Author’s response to reviews


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Author’s response to reviews:

Dear Dr Oerlemans,

Thank you for your valuable review for our manuscript. Your review really helped us to improve it. Following the comments of the reviewer Dr Heidi Beate Bentzen about the language of the manuscript, we have sent it to professional editing service for proofreading. The attached version is the modified one. For other comments by the reviewers, kindly find our responses below.
Review 1

There are no clear objectives of this study. The authors failed to define their aims and how they can reach these aims.

- The objectives of this study, as mentioned in the background section of the manuscript are the following

1. To determine the knowledge of the Egyptian patients about the term "Biobanking". This is important since the term is new and it could be confused with other "Biological banks". In a previous experience with biobank education for medical students (reference no 19 in the manuscript), they confused the term with stem cell banks, corneal banks, as well as sperm banks. We wanted to estimate the level of knowledge about the term and to know if this knowledge will affect the level of participation in biobanks.

2. The second objective is to assess the attitudes towards participation with their samples, and to identify sociodemographic factors associated with these attitudes. We also explored possible factors that might influence participation. Although the attitude towards participation with samples in medical research has been studied in Egyptians in other studies, we tried to explore other aspects that can affect this attitude. Moreover, the correlation with knowledge about the existence of biobanks has never been studied here before.

This has been explained in the background as follows" Since all biobanks in Egypt are disease-based, the objectives of this study were to determine the degree of knowledge of the Egyptian patients with regards to biobanking, their willingness to contribute samples to biobank-based research, and to detect any possible correlation between knowledge and attitudes. We also aimed at identifying sociodemographic factors associated with these attitudes. We sought to detail the possible factors and fears that may discourage the patient group of stakeholders from participating in biobank-based research, including possible concerns with regards to confidentiality, and the degree with which they perceived personal gain from such research. Information obtained from this preliminary survey can be used to create more focused surveys in the future. The results of this study should also be a helpful to individuals involved in research in Egypt as well as other developing countries with similar demographics. The conclusions presented in this study should also help in the development of educational campaigns geared towards addressing patient concerns and misunderstandings. Hopefully, our findings will also help in the development of a set of national ethical biobanking guidelines for Egypt."
The used tool is not built on concrete bases, and lacks validity. Moreover, the questions were about many issues; however none of these issues had been sufficiently and deeply addressed. It is difficult to recognize how and why these questionnaires have been selected.

- It is true that we tried to cover many issues. This survey is an exploratory survey that tries to cover different issues that might concern potential biobank participants in Egypt. The questions were created based on the published literature taking into account the unique characteristics of the Egyptian society. We tried to consider the concerns of members of this community including political aspects. This can be followed by more focused surveys and educational activities according to the results of this study. Moreover, the corresponding author of this manuscript is working with others on the development of biobanking ethical guidelines in Egypt. The results of this study will also be taken into consideration during development of these guidelines.

Concerning validity, the following paragraph was added to the methods section under recruitment title "A preliminary phase was conducted to assess validity and reliability of the questionnaire before its wider use. Initially, three Egyptian experts in the field of biomedical research were asked to assess the degree to which items in the questionnaires are relevant and correctly measure the knowledge and attitudes of patients with regards to biobanking. After that, minimal corrections were done. The next step was pretesting of the questionnaire. We included 30 randomly selected patients; 10 from each of the three institutions. They were asked to respond to the questionnaire twice; the two settings conducted three weeks apart. Data collected were used to assess internal consistency reliability using Cronbach’s alpha and to check test retest reliability (by computing the intra-class correlation coefficient). The results showed adequate internal consistency reliability (Cronbach’s alpha =0.75). Moreover, the intra-class correlation coefficient was 0.98.”

The questions (especially in the questions presented in the tables 3 & 4) are fragmented, and could not been well gathered in the chosen themes which appeared vague and none harmonized.

- To be more consistent, few questions have been removed from table 3. So, that the theme of table 3 will be related to the issues of privacy of data (security, access and sharing). And table 4 will address potential rights of participants (including return of results).
The other problem is related to research community which may not be the proper participants for such research except for the first part about "Knowledge about the term Biobank", and the part titled: "Attitude about sample donation for research". When 81.1% of participants never heard about Biobank, how we expect they will be able to develop sufficient understanding of its ethical challenges, which in fact complicated aspects, such as privacy, confidentiality, ownership, etc. As an example, there is a question about maintaining privacy and confidentiality of information during courses scientific research. This is not an easy question! How we can expect participants (75% of them have less than university education, and 25% are illiterate) will be able to perfectly understand it, and how they can distinguish the two terms (privacy & confidentiality) even as we know that very educated people may not be able in fact to recognize the difference.

