work.

Update on progress with the genotyping project:

- High-throughput automated DNA extraction systems have been established at UK Biobank coordinating centre, conducting DNA extraction as a 24/7 operation and currently extracting 6,500 DNA samples per week.
- DNA is shipped to Affymetrix in California for genotyping, ~250,000 participants have been genotyped with a 99.9% pass rate for genotyping and 99.6% SNP call rate.
- Genotyping data are to be released for the first 150,000 participants by end 2014 and all 500,000 participants by 3Q 2015; followed by imputed data during 2016.

Discussion

The following key points were raised during the discussion:

- The aims of Genomics England's 100,000 Genomes Project and current thinking regarding the project's feedback and access arrangements.
- The language of access and what is understood by the terms 'open' and 'controlled'.
- The benefit of centralised approaches whereby a biobank turns depletable samples or data into accessible information for the research community (e.g. by performing genotyping and biochemical assays or by analysing MRI images or accelerometer data).
- The role and responsibility of the principal investigator, including in relation to access.
- UK Biobank's access procedures and plans to streamline the process (see also the session on 'Governing access').
- Administrative challenges in relation to health record linkage and how access to these data by researchers is managed.
- The scope of the term 'health-related record' and whether this could include, for example, criminal records.
- Criteria for establishing whether a researcher is *bona fide*.
- Policies in relation to access for non-research purposes (e.g. law enforcement).

5 UK Biobank participant materials are available at www.ukbiobank.ac.uk/resources.

View this presentation online:
https://youtu.be/6aZbToN7k90

View the discussion online:
https://youtu.be/KT8FAnd9BeI

Governing access

Chair and respondent: Dr William Lowrance

Access governance mechanisms

Professor Martin Bobrow

The Expert Advisory Group on Data Access (EAGDA) was set up by four big UK funding agencies to advise them on growing issues and governance matters in relation to data access. EAGDA is looking at data access issues across the board, however, while the Group has not yet produced a draft paper, what follows is a personal reflection on the issues.

Desirable features of data management systems are: easy discoverability; data quality, clarity and help; facility/clarity/transparency of access process; fair conditions of access and transparent independent appeal process.

Some potential issues in data sharing are:

- Over-complex application processes.
- Repetitive access procedures to multiple datasets.
- Disproportionate expectations of scientific merit.
- Disproportionate expectations of researcher experience.
- Over-dominance of data-generating team in access adjudication.
- Access by collaboration only.

Some of the whole system issues are:

- Relevant funding applications should have costed data management plans.
- These should be explicitly assessed and funded during peer review.
- Data management should be audited for compliance during and after grant period.
- Data release costs money – either funded centrally or cost recovery.

In summary:

- Most data generators are trying to support data sharing.
- There is no reason to believe that sharing data under current circumstances is creating significant risks for research participants (that haven't been made explicit and are being controlled for).
- Data access is still often a clunky, variable process, highly dependent on goodwill.
- There are opportunities for convergence and consolidation.
- Good transparent governance may improve public confidence in science.

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https://youtu.be/mRffhOVpNE0

Access in practice at UK Biobank

Mr Jonathan Sellors

UK Biobank's access application process involves four key steps: registration, the preliminary application, the main application and signing of the Material Transfer Agreement and dispatch of the data/samples. The review process involves UK Biobank's Access Administration Team, UK Biobank's Scientific Team and the Access Sub-Committee (ASC); ethics input is provided by Professor Mike Parker of the Ethox Centre. The ASC considers the UK Biobank principal investigator's recommendation and oversees the access process. UK Biobank orientation is to make the access process as straightforward as possible for researchers. The principal check is to ensure that researchers are who they say they are and that they are conducting health-related research in the public interest. UK Biobank reviews applications to ensure that they are viable (i.e. that they may be able to generate coherent results): it does not try to judge the science for data-only applications. It takes a more rigorous view (as to the science) with its depletable resources, namely samples and re-contact, and with these it does review the quality of the science behind the application. Access charges are kept at a cost recovery rate to encourage research.

Access to UK Biobank was launched in March 2012. Over 1,000 researchers have registered, over 220 applications are in progress and over 90 projects have been approved. Eight projects have not been approved and four applications have been deferred. Reasons for no approval include requests for too large a sample quantity with insufficiently strong scientific rationale or requests for samples to pilot an assay methodology. To date there have been 18 peer-reviewed publications and 55 conference presentations and results are being returned to UK Biobank. UK Biobank expects that with the advent of the genotype, biomarker and imaging data the number of applications will increase substantially in the coming years and the access process will need to be streamlined to address this situation.

Submitted application split by type (n=224):

- Commercial 4% vs Academic 96%.
- International 17% vs UK 83%.
- Data only 82% vs Samples 14% vs Re-contact 4%.

