Author's response to reviews

Title: Biobanking from the patient perspective

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Author's response to reviews: see over
Dear Research Involvement and Engagement Editorial Team,

Thank you for the opportunity to re-submit our proposed article. We greatly appreciate the comments and suggestions of the four reviewers, and have worked hard to address the multiple points and questions. Find below a point-by-point breakdown of each comment.

**Reviewer 1 (Iain Chalmers’) comments:**

<table>
<thead>
<tr>
<th>Abstract</th>
<th>New Draft of Article / Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I didn’t understand the reference to ‘medicine becoming more personalised’</td>
<td>Explanation: This reference to ‘personalised medicine’ is relevant here as carefully-designed, high-quality biobanking services and research can provide the critical research infrastructure for clinical genetics in order to serve the needs of personalised medicine. (High-quality biobanking encompasses high professional standards, international networks, adequate funding, training and certification emphasized, and enhanced communication with key stakeholder groups including patients). This point is also further highlighted in the “Main Theories and Background” 2nd paragraph.</td>
</tr>
<tr>
<td>2. Avoid claiming without evidence that a perspective is ‘unique’.</td>
<td>Replaced ‘unique’ with ‘to identify’</td>
</tr>
<tr>
<td>3. In last para, insert ‘identify’ before ‘perspective’.</td>
<td>Done</td>
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</table>

**Introduction**

1. This section should begin with a brief description of what biobanks are and what different kinds of biobanks are for, giving references to more substantive expositions. It should go on to make clear at this point that the specific type of (patient/disease-focused) biobank that this article is about – as indicated in the title of the paper. Thereafter, I suggest that there should be no references to ‘the public’ or ‘PPI’.

The following clarification and references have been inserted:

*Biobanks collect, process, store, and distribute biospecimens and related data to research organisations. These biospecimens and data are used by scientists to learn more about human diseases, their causes, their effects, and to develop better prevention measures, better diagnostic tests and better therapies (Riegman et al. ref below).*

*Different types of biobanks exist and are described in greater detail in the Definitions section. Unless otherwise stated, the term “biobank” in this article refers to disease-oriented general biobanks based, human, comprising of human tissue, cell or DNA biosamples and associated clinical data. (see definition section)*


In terms of references to ‘the public’ or PPI, we have removed all references to ‘the public’ which relate to the content of this article. However, there is a larger context to this article which is ‘public involvement in research’. Therefore we have...
<table>
<thead>
<tr>
<th>2. In the penultimate line of para 1 I didn’t understand what ‘translate’ means in practice.</th>
<th>Replaced ‘translate’ with ‘interpret’ to increase clarity.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Because it refers to ‘research in general’, the first sentence of para 3 claims more for the article than it delivers. The article focuses only on patients/carer partnerships in biobanks, and even then patient-focused biobanks (as distinct from Population biobanks like UK Biobank), let alone ‘research in general’</td>
<td>Term ‘research in general’ removed</td>
</tr>
<tr>
<td>4. In the penultimate line of para 3, insert ‘identify’ before ‘perspective’.</td>
<td>Done</td>
</tr>
</tbody>
</table>

**Definitions**

1. It would probably be appropriate to add ‘carers’ to those mentioned in the definition of ‘patient’

   Done

2. The specific definition of ‘biobank’ for this paper is very important (See Point 1 in Intro, above).

   Addressed in Point 1 (Intro).

   Additional definitions of biobanks inserted into definitions section

**Main theories and background**

1. I suggest purging references to ‘the public’ and ‘PPI’ in this section and the rest of the article. The article is clearly about patients, specifically, not about the public in general.

   We have removed all references to ‘the public’ which relate to the content of this article. However, there is a larger context to this article which is ‘public involvement in research’. Therefore we have not removed ALL references to the public, just the ones that relate to this article and its contents. See Point 1 (Intro) above.

2. I did not understand the meaning of the sentence ‘The idea of patient involvement can be difficult for researchers as it does not adhere to the traditional “scientific method”’, or the following sentence.

   Explanation:
   ‘Experiential knowledge’ (knowledge gained by having a personal experience of something) is not measured or evaluated using the same criteria as ‘scientific knowledge’. Therefore, in the eyes of many scientists, its value can be difficult to ascertain.