As mentioned, the objectives of this study are to assess knowledge about biobanking and related ethical issues and to correlate this with sociodemographic factors including educational level. Our goal was to ask about sensitive ethical issues in a simple way that is easily understood by the average person. Since potential participants of biobanks come from different educational backgrounds, and the informed consent should be discussed with them, we wanted to explore the opinions of persons from different levels of education. As mentioned in the manuscript, the questions were delivered in Arabic. It was communicated through trained persons using colloquial language. Participants were encouraged to ask questions if they don't understand the question.

For the question about privacy, the Arabic for words for "privacy" meant also "secrecy", which can be easily understood by different educational levels. Other questions in table 3 also explained this point in different forms. This included the following question about data "My medical and personal information may be stolen from the biobank and used against me in some way." And this question about access "The police have the right to access the donated samples when necessary."

In the same line, the sample size seems very small for a big country, such as Egypt, with a population around 100 million.

Concerning sample size, it was mentioned in the limitations section that this represents one of the limitations of the study. However, we tried to use a sample from the big 3 main regions in Egypt (North, capital and south) as mentioned in the methods, and sample size was calculated through an expert statistician. This was explained under the Recruitment Part in the method section" The sample size was determined using the Epi Info 7 software based on the expected probability of positive attitude of patients towards biobanking (83.7%) to achieve 80% power of study at 95% confidence limits. The calculated sample size was 210 patients (70 from each study setting)."
The reference used to proof that limited studies were conducted in developing countries is an old reference (2005), while there are many other research had been conducted later.

- This has been modified into" Recently, some studies have attempted to examine the willingness of patients in some developing countries to contribute their biological samples to biobanking activities. These studies have however come short of examining every possible aspect of this key stakeholder group’s possible perspective." And the reference was removed.

- A pilot study was not conducted. This should be done first, and it will be very helpful.

- The following paragraph was added" A preliminary phase was conducted to assess validity and reliability of the questionnaire before its wider use. Initially, three Egyptian experts in the field of biomedical research were asked to assess the degree to which items in the questionnaires are relevant and correctly measure the knowledge and attitudes of patients with regards to biobanking. After that, minimal corrections were done. The next step was pretesting of the questionnaire. We included 30 randomly selected patients; 10 from each of the three institutions. They were asked to respond to the questionnaire twice; the two settings conducted three weeks apart. Data collected were used to assess internal consistency reliability using Cronbach’s alpha and to check test retest reliability (by computing the intra-class correlation coefficient). The results showed adequate internal consistency reliability (Cronbach’s alpha =0.75). Moreover, the intra-class correlation coefficient was 0.98."

- In the paragraph titled: "Attitude towards donations", only the first question was about biobanking, while the three other questions were about scientific research in general.

- Since we explained the definition of biobanks and their role in research in the first paragraph, we used the term "scientific research" in addition or exchange for the term "Biobank" in some questions.

- Why the participants were asked about sending samples to persons and institutions outside, but not inside?

- We asked about what we assumed could be a potential concern for participants. As mentioned in the discussion "Sample sharing across borders raises social and political debates in Egypt. Recently, a law tackling clinical research was proposed and discussed in the Egyptian Parliament. In its current version, the proposed legislation would put restrictions on transporting samples out of Egypt except after the approval of the county’s security apparatus. Again, this reflects the public concerns as well as the concerns of some policy makers regarding the possible abuse of these samples and data that would be collected from research conducted on them." And
as mentioned in reference 25 "In a previous study, Egyptian patients preferred sample sharing with Arab countries to Western countries"

o The question; "Anyone can have an access to donated samples". What do you mean by "Anyone"?

• The aim of this question was to assess the level of knowledge about access to samples and data. Anyone here means there is no security for protection of samples and data. However, and since we now think it is too broad and non specific, this question has been removed from table 3.

o The discussion part was mainly just a comparison with other studies, but no real analysis was provided.

• Few statements were added to provide more analysis of the data. Here are two examples

"We think that this limited knowledge is not just related to the novelty of the concept in Egypt, but also because the term itself might be confusing to many people. The prefix "Bio" in the word "biobank" does not refer exactly to the function of a biobank. In a previous work that attempted to introduce biobanks to undergraduate students of life sciences, they confused the term “biobank” with stem cell banks, corneal banks, as even sperm banks."

"These results make sense, since about 25% of participants in our study were illiterate, making it difficult for them to have proper knowledge of biobanks or their roles as research institutions."