The main areas under consideration are:

- How to prioritise sample requests and ensure that samples are used in the most efficient manner (particularly for case control research).
- Re-contact, where there are two issues, how to avoid making a participant aware of a risk factor or disease (of which they are not previously aware) and how to address differing feedback policies which re-contact studies (not run by UK Biobank) may adopt.
- Linkage to other medical research resources (as distinct to linkage to health care records), including issues around the scope of the consent and the control of access to data.

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https://youtu.be/6VdC9dbyKlw

Role and experience of the EGC in relation to access

Professor Søren Holm

The basic parameters to access are that:

- UK Biobank is a pure resource, i.e. it is not 'owned' or controlled by any particular group of researchers. There is no exclusive use and there are equal access requirements for all *bona fide* researchers.
- The UK Biobank Ethics and Governance Framework (EGF) explains that 'UK Biobank will serve as the steward of the resource, maintaining and building it for the public good in accordance with its purpose'.
- The EGF goes on to say that 'The Ethics and Governance Council will keep use of the resource under review in order to advise on conformance with this Framework and the IP and Access Policy, and to assure itself, and others, that the resource is being used in the public interest.'

There are two depletable aspects of the resource:

- The goodwill of participants (both in general and in relation to re-contact). The EGF recognises that re-contact is a special case and states that 'decisions on whether recontact is appropriate for particular proposals will be made by UK Biobank with advice from the Ethics and Governance Council'.
- The samples.

The EGC has engaged with UK Biobank during the development of the access procedures, during the initial experiences of giving access and during the ongoing review of the access process and use of the resource (e.g. looking at who makes the decisions, whether ethical issues are being picked up and generally seeing how the process works in practice).

The main issues in designing a model for ongoing ethics and governance oversight are:

- Robustness of internal ethical governance.
- Transparency of the access process (to EGC, but also wider).
- Easy to operate without imposing any undue burden on UK Biobank or its users.

In the light of experience to date, and confidence in UK Biobank's internal processes, a new model for EGC access oversight has been agreed which involves:

- UK Biobank will alert the EGC to applications that raise significant ethics or governance issues.
- UK Biobank will provide access summary reports for the EGC's quarterly meetings.
- Regular external audit of the access processes.

Discussion

The following points were raised during the discussion:

- The university sector's move towards commercial endeavours and what implications, if any, this has for biobanks hosted by, or working with, university institutions.
- Sustainable strategies for funding of longitudinal data infrastructures and the need to consider what business models work best.
- How, when and by whom should the public interest be considered?
- The need to engage the scientific community to promote the use of biobanks.
- Models for cost recovery and UK Biobank's access charges.

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https://youtu.be/GhGlT1gf3QM

View the discussion online:
https://youtu.be/b7FWlDgPAv8

Engaging participants

Chair and respondent: Dr Mairi Levitt

UK Biobank practice and the challenges faced

Mr Andrew Trehearne

The UK Biobank Ethics and Governance Framework states that 'Regular communication will be important to inform participants of general findings from research based on the resource and to encourage continued participation. UK Biobank will, therefore, look for a variety of ways for communicating with (including listening to) participants, the general public, research users and the scientific community.'

Who: UK Biobank has two key audiences, participants and the health research community. However, many others have an interest in the project including funders, the scientific community more broadly, the media and the public.

What: UK Biobank communicates about a range of topics, including the use of the resource (e.g. new uses of the data and published papers), new data collections (e.g. the genotyping work and linkage to health-related records), re-contacts (e.g. in relation to enhancements such as the imaging), talks, conferences and linked events and consultations.

How: UK Biobank communicates in a range of ways including:

- Via letters and talking to participants (in one 12-month period the Participant Resource Centre received up to 40,000 calls or emails).
- Via the media (including TV, newspapers and radio).
- Via the project's website (videos, news stories and the creation of micro-sites e.g. for the imaging).
- Public meetings (both 'frontiers' meetings for scientists, speaking at conferences and public meetings specifically for participants).
- Journals (e.g. published papers, which are also highlighted on the website).
- Newsletters (sent annually to participants).
- Twitter and – currently under discussion – webinars.

Challenges include:

- Keeping up with published research.
- Making sense of new developments in research and their likely impact on participants and the public more generally.
- Staying in touch with an ageing population.

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https://youtu.be/FLDYckTZU9w

The EGC's experience of participant engagement: to engage or not to engage?

Mr Andrew Russell and Mr David Walker

Andrew Russell

During the recruitment phase of UK Biobank the EGC held a series of public meetings in the towns where recruitment was taking place. While the EGC is charged to 'advise on the interests of research participants and the general public in relation to UK Biobank', the purpose of these meetings was to listen to the meeting attendees and see whether the EGC was reflecting their interests in its advice to UK Biobank.