**Key messages**

1. I suggest adding ‘diagnosis’ to the options in the first sentence.

   Done

2. The emergence of patient-led biobanks is a very significant development. I was surprised that there was no mention of ‘Patients like me’ (http://www.patientslikeme.com/) and the evaluation of Librium done by AMLD patients.

   Patientslikeme is a ‘for-profit’ company that provides an online service to share/sell patient data for appropriate research. This does not match with our description of patient-representative organisations (i.e. not-for-profit – see new Definitions section), so it is not appropriate to highlight it here.

   As we are not familiar with the Librium evaluation, nor can find any readily-available information on it, we have been unable to include it.

3. I found it difficult to understand the relationship between the use of brief accounts of specific illustrative exemplars in this section and the longer Case Studies in the next section. The latter would seem better place in an Appendix, rather than breaking up the text in the way that they do.

   Explanation:
   We used brief accounts of AFM +Genetic Alliance as these are two well-established exemplars which we could not obtain sufficient information to warrant a case-study, but were deemed ground-breaking to warrant mentioning them at some point in the text.
**Conclusion**

The last sentence of para 2 notes the need for training if there is to be active participation by patients. You might mention what learning resources you recommend for this. Two with which I am familiar are Consumers for Evidence-Based Healthcare (http://us.cochrane.org/CUE) and Testing Treatments interactive (www.testingtreatments.org). [I edit the latter]

We have added the following text:

In-depth training and educational resources are made available (e.g. through the EUPATI Patient Expert Patient Training Course in 2015 and 2016, the EUPATI Internet Library which will become available in 2016 in seven languages, or Cochrane’s “Consumers for Evidence-Based Healthcare” (54)

**Reviewer 3 (Simon Denegri) comments:**

Minor revisions suggested for the case studies include the addition of information which gives some sense of the size of the biobanks; the inclusion of links within the case studies themselves as well as in the references and; some formatting of the case studies so they each begin with the name of the biobank, date established, host organisation and country or region.

Completed for all case studies.

A discretionary revision might be for the authors to identify in their conclusion areas of future work and research including the opportunity to assess the extent of public involvement across all biobanks etc, how to embed public involvement in other biobanks etc (these are simply suggestions).

Suggestion accepted and added into conclusion.

**Reviewer 4 (Eric Low) comments:**

1. Additional information could be included as to the benefits of bio-banking research for current and future patients as well as payers and healthcare systems.

See point 1 (Intro) in Reviewer 1’s comments

2. Clearer delineation could be made between the role of patients and the public. The words patient and public are often used together and interchangeably but the issues, interests and roles of each are likely to be quite different. Patients who are contributing to a disease-specific bank are likely to have different interests to a member of the general public giving tissue to a general bio-bank or who are involved in governance or consent. Clearer delineation could be made in the article and more consistent use of the each word when referring to levels and types of involvement

See point 1 (Intro) in Reviewer 1’s comments

3. more information on the role of PPI in ensuring the processes and mechanisms by which tissue is used for research and by whom could be included. Given the scarcity of samples and the difficulty involved in getting the right amount and type of tissue from which to do research is very difficult and therefore it can’t be wasted on doing mediocre research. it must only be used for the best possible research. Too often, tissue is seen as the property and asset of an institution or researcher - they may not be the ones best placed to use it as a research resource.

We believe this could be difficult as we cannot expect lay people to have the necessary expertise to distinguish between mediocre research and good research. We believe their role is to ensure the processes by which biobanks review applications is transparent and fair with the correct mix of people to ascertain the scientific value of the research.

We are aware of an example in this regard - the UK Breast Cancer Campaign Tissue Bank – where lay representatives are members of the Tissue access committees.
Also, as highlighted in our case study of the I.B.AHC Biobank, A.I.S.EA requested that one of the main evaluation criteria of the access requests, defined in the I.B.AHC protocol, was the non-duplication and the non-lucrative nature of the research projects requesting the access.

**Reviewer 2 comments:**

To be read and understood by a broad audience, it would be very helpful to have additional ‘explanations’ included in the text (and/or the Definitions section). This would also provide a better understanding of the excellent examples (to highlight the points) and case studies.