Reviewer 2

o Page 5, Line 14: There's an opportunity here to touch on the scope and diversity of different kinds of biobanks and to reinin the reader's expectations about the paper's focus. It may be useful to specify that this research was conducted with a fairly broad conception of 'biobank' and that it didn't focus specifically on only one mode of conducting biobank research. With that said, the authors might want to think about the extent to which the recruitment of patients from a hospital setting might suggest tacitly that the kind of research under discussion is specific to a certain disease or set of conditions.
- A line was added in background section about the types of biobanks "Several types of biobanks exist, including disease-based, population-based, genetic, commercial, and virtual biobanks." This was followed by explaining why we focused on patients only as potential participants "Since all biobanks in Egypt are disease-based, the objectives of this study were to determine the degree of knowledge of the Egyptian patients with regards to biobanking". Although data was collected from patients only, their groups were diverse, where data was collected from different regions and from patients with different clinical conditions, which was mild in some cases or more serious (cancer patients).

- Page 7, Lines 20-23: The authors might want to give some attention to their chosen definition of 'biobank.' As it's communicated in the paper, the definition that was conveyed to participants doesn't seem exceptionally clear or accessible. I'm worried that participants might not have completely understood the subject in issue based on this statement. Was there a strong reason for using the definition that's expressed in the paper and did participants have an opportunity to ask clarifying questions? In the alternative, it might be that this way of explaining what biobanks are did actually lead to a decent degree of understanding on the part of participants.

- We tried to communicate a definition that is both scientific and easy to understand. Our definition is close to the definition of BBMRI-ERIC where they define a biobank as “a place to store all types of human biological samples, such as blood, tissue, cells or DNA. It also stores data related to the samples as well as other biomolecular resources that can be used in health research.” The following statement was added to the methods section “The entire interview was conducted using colloquial Arabic language. Participants were encouraged to ask for explanations if they did not understand any question.”

- Page 10, Table 2: This is a general comment about the way questions are phrased. At the moment, the questions are worded with various forms of 'I think I will donate samples to the biobank…' It sounds like researchers were trying to measure the degree to which participants are planning to participate in biobanking research. I can't imagine that this was the intention. Given the context of the article it sounds like researchers were trying to measure something like the extent to which participants would be comfortable with donating samples to a biobank. I assume that these questions have been translated to English. It would be interesting to know if the subtle connotation in favour of planning rather than comfort is attributable to this.

- Several questions were created to assess the willingness of the patients to participate with their samples. We started with the general question " I think I will donate samples to the biobank…" , then more specific questions about a non invasive sample (urine), more invasive sample (blood), and a specific type of research (genetic research). This was added in the text of the manuscript.
This section of the paper is a bit unclear. It's hard to know if researchers are describing views about the rights participants should have or do have. Was this set of questions trying to assess what rights biobank donors ought to have? Or were researchers trying to understand how well participants understand what their rights are in practice? As in the comment above, this is a subtle, but important difference.

- We wanted to explore what participants assumed their rights are. This might be an established right such as the right to withdraw consent, or a debatable right such as return of research results, or even something like a financial compensation for participation, which is not a right at all. We added the word "potential" to clarify this point.

Page 16, Line 16: The authors say that participants 'did not have any obstacles that could affect their decision' to participate. This overstates what the data supports. At best, the data shows that a majority of study participants were not concerned about the specific potential obstacles presented by the research team. I think the authors can keep this claim but should address the nuance represented in the data.

- This has been modified in the discussion into the following statement "Interestingly, most interviewees in this study believed in the benefits of medical research and participation. The majority of them were not concerned about the specific potential obstacles presented to them"

Page 19, Line 10: The view that participants did not 'think that the samples and data should be used against their will' is unclear. Does this mean that participants expressed the need for researchers to obtain consent for each proposed use of donated samples and data, or does this mean something more general? Consider clarifying.

- We added this statement "We did not ask participants about whether this would mean a willingness to give broad consent to the use of samples for several biobank-based research purposes at the same time, or only a specific consent. This represents a limitation of this study, which should be taken into consideration in future specific surveys."

Page 19, Line 17: The term 'security authorities' should be defined. This could mean a range of things and it's unclear to what the authors are referring.