The last public meeting was held in 2010 when, on the recommendation of a funding review panel, the EGC stepped back from its public engagement work; the Panel considered that such work would more appropriately fall to UK Biobank.

In order to inform its advice to UK Biobank, the EGC held a workshop in 2009 on 'Involving publics in biobank research and governance'. The workshop showcased a variety of methods for involving publics including consultative panels, citizens' inquiry, a shareholder model and through membership of strategic decision-making groups.

In the workshop report, and subsequently, the EGC has strongly urged UK Biobank (and its funders) to consider the opportunities and threats of public involvement carefully and closely, understanding that a variety of approaches will be relevant to UK Biobank and its relationship with participants and society over time. While there are a number of reasons to limit engagement (e.g. due to cost and other resource implications) these need to be balanced against the reasons for taking further steps towards participant and public engagement, including:

- The principle of respecting partnership with the participants.
- It demonstrates accountability in the use of public funds.
- It improves the capacity to gauge public opinion and may flag up new concerns.
- It recognises that participants are a depletable resource and if they are not engaged they may come to feel that their participation is not valued.

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https://youtu.be/KNkTqolHSx0

David Walker

A strategy for engagement should consider audience segmentation (e.g. whether to address the public at large versus directing messages at particular groups such as a particular region, those who participate in UK Biobank, the research community, policymakers or funders). Brands are also important in winning public attention, such as UK Biobank's association with the National Health Service, which command universal recognition and support. When developing strategies we must not make large assumptions about public knowledge. Understanding of scientific method and research protocols may not be widespread and statistical literacy low. The public won't know much either about institutions e.g. UK Biobank's relationship with universities, funders etc.

Engaging with the public brings costs, which have to be weighed against benefits. There is a risk, too, of 'stirring up apathy' and drawing the public's attention to areas of controversy, which might lead to negative consequences. Tabloid and online media responses may be critical, giving rise to ill-informed 'media storms'.

UK Biobank engages with a set of segmented audiences (participants, the funders, researchers etc.). It should concentrate on specific groups, rather than attempt a costly campaign aimed at the public at large.

Discussion

The following points were raised during the discussion:

- The need for qualitative research in addition to harder scientific research and the importance of asking people's views on their involvement in research.
- The potential disconnect between the opinions of elected officials and the general public regarding the funding and use of biobanks.

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https://youtu.be/csv9z9Y-uwY

View the discussion online:
https://youtu.be/1l5jcNYk_7E

Participant follow-up through medical and health-related records

Chair and respondent: Mr Peter Singleton

Governance challenges for linkage to medical and health-related data: UK perspective

Professor Graeme Laurie

One of the challenges in this area is dealing with attitudes around data sharing. The Academy of Medical Sciences reports in 2006 and 2011 lament the 'culture of caution' around data linkage and sharing; the absence of *proportionate governance*; and the failure to take advantage of flexibilities *within law*. Further, the Caldicott 2 review (2013) pointed out that: '[t]he duty to share information can be as important as the duty to protect patient confidentiality.'

A further challenge relates to regulators who face what might be conceived as conflicting responsibilities. For example, the Care Act 2014, s.111 states that [The Health Research Authority, *inter alia*] must '...have regard to both the need...

- to protect participants and potential participants in health or social care research and the general public by encouraging research that is safe and ethical, and
- to promote the interests of those participants and potential participants and the general public *by facilitating the conduct of such research*.'

Legal and ethical considerations:

- Consent is neither necessary nor sufficient to discharge your obligations under data protection law, while anonymisation is a technical not an ethical solution.
- Consent, de-identification and authorisation should work in tandem. In this context authorisation could come in the form of advice from bodies like the Confidentiality Advisory Group [England] or the Privacy Advisory Committee [Scotland] to data controllers; but questions arise in term of the social licence of such bodies to provide this authorisation.
- It is important to draw on good practice e.g. SAIL/CIPHER in Wales with a paradigm safe haven and SHIP in Scotland as an example of principled proportionate governance.
- There are existing examples of stakeholder engagement in iterative design.
- It is crucial to demonstrate public interest potential in access.

Tentative conclusions:

- There is no magic bullet in delivering good governance: a variety of approaches is required.
- Guiding principles of responsible data linkage are a defensible, flexible and adaptable approach that can be of value across sectors and countries. Of central importance are proportionality and mutual recognition of what counts as good practice.
- Stakeholder and public engagement is key both to inform and to shape governance over time – models must be receptive and adaptive.

View this presentation online:
https://youtu.be/zHToOCPXv8U

Chair and respondent: Mr Peter Singleton

UK Biobank approach and experience

Professor Sir Rory Collins

UK Biobank's centralised approach to follow-up of participants' health includes linkage to:

- Death and cancer registries.
- Inpatient and outpatient hospital episodes (including psychiatric) and related procedure registries.
- Primary care records of health conditions, prescriptions, diagnostic tests and other investigations.
- Other health-related: disease registries; dispensing records; imaging; screening; dental records.
- Direct to participants: self-reported medical conditions; treatments actually being taken; degree of functional impairment; cognitive and psychological scores.