**Done**

<table>
<thead>
<tr>
<th>Reading the paper I needed: clarity on what a biobank is; and how patients/patient groups can contribute to their management and use for research/technology development: Biobank: an organized collection of human biological material and associated information stored for one or more research purposes. Specimen types include blood, urine, skin cells, organ tissue, and tumour tissue etc. Biobanks give researchers access to data representing a large number of people.</th>
<th>What a biobank is: Have added detailed biobank explanations as per Reviewer 1’s comments.</th>
</tr>
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<tbody>
<tr>
<td>How patients can contribute to their management/use;</td>
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<tr>
<td>In our view, the Case studies + Figure 1.1 provide clear evidence and examples on how patients and patient orgs can contribute to the management and use of biobanks.</td>
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<tr>
<td>It would be really helpful to have a description of biobanks, and the scope that they can cover. This is really important, particularly when talking about both patient led/controlled (and affiliations required eg with hospitals/clinicians for collection) and researcher/clinician controlled biobanks. For example, do they differ in collection; access to the samples/derivative information etc? Any differences need to be acknowledged. It is important to discuss how specimens are collected; the ‘ownership’ of the specimens and the information obtained from them; the size of the specimens, and so how much can be done with them and guidance on further testing. One controversy of large databases, of in particular genetic material, is the question of ownership of samples. Another important consideration is how the different biobanks are funded and if they are ‘commercial’ in any way (eg in development of new drugs, diagnostics). Biobanks in a range of countries are referred to – do they all follow similar standards (also patient led and clinician led)? Questions on governance, privacy, research ethics and medical ethics. In my following comments on the text I am again seeking clarity, from a patient/patient group and</td>
<td></td>
</tr>
<tr>
<td>Have added detailed biobank explanations as per Reviewer 1’s comments.</td>
<td></td>
</tr>
<tr>
<td>The variability of biobanks, as well as issues of access, collection, ownership, funding, standards, governance, ethics are all MAJOR issues in biobanking research practices and as such, are beyond the scope of this article. These issues are described (albeit briefly) in the ‘Key Messages’ section (paragraph III), with references provided in each case/issue. We hope this provides the level of clarity that reviewer 3 is seeking?</td>
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</table>
public perspective, and how this fits with the 'medical model'.

**Abstract**

Biobanks and biobanking research plays an increasingly important role in healthcare research and delivery as health systems become more patient-centered and medicine becomes more personalized. There is also growing acceptance and appreciation of the value that patients, patient advocacy organizations and the public can bring as stakeholders in biobanking, and more generally in research. Therefore the importance of active, early, and sustained engagement and involvement of patient and public representatives in biobanks will become increasingly relevant.

Point: **WHAT SPECIFICALLY DO THEY/ PATIENTS, PATIENT ADVOCACY ORGANISATIONS AND THE PUBLIC OFFER, IS IT TRANSPARENCY AND ACCOUNTABILITY (ESPECIALLY WITH REGARD TO GOVERNANCE AND ETHICS OR IS THIS A TWO-WAY RELATIONSHIP WHERE INDIVIDUALS CAN HAVE MORE CONTROL OVER HOW THEIR TISSUES [AND THE INFORMATION FROM THEM] ARE UTILISED AND HOW THIS MAY BENEFIT THEM?)?**

We believe it is transparency, accountability and the insight they have as patients. What they bring is (i) assessing and defining the right priorities in research that will make it meet patients’ needs, (ii) facilitating communication and increasing patients’ consent that patients give to donate their tissue, (iii) contribute to decision making on use of tissue etc. All of this is stated at different points in the article.

Organising and facilitating patient and public involvement in biobanking takes considerable time and effort for all stakeholders involved. Therefore, for any biobank operator considering involving patients and the public in their biobanking activities, consideration of best practices, current guidance, ethical issues, and evaluation of involvement will be important.

Point: **IS THIS MORE ABOUT EVALUATION OF THE PROCESSES FOR INVOLVEMENT (AS FIRST STEP)?**

Explanation: We consider this important point not as a “first step” but as a “next step”. As addressed following Reviewer 3 (Simon Denegri)’s comments, there is now a significant opportunity to assess the extent of patient and public involvement across all biobanks, and to evaluate how to embed public involvement in other biobanks. This could be done via several of the leading international biobanking networks (e.g. BBMRI-ERIC, ESBB, ISBER, P3G, etc.).