- This has been replaced by "law enforcement" to state that these are the meant authorities.
Page 21, Line 17: The claim that there are 'no cultural or religious barriers against [biobanking]' seems much too strong. Given some of the methodological constraints expressed by the authors, this claim might warrant being dialed back. This claim might also be somewhat more sweeping than one would expect in light of other research in this area. Ma'nZawati and colleagues ('Barriers and Opportunities in Consent and Access Procedures in Low- and Middle-Income Country Biobanks: Meeting Notes from the BCNet Training and General Assembly,' 2018), for example, found that religious considerations among LMIC biobank managers were a prominent issue. The important role of religion in the cultural practices of a number of LMICs, while potentially not a major barrier, was nevertheless found to be of sufficient interest to warrant careful consideration. On this point, the authors may wish to put their findings in conversation with the literature, in which there is some indication that religion will end up playing a key role in achieving the public trust with respect to biobanking initiatives.

- The text has been modified into the following "Although there is limited knowledge about biobanking among Egyptians, there is a general positive attitude towards sample donation and no specific cultural or religious barriers against it according to our findings." Concerning the role of religion, we tried to compare our results with the situation in countries with similar situation and culture (Jordan), and with other countries with different culture (USA). We also tried to search for the opinions of scholars of the two main religions in Egypt (Islam and Christianity). While we found the results for the opinions of Muslim scholars, we couldn't find sources for Christian scholars, which might be a point for further research. The corresponding author of this manuscript was collaborating on a manuscript about the relationship between religion and biobanking in Africa, but this project is on hold at the current moment.

- Some aspects of the methodology section would benefit from clarification, particularly with regards to the recruitment of participants. It is mentioned that the questionnaire was pre-tested during a pilot study (line 6-7). However, it is not mentioned who was involved in the pre-testing. I'm assuming the pilot study was done with a similar population than the one under study, but this should be made explicit.

- This was explained in the following paragraph "A preliminary phase was conducted to assess validity and reliability of the questionnaire before its wider use. Initially, three Egyptian experts in the field of biomedical research were asked to assess the degree to which items in the questionnaires are relevant and correctly measure the knowledge and attitudes of patients with regards to biobanking. After that, minimal corrections were done. The next step was pretesting of the questionnaire. We included 30 randomly selected patients; 10 from each of the three institutions. They were asked to respond to the questionnaire twice; the two settings conducted three weeks apart. Data collected were used to assess internal consistency reliability using Cronbach’s alpha and to check test retest reliability (by computing the intra-class correlation coefficient). The results showed adequate internal consistency reliability (Cronbach’s alpha =0.75). Moreover, the intra-class correlation coefficient was 0.98."
More importantly, the authors mention that patients were recruited at clinical site (lines 12-13), without giving any more background information on the patients who were recruited. Why were they at those clinical sites? Were they recruited before or after meeting with a doctor? Were these patients accompanied? Were they experiencing any symptoms (pain, discomfort, etc.) at the time of the survey? Etc. All of these factors can be sources of bias and it would be important to address them.

- This was clarified in the following statements "These research coordinators approached individuals while waiting for their turns to be examined at the outpatient clinics and briefly informed them of the aim of this interview-based study." And "Critically ill and apparently easily irritable patients, as well as patients in apparent pain or those with apparent diminished cognitive capacity were all excluded from the study."

The use of the term 'interview' (line 19) is confusing. Given the high number of illiterate 25.5% and lower literacy participants (p.9), I'm assuming the authors relied on a researcher-administered questionnaire as a method of data collection. If that is the case, some information should be provided regarding who administered the questionnaire and what steps have been taken to minimize experimenter effect.

- This statement was added "Research coordinators who were trained to communicate the idea of the survey then visited the three clinical sites three times a week to recruit patients. While some of these coordinators were public health physicians; others were house officers who received specific training before visiting clinical sites."

Reviewer 3

- Language: The language is poor, and needs extensive editing throughout the paper. There are many grammatical errors.

- The manuscript was sent to a professional language editor for improvement. The attached version is the modified one.
Abstract: You report that «Fifty eight percent were willing to participate in a genetic research project, 45.6% didn't support sharing their sample with pharmaceutical companies, and 32.4% agreed to share their samples with institutions abroad.» and further that «However, they showed concerns regarding participation in genetic research and with sharing their samples across borders or with pharmaceutical companies.» These sentences should be rephrased so that the percentages either all describe the ones who were positive or all the ones who were negative to sharing.

- This has been modified into "55.4% supported sharing their sample with pharmaceutical companies"

Page 5 Lines 5-7: I would also mention fundamental rights (human rights)

- Yes. Sure

Lines 11-13: Please specify what type of data you have in mind (Demographic data? DNA data? Phenotypic data?)