Key challenges have been:

- Regulation, bureaucracy, and permissions (despite explicit consent from participants).
- Data transfer, matching and coding queries.
- Understanding different data structures.
- Mapping between coding systems.
- Mapping between different countries.
- Presenting outcome data to researchers (both original outcome codes and post-adjudication outcomes).

UK Biobank takes a staged approach to outcome adjudication involving:

- Ascertainment of suspected cases (possible data sources: death and cancer registers, hospital records, primary care records and web questionnaires).
- Confirmation of 'case-ness' (possible data sources: cross referencing e-records and by reviewing disease registers).
- Classification of disease cases (possible data sources: review of clinical records, tumour collections/assays, specialised databases (e.g. imaging)).

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https://youtu.be/t6tQGrs_u58

View the discussion online:
https://youtu.be/B1kpyCjsKEU

UK Biobank is receiving expert advice on methods for ascertainment, confirmation, and sub-classification of disease outcomes through a number of Outcome Adjudication Working Groups in the fields of: cardiac outcomes, neurodegenerative outcomes, stroke, musculoskeletal outcomes, diabetes, respiratory outcomes, cancer, renal disease, ocular outcomes, liver disease, mental health outcomes and infections.

Discussion

The following points were raised during the discussion:

- The responsibility and work of the Health Research Authority.
- The need for robust IT systems to underpin secure linkage to help build the trust of the public and data controllers.
- Problems with realms of control (e.g. a biobank having consent from participants for linkage but encountering difficulties from the data controllers who may have different priorities or governance considerations).
- The importance of participant reported outcomes.
- Legal issues regarding coded data and the ambiguity over whether and when these data should fall under personal data legislation.
- UK Biobank's approach to outcome adjudication and the issue of false positives and false negatives.
- The notion of consent and how this has changed with the advent of longitudinal cohort studies where future uses are unknown.
- Linkage to health-related records (including records that tell us something about exposures and environmental issues). Where there is ambiguity over whether such linkages are covered by the consent, this can be an opportunity to ask participants for their views.
- The need to learn from others who have experience of linking to health-related records, such as ALSPAC.

Data sharing between cohort studies

Chair and respondent: Dr Susan Wallace

Frameworks for data sharing

Professor Jane Kaye

Pop-up governance is a governance structure that has been evolved for research consortia that have a defined objective but are often multi-disciplinary, multi-institutional with an international membership. It provides a way to deal with both management of project deliverables and potentially contentious issues, such as sharing data. It is also designed to facilitate efficiency, transparency and accountability. It is 'pop-up' because it:

- Can be put together quickly.
- Exists for a specific period of time.
- Can be dismantled easily when no longer needed.
- Is designed for optimum productivity.
- Is tailored for a specific project's needs.
- Enables the project to be accountable to external bodies such as funders.

It is a new form of networked governance (not simply good project management) because there is a common purpose where individuals promote the objectives of the group. Also, there is interdependency; the team goals can only be achieved by people working together.

The benefit of this type of governance structure is that it provides a cocoon for research because:

- The basis for data generation and sharing is clear at the beginning of the project.
- Regulatory approvals and consents have usually been obtained by the project as a whole, relieving the burden on individual researchers to some extent.
- It sets up processes and committees to resolve potentially contentious issues as they emerge such as attribution in publications, data access etc.

But what happens when the project finishes?

- We no longer have the project infrastructure because it has been dismantled.
- People responsible leave their institutions or retire.
- It is not always clear where data should be deposited or whether it is in a form that is useful for others.
- However, institutions such as the Sanger Centre have put in place ongoing governance structures to manage data access once the project has finished and the pop-up governance is dismantled.

In conclusion, pop-up governance works well, it addresses many of the concerns about data sharing that have been found in the literature because it builds relationships and provides a framework for sharing and access. There are issues around sustainability and a question over how we engage participants and make them visible in the project. If the Data Protection Regulation is passed we will need to think about what structures we put in place to inform participants about how their data are being used and there is the potential to explore mechanisms such as 'dynamic consent'.

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https://youtu.be/3XErtYxjHgA

Chair and respondent: Dr Susan Wallace

Data security and management

Professor Paul Burton

Combining data from multiple sources is fundamental to modern bioscience. There are two common approaches to data synthesis for horizontally partitioned data (i.e. where there are several studies that hold data on different individuals):

- Study level meta-analysis (SLMA): obtain result for each study separately – e.g. odds ratio for a single nucleotide polymorphism (SNP). Calculate an appropriately weighted mean and standard error for that odds ratio across *all* studies = 'conventional meta-analysis'. This method is quick, easy and works but it lacks the flexibility required for a research environment which is increasingly complex, unpredictable and exploratory.
- Individual level meta-analysis (ILMA): pool all of the individual level data from each of the studies into one large data set and then analyse that data set as if it was one single study (with parameters for heterogeneity) = 'direct pooling'. This method is preferable to SLMA.