In this article we demonstrate that patients are much more than donors to biobanks - they are collaborators at the heart of biobanking with an important voice and a unique perspective, which can be an extremely valuable resource for all biobanks to utilise. NEED TO ALSO EMPHASISE THE ETHICAL ASPECTS AND THE ROLE OF PATIENTS, PATIENT GROUPS AND THE PUBLIC IN THAT

Ethical aspects are highlighted in “Key Messages” Section - Establishing the patient position on biobanks:

“In particular, the document recommends that patient involvement should be extended to ethical aspects such as informing Research Ethics Committees (RECs) of patients’ interests; patient rights over their donation; access to samples from research groups out of the country; possible new use of existing samples and/or discontinuation of the biobank.”

And the section III: Capturing Patient and Public Perspectives and Concerns:

“Biobanks create a number of ethical and legal issues related to research governance, privacy, informed consent (32), control and ownership (33), withdrawal of samples and consent (34), commercialisation (35), return of results and
incidental findings (36). For biobanking operators, gaining a greater understanding of the perspectives of different stakeholders, including patients and the public, can offer insight into the nature and context of these ethical challenges and can assist in public engagement.”

In addition, several of the case studies (e.g. Italian Biobank IHC; Wales Cancer Bank) describe in detail how the role of patients has contributed to improving ethical aspects of their respective biobanks.

The case studies herein provide examples of good practice of patient and public involvement in biobanking as well as outcomes from these practices, and lessons learned. Our aim is to provide useful insights from these efforts and potential future strategies for the multiple stakeholders that work with patients and the public involved in biobank-based research. – I SEE THE IMPACT AS BEING IN THE LONGER TERM, IN COLLABORATION WITH CLINICIANS/OTHER STAKEHOLDERS AND THE RESEARCH AND PRODUCTS OF THAT RESEARCH. MAY ALSO BE FINANCIAL ISSUES WHERE THE PUBLIC/TAXPAYERS HAVE A RIGHT TO A SAY.

We agree that the ultimate impact of patient involvement in biobanking is in the long-term.

**Introduction**

Biobanks do not operate in isolation. They exist within a diverse “ecosystem” of stakeholders which includes the public, patients, healthcare workers, scientists, government, funders, healthcare providers, ethicists, regulators and others. The sheer variety of stakeholders involved in maintaining biobanks reflects the diversity of biobanks themselves (1). Biobanking operators such as hospitals, research institutes, pharmaceutical companies and patient organisations translate their own biobanking activities differently, very often according to the background of the founding organisation and the particular context in which the biobank is embedded. Point: THE GEOGRAPHICAL LOCATION AND WHETHER LOCAL, NATIONAL OR INTERNATIONAL IS ALSO IMPORTANT.

The role of patients and the public in biobanking activities has been viewed traditionally as biobank participants rather than as collaborators in the design, development and ongoing operation AND GOVERNANCE of biobanks.

Text modified to include ‘geographical considerations’

**Definitions**

The term ‘patient’ in this article refers to the patient, his/her relatives, or patient advocates as collaborative or representative voices of patients. The term “patient involvement” in this article refers to ‘involvement in research’ (i.e. being actively involved in the research process itself, rather than being participants or subjects of the research).

As recommended by Reviewer 1, specific references to the public have been removed.

Definition of patient organisation added.
<table>
<thead>
<tr>
<th>Discretionary changes</th>
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<tbody>
<tr>
<td>Re quote: DOES NOT EXPLAIN IN WHAT WAY – SO NOT PARTICULARLY HELPFUL?</td>
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<tr>
<td>I: Emergence of patient-led biobanks</td>
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<tr>
<td>Although an ever-increasing number of patient organisations are establishing their own biobank, the emergence of patient-led and patient-run biobanks began only relatively recently. Individual patients, and representative patient organisations, many unsatisfied with the speed of research into their respective conditions, established their own biobank, primarily to enable them to provide a greater contribution and influence on research in their disease area. This may be a good place to say something about the patient organisations that are active in this area (or refer to in an appendix or the like); and it would be really helpful in providing an understanding of ‘the different ‘types’ of patient groups’ and therefore the different roles (which are really clearly set out here)</td>
</tr>
<tr>
<td>Three case studies of patient-led biobanks in the USA, Germany and Italy are provided in this article as examples in this regard. List – as is not the immediate following text</td>
</tr>
<tr>
<td>Another example worth highlighting is the Généthon DNA and Cell Bank driven by the French patient organisation Association Française contre les Myopathies (AFM). AFM become active in genetic research in the 1980s how/in what way?</td>
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<tr>
<td>IV: Education and Training</td>
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<tr>
<td>It is commonly accepted that in order to ensure that biobanks are developed and used to their full potential, it is essential that both researchers and other stakeholders associated with biobanking have access to the best possible training and career development opportunities at all stages of their professional life. Therefore, in order to facilitate</td>
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</table>
**active participation of patients and patient organisations in biobanking activities, IN PARTNERSHIP WITH HEALTHCARE SERVICES/CLINICIANS (AND RESEARCHERS)?**