Although preferable, there are constraints on sharing individual-level data:

- Use of data restricted to researchers participating in the original study.
- Use of data restricted to researchers in one country.
- The need to obtain ethico-legal and scientific permission to access the data (which often needs multiple clearances and can often be protracted and time consuming).
- Intellectual property issues.
- Physical size issues (e.g. for genome sequencing data, imaging data etc.).

DataSHIELD (Data Aggregation Through Anonymous Summary-statistics from Harmonised Individual-Level Databases)[6] provides an alternative approach:

- Takes 'analysis to data', not data to analysis.
- Leaves the raw data from each study on a local server at that study.
- Analysis centre co-ordinates parallelised analyses in all studies simultaneously.
- Tie analyses together with non-disclosive *statistics* of an appropriate nature.

Current status:

- Multi-site horizontal DataSHIELD: proof of principle and practical implementation has been successful. Work is now underway to enhance a range of functions and ease of use and the capability of working with large genomic data is being explored.
- Single-site horizontal DataSHIELD: the potential is currently being explored. This has the potential to be a cost-effective, open source and secure data enclave that makes updatable summary statistics freely available for cohort studies over the web while preserving sensitive intellectual property e.g. in H3AFRICA.
- Vertical DataSHIELD (e.g. linked data such as health records): the proof of principle has been successful but extensive work is required on the practical implementation.

6 Murtagh *et al Public Health Genomics* 2012; 15:243-253 and Gaye *et al International Journal of Epidemiology* 2014; 1-16

View this presentation online:
https://youtu.be/dRxH7FpNmjs

Chair and respondent: Dr Susan Wallace

Nuffield Council on Bioethics Working Party on biological and health data

Professor Martin Richards

The remit of the Nuffield Council on Bioethics Working Party on biological and health data is:

- To identify developments in the collection, linking, use and exploitation of biodata.
- To identify, define and examine significant ethical questions raised by these developments.
- To consider the implications of these developments with regard to: a) meaning and practical exercise of privacy, autonomy, anonymity; b) ownership, control and interest in data; c) interaction between interests of data subjects, public interests and commercial interests; d) moral and legal duties of those involved in the collection, linking, use and exploitation of data; e) the appeal to autonomy, rights, dignity and common interest as justification for processing data.

There are new opportunities to collect more and make more use of data, for example, in the context of improving medical treatment, effectiveness and efficiency of medical care and increasing the power and pace of research and other matters of public interest. The repurposing and reuse of data are driven by a desire to realise scientific, economic and policy opportunities. The privacy risks and public concern need to be weighed against the risks associated with 'doing nothing'.

Ethical use of data will need to build on reasonable expectations of data use, with a background in principles of respect for persons and respect for human rights. Governance of uses of data will need to involve participation and accountability. However, given that different data initiatives have different objectives, engage different interests and give rise to different expectations, the Working Party cannot suggest a specific set of governance arrangements and procedures (e.g. mode of consent, oversight, accountabilities, review processes) which will be appropriate for all initiatives. Instead, the Party's report will discuss examples of good and poor practice which may provide lessons for future initiatives.

View this presentation online:
https://youtu.be/Y6qJkF7yz8w

View the discussion online:
https://youtu.be/f-Q9HtiPnZM

Personal reflections on UK Biobank: participants gave their 'broad' consent but in the context of other arrangements designed to protect their privacy and other interests, namely the Ethics and Governance Framework (EGF) and the independent Ethics and Governance Council. As a public document that can be revised, the EGF is a critical aspect of adaptive governance and is a novel and an effective instrument. Arguably, all projects could benefit from developing and adopting their own EGF.

Discussion

The following points were raised during the discussion:

- Lessons to be learnt from the NHS England's care. data initiative.
- Privacy harms and whether there have been instances of real harms or poor practice in the research setting.
- The scope of DataSHIELD and whether the processed data would fall under data protection legislation.
- The need for trust in any data sharing system, based on clear agreements.
- The need for data curation and preservation over the long term.

The ethics and governance of big biobanking: the future

Chair and respondent: Professor Nils Hoppe

P3G and the Global Alliance for Genomics and Health

Professor Bartha Maria Knoppers

The Public Population Project on Genomics and Society (P3G) is an international consortium supporting networks and research collaborations. Dedicated to the development and management of biobanks, research databases and other similar health and social research infrastructures, through its tools, support and networks, P3G helps the international research community to prepare and undertake effective policy strategies. P3G is currently a network of more than 560 members and institutions from 40 countries.

P3G research programmes include Maelstrom, the Paediatric Research programme, the policy programme of the Centre of Genomics and Policy (CGP; McGill) and the ELSI 2.0 programme. P3G also coordinates the International Policy interoperability and data Access Clearing house (IPAC) which is a one-stop service for researchers offering:

- ELSI Clauses/Agreements Database: an open access resource allowing users to search and select models of clauses that best suit their needs.
- Policy Interoperability Screening: validate whether studies can work together (e.g. consent; confidentiality; etc.) and if not, create tools.
- Data Access Clearinghouse: authorize studies to access controlled databases (e.g. ethics approval/ waiver; institutional sign off; etc.).

The mission of the Global Alliance for Genomics and Health (GA4GH) is to accelerate progress in human health by helping to establish a common framework of harmonized approaches to enable effective and responsible sharing of genomic and clinical data, and by catalyzing data sharing projects that drive and demonstrate the value of data sharing. Four Working Groups have been established: Regulatory and Ethics; Data; Security and Clinical.

The Regulatory and Ethics Working Group (REWG) has a number of task teams, including:

- Consent: developing core elements and policies of consent to enable responsible data sharing, including clauses relating to privacy, international research collaboration, and processes and methods for data storage.
- Safe Havens: developing platforms for the secure and efficient exchange of clinical and genomic data.
- Safe Harbour: developing a system that allows for mutual recognition of data access and ethics review.
- Data Protection Regulation: analyzing and rapidly responding to data protection regulation development occurring around the world, as it affects biomedical research and sharing of health-related data for research purposes.
- Privacy and Security Policy: developing a Privacy and Security Policy in line with the aims of the Security Working Group's 'Security Infrastructure', in conformity with the Framework for Responsible Sharing of Genomic and Health-Related Data developed by the REWG, and international privacy norms and security standards.

In 2014, the Framework for Responsible Sharing of Genomic and Health-Related Data was developed and adopted by the REWG and the GA4GH. Both an aspirational and practical instrument, the Framework is founded on human rights (right to the benefits of science; right of attribution, and right to scientific freedom) and aims to:

- Foster responsible data sharing.
- Protect and promote the welfare, rights, and interests of groups and individuals who donate their data.
- Provide benchmarks for accountability.
- Establish a framework for greater international data sharing cooperation, collaboration, and good governance.
- Serve as a dynamic instrument.

View this presentation online:
https://youtu.be/KiPMHlUxsec

Chair and respondent: Professor Nils Hoppe

International Society for Biological and Environmental Repositories

Ms Marianna Bledsoe

The International Society for Biological and Environmental Repositories (ISBER) is a global organisation that creates opportunities for sharing ideas and innovations in biobanking and harmonizes approaches to evolving challenges for biological and environmental repositories. Currently the Society has 1066 individual and organisational members from 37 countries.

The Society's goals are to:

- Disseminate information on repository management issues.
- Educate and share information and tools within the Society and with stakeholders.
- Act as the voice for repositories to influence regulations and policy.
- Develop best practice guidelines.
- Provide centralized information about existing repositories.
- Bring members together to work on emerging issues.

ISBER's ELSI contributions include:

- Developing best practice guidelines including the legal and ethical issues in biobanking specimen collection, access, distribution, use and destruction.
- Responding to, and communicating about, emerging science policy issues (including responses to requests for public comment).
- Holding discussions and workshops at annual meetings including many ELSI topics such as: governance, return of research results, international policy developments, global harmonization, commercial use and ownership, identifiability, privacy, genomic data sharing, sustainability, and engaging research participants.
- Co-sponsoring advanced tissue banking programs in 2013 and 2014 with Public Responsibility in Medicine and Research (PRIM&R) to engage and educate the IRB/ethics review committee communities on biobanking activities.

The ELSI challenges in the field moving forward are:

- Broad variation in the types of biobanks: one size does not fit all.
- Variation in regulations and policies and ethics review committee requirements globally.
- The evolving ethical and regulatory landscape.
- Education of stakeholders (including policy makers).
- Unresolved, emerging ethical issues.

View this presentation online:
https://youtu.be/5snD8giBwbU

BBMRI-ERIC

Professor Jan-Eric Litton

The Biobanking and BioMolecular resources Research Infrastructure (BBMRI) has legal status as a European Research Infrastructure Consortium (ERIC); bringing together 12 founding members and four observers including the International Agency for Research on Cancer. It is the largest health orientated ERIC ever to be launched in Europe and has a total population of 408 million individuals.

The seven pillars of BBMRI-ERIC are:

- Scientific excellence.
- One type of infrastructure for Europe.
- Access to high quality human biological samples and associated data.
- Access to high quality biomolecular resources.
- Ethical and legal compliance.
- Long-term sustainability.
- International integration.