We have revised the section as follows:

A number of ongoing patient-led training initiatives in this area are helping to raise awareness of the contribution that patients can make as partners in research. The European Patients’ Academy (EUPATI), an EU-wide, public private partnership that is led by the European Patients’ Forum and is funded by the Innovative Medicines Initiative (IMI), provides in-depth training of patient advocates as well as educational material on all aspects of medicines research and development (R&D) including key topics relevant to patient involvement in biobanking (e.g. the principles of non-clinical development, exploratory and confirmatory clinical development, informed consent processes and regulatory affairs). EUPATI’s Expert Patient Training Courses is currently training 50 patient advocates, and its Internet Library will provide this information in the form of web-based educational resources to the health-interested general public in seven languages in 2016 (12).

<table>
<thead>
<tr>
<th>Chordoma Foundation Biobank, USA</th>
<th>The Biobank is funded by the Chordoma Foundation. The Board of the Chordoma Foundation is also the Board of the Biobank.</th>
</tr>
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<tbody>
<tr>
<td>FUNDING/GOVERNANCE?</td>
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<tr>
<th>Case Studies Patients’ Tumor Bank of Hope (PATH Biobank) run by the PATH Foundation, Germany</th>
<th>PATH’s board consists of three persons. At the moment all three are breast cancer survivors. As stated in the text and cited by the referee, PATH’s statutes say that at least 2 of the members of the board have to be breast cancer survivors. Text modified in new version to: The current PATH board consists of 3 breast cancer survivors, which according to its statutes, at least two members have to be former patients.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL ARE SURVIVORS? (ALSO SEE LAST SENTENCE OF THIS PARA)? THIS IS HOW IT READS AND SO DOES NOT AGREE WITH THE FOLLOWING SENTENCE: According to its statutes, at least two members of the PATH board have to be breast cancer survivors. In addition to the representation (e.g. at conferences and towards scientific partners), the board guides the activities and direction of PATH biobank. As breast cancer survivors, all board members have an inherent motivation to contribute to the cure of this disease.</td>
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| Italian Biobank AHC, Italy | The I.B.AHC Biobank and Clinical Registry is entirely funded by the Italian Patient Association A.I.S.EA. The I.B.AHC Project was designed and it is coordinated and managed by A.I.S.EA in partnership with its Scientific Committee and with the Ethics Committee of the Scientific Institute “E. Medea” that hosts the biobank. In particular, A.I.S.EA defined the I.B.AHC protocol together with all its partners, for the governance and the management of the biobank and of its linked clinical registry. According to the I.B.AHC protocol, A.I.S.EA is actively involved not only in the management of the I.B.AHC Biobank and Clinical Registry (for the recruitment of |
| Patient involvement as part of biobank governance – IN THE MEDICAL MODEL? | the patients and of their referring physicians and for the data and samples collection), but also in its Governance. In particular, A.I.S.EA participates in the evaluation of the access requests and in the communication of the research results to the patients, in a close and equal collaboration with its Scientific Committee and with the Managers of the Biobank and of the Clinical Registry). |
| Wales Cancer Bank, United Kingdom QUITE A BIT OF DETAIL – TOO MUCH? | We are not certain what this point means? |
| Nottingham Health Science Biobank, United Kingdom SIMILARLY | Having reviewed the level of detail in both the Wales Cancer Bank and Nottingham Health Science Biobank, we conclude that the level is consistent with that of the other case studies, and have chosen not to reduce either. |