The BBMRI-ERIC Work Programme 2014 describes a number of work streams, including the setting up of the ELSI Common Services. A tender for these services was issued and included, amongst others, the following requirements:

- Provide solid monitoring of ELSI issues related to biobanks and biobanking.
- Follow up relevant evolution in legislations/ regulations at the European level and organise coordinated answers to relevant public consultations etc.
- Intervention to address joint matters for the biobanking community on the European level.
- Build conclusions and advise on a sound scientific/ academic basis and experience in ethical reviews of European/international projects.
- Provide updated background information and practical guidance to biobankers to respond to ELSI issues, especially in relation to the exchange of human samples and data for research use in Europe ('help-desk'-format); ensure the dissemination of results of relevant surveys and studies toward the various audiences.
- Organize tools and services to address ELSI issues related to biobanks and biobanking by building on already available tools and generating new ones if necessary.
- Organize experience sharing and exchanges regarding ELSI aspects between BBMRI-ERIC members and set up training and education on ELSI issues related to biobanks and biobanking.
- Provide an ethics check of compliance for research proposals submitted to BBMRI-ERIC in compliance with the BBMRI Business Plan and Statutes and with the European Commission research ethics framework.

One joint consortia proposal was received including representatives from all BBMRI-ERIC Member States and observers. The proposal identifies a Board of Co-Directors consisting of Anne Cambon-Thomsen (France), Marialuisa Lavitrano (Italy), Mats Hansson (Sweden) and Jasper Bovenberg (The Netherlands) and builds on existing tools and expertise (e.g. hSERN, legal WIKI etc.). The ELSI Common Service should commence in February 2015.

View this presentation online:
https://youtu.be/AixOpbLiiZY

Chair and respondent: Professor Nils Hoppe

ELSI 2.0

Professor Jane Kaye

The ELSI 2.0 infrastructure – or collaboratory – aims to:

- Enable the engagement of a broad range of stakeholders to share expertise, ideas and approaches to ELSI issues.
- Facilitate and sustain global collaborations and networking.
- Influence policy making and scientific practice at a global level.
- Develop new ways of working including using 2.0 technology.

But what is a 'collaboratory'?

- A fusion of the words 'collaboration' and 'laboratory'.
- A combination of technology, tools and infrastructure to allow remote collaboration.
- Working without walls – a culture change project.
- New paradigm for conducting ELSI that enables stakeholders from any field to easily access expertise and knowledge and to work together.

In addition to a series of launch meetings (in the Netherlands, UK, USA and Japan) ELSI 2.0 has arranged a number of topic specific meetings on: safe harbours, incidental findings in biobanks, personal data protection (with a focus on regulations in the UK and Japan), data sharing in consortia and personalised medicine.

ELSI 2.0 objectives for 2014–2015 are:

- To build the IT infrastructure for a global e-workspace.
- To extend the involvement of the global community.
- To strengthen the network for students and early career researchers to enable capacity building.
- To develop the methods for policy acceleration.
- To develop a sustainable funding model.

Discussion

The following points were raised during the discussion:

- The recent trends towards global rather than regional and towards providing tools and advice (e.g. templates and clauses).
- The need for engagement with a broad stakeholder community and for policy to be taken out beyond the biobanking community.

View this presentation online:
https://youtu.be/vrt-Y_4I84E

View the discussion online:
https://youtu.be/TSCYzKytpz8

Appendix 1
Conference programme

Free evening public lecture — Monday 3 November 2014

19:30 – 19:40	**Welcome**	*Professor Roger Brownsword*
19:40 – 20:30	**Lecture with Q&A: 'Biobanks – can ethics keep pace with the science?'**	*Professor Alastair Campbell*

Conference — Tuesday 4 November 2014

10:00 – 10:10	**Welcome and introduction**	*Professor Roger Brownsword*
10:10 – 10:30	**UK Biobank in 2014 and beyond**	*Professor Sir Michael Rawlins*
10:30 – 11:45	**Governance of UK Biobank: the EGF and the EGC**	*Chair and respondent: Professor Bartha Maria Knoppers*
	Drafting the Ethics and Governance Framework	*Professor Alastair Campbell*
	The Ethics and Governance Council (EGC) as a 'critical friend'	*Professor Graeme Laurie*
	Today's governance challenges for the EGC	*Professor Roger Brownsword*
	Response and discussion	
11:45 – 12:15	Break	
12:15 – 13:30	**Learning from the governance experience of others: case studies**	*Chair and respondent: Dr Jonathan Hewitt*
	Estonian Genome Center of Tartu University	*Professor Andres Metspalu*
	Taiwan Biobank Ethics and Governance Council	*Professor Michael Tai*
	ALSPAC Ethics and Law Committee	*Professor Madeleine Murtagh*
	Framingham Heart Study	*Dr Daniel Levy*
	Response and discussion	
13:30 – 14:30	Lunch	
14:30 – 16:00	**Feedback**	*Chair and respondent: Dr Jasper Bovenberg*
	Wellcome Trust and Medical Research Council Framework on feedback	*Ms Katherine Littler*
	Framingham Heart Study	*Dr Daniel Levy*
	Deciphering Developmental Disorders project	*Dr Anna Middleton*
	UK Biobank's policy and the role of the EGC	*Dr Sheelagh McGuinness*
	Response and discussion	
16:00 – 16:30	Break	
16:30 – 18:00	**Genomic data and governance: case studies**	*Chair and respondent: Professor Mike Parker*
	UK10K	*Dr Lucy Raymond*
	1958 Birth Cohort	*Professor Paul Burton*
	UK Biobank	*Professor Sir Rory Collins*
	Response and discussion	

9:00 – 10:30	**Governing access**	*Chair and respondent: Dr William Lowrance*
	Access governance mechanisms	*Professor Martin Bobrow*
	Access in practice at UK Biobank	*Mr Jonathan Sellors*
	Role and experience of the EGC in relation to access	*Professor Søren Holm*
	Response and discussion: What are the appropriate responsibilities of an oversight body in relation to access?	
10:30 – 11:00	Break	
11:00 – 11:45	**Engaging participants**	*Chair and respondent: Dr Mairi Levitt*
	UK Biobank practice and the challenges faced	*Mr Andrew Trehearne*
	The EGC's experience of participant engagement: to engage or not to engage?	*Mr Andrew Russell and Mr David Walker*
	Response and discussion: To what extent, if any, is it the role of an oversight body to engage participants?	
11:45 – 12:30	**Participant follow-up through medical and health-related records**	*Chair and respondent: Mr Peter Singleton*
	Governance challenges for linkage to medical and health-related data: UK perspective	*Professor Graeme Laurie*
	UK Biobank approach and experience	*Professor Sir Rory Collins*
	Response and discussion	
12:30 – 13:30	Lunch	
13:30 – 15:00	**Data sharing between cohort studies**	*Chair and respondent: Dr Susan Wallace*
	Frameworks for data sharing	*Professor Jane Kaye*
	Data security and management	*Professor Paul Burton*
	Nuffield Council on Bioethics Working Party on biological and health data	*Professor Martin Richards*
	Response and discussion	
15:00 – 15:30	Break	
15:30 – 16:45	**The ethics and governance of big biobanking: the future**	*Chair and respondent: Professor Nils Hoppe*
	P3G and the Global Alliance for Genomics and Health	*Professor Bartha Maria Knoppers*
	International Society for Biological and Environmental Repositories	*Ms Marianna Bledsoe*
	BBMRI–ERIC	*Professor Jan-Eric Litton*
	ELSI 2.0	*Professor Jane Kaye*
	Response and discussion: How, going forward, should the experience of ethics and governance bodies be disseminated and shared?	
16:45 – 17:00	Closing remarks	*Professor Roger Brownsword*

Appendix 2
Speaker and chair affiliations

Ms Marianna Bledsoe
Co-Chair, International Society for Biological and Environmental Repositories Science Policy Committee

Professor Martin Bobrow
Chair, Expert Advisory Group on Data Access

Dr Jasper Bovenberg
Practicing attorney in The Netherlands, specializing in life sciences

Professor Roger Brownsword
Chair, UK Biobank Ethics and Governance Council (EGC)

Professor Paul Burton
Professor of Infrastructural Epidemiology, Bristol University

Professor Alastair Campbell
Director, Centre for Biomedical Ethics, National University of Singapore and first chair of the EGC

Professor Sir Rory Collins
Principal Investigator and Chief Executive, UK Biobank

Dr Jonathan Hewitt
EGC Vice Chair and Clinical Senior Lecturer at Cardiff University

Professor Søren Holm
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Professor Nils Hoppe
EGC member and Professor of Life Sciences Regulation, Hannover University

Professor Jane Kaye
Director of HeLEX, Oxford University

Professor Bartha Maria Knoppers
Director, Centre of Genomics and Policy, McGill University, Canada Research Chair in Law and Medicine and founder of P3G

Professor Graeme Laurie
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Dr Sheelagh McGuinness
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Professor Andres Metspalu
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Professor Madeleine Murtagh
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Professor Mike Parker
Professor of Bioethics, Oxford University and Chair, Genomics England Ethics Advisory Committee

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Dr Lucy Raymond
Reader in Neurogenetics and Consultant in Medical Genetics, Cambridge University

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Mr Andrew Trehearne
Head of Communications, UK Biobank

Mr David Walker
EGC member and a writer specializing in
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Dr Susan Wallace
EGC member and Lecturer of Population and
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Appendix 3
List of delegates

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