- This has been modified into "In biobanks, the process of collecting and storing of harmonized high quality biospecimens and the careful recording of demographic, clinical, genetic and other data"

Page 6

Lines 1-2: Only misconceptions? Can't participants also be hesitant due to a correct understanding of the research methodology? Also, «level of understanding» seems to similarly imply that the problem is a lack of knowledge or understanding, however, well-informed individuals may also choose not to participate in research.

- The mentioned factors are just examples, and are not all the factors that may affect participants' decision. We modified the text into "Unexamined factors that may influence patients’ willingness to participate in biomedical research include the possible lack of perceived benefits from participation, the degree of availability of information with regards to the natural and methodologies of biobank-based research, and the level of confidence patients have in the integrity of clinical investigators"

Page 7 Line 10: From here on, they should be referred to as research participants.

- Done. The word "patients" was replaced with "participants".
Page 8 Line 9: Please also mention when the study was conducted.

- Done. Statement was modified into "The data was collected between March and June 2018."

Page 9 It said on page 7 line 5 that only patients over 18 years of age were recruited. However, in the table on page 9, the age of the participants ranges from 14-80.

- Thanks. This was corrected in the table.

Page 12: Please also explain the other findings from table 3 in the written text regarding international sample sharing and access by pharma, police and others.

- The following statement was added "Of those interviewed, 32.4% agreed to allow the sharing of their samples with researchers abroad. Only 27.8% supported giving access to such samples to pharmaceutical companies. On the contrary, as many as 71.8% believed that law enforcement agencies should have an access to biological samples stored at biobanks, whenever they deemed it necessary."

Page 13: Please also explain the finding regarding payment from table 4 in the written text.

- The following statement was added "When we asked participants what they believed the rights of donors of biological samples to be, only about 25% thought donors should receive financial compensation in exchange for donating samples to research, while 51.3% thought that a participant should be able to ask to collect his samples after participation."
Page 17: Line 1: Please explain what you refer to by «playing God». Were the participants asked why they answered as they did? Or are these guesses based on the literature?

- Playing God means manipulation of genes and traits. Participants were not asked more details about their answers. So, these are guesses based on the literature.

Page 18: Lines 2-3: Why is sample sharing with Arab countries preferred? Did they say?

- This was added in this statement "This perhaps reflects more trust of Egyptians in Arab countries which share some aspects of culture as norms, values and religion with Egypt. In the aforementioned study, researchers based this preference by pointing to concerns regarding the type of research that might be conducted on their samples, commercialization issues, as well as their religious beliefs."

Page 18 Line 7: Interesting. Which authorities?

- Security. Transfer of samples outside Egypt must pass through security apparatus.

Line 15: Often such laws make exceptions if the samples have been processed. Does the proposed Egyptian law make any such exceptions? A lot of research is conducted in collaboration between private and public partners; do you see any challenges with this given your findings? Will such collaborations be difficult?

- The law has not been approved, yet. There is a lot of debate about it. After approval by the parliament, the president objected to it (ref no 33). The article about transfer of samples across borders is one of the articles that the president objected to. That's why we were cautious and used the following statement "Sample sharing across borders raises social and political debates in Egypt. Recently, a law tackling clinical research was proposed and discussed in the Egyptian Parliament. In its current version, the proposed legislation would put restrictions on transporting samples out of Egypt except after the approval of the country’s security apparatus." Answering your question, there is a lot of collaboration between Egyptian researchers and researchers abroad. However, transport of human samples is quite difficult, but possible once the needed approvals have been acquired.

Line 19: …shared with specific entities or (I would think also) if it is genetic data.

- Yes.
  • The following statement was added "This data includes clinical, laboratory as well as genetic data."

o Lines 12-13: This is also in line with human rights
  • Yes, sure.

o Page 20: Line 9: Only one (quite old) reference. This is a much debated issue in the literature so I would add some more references to show the current state of the debate.
  • A new reference from 2017 in the form of guest editorial (no 43) was added.

o Lines 9-11: Yes, and there are also practical issues that have been reported in the scientific literature related to whether it is feasible to feed results back to research participants.
  • Yes. Sure. And we added a statement about this" Dealing with this issue is not easy, since researchers and physicians may not know exactly what and how to communicate research results with participants. We think that the development and communication of national ethical biobanking guidelines in Egypt can help settle these questions and give guidance to medical researchers."

o Page 21: Lines 2-3: I would think that similarly to Islam, one can probably find literature related to principles + to charity as mentioned on line 10
  • Yes. We also think so, but we couldn't find sources to support this.
Page 22: Lines 7-8: Only verbal consents have been obtained from the research participants, according to the authors because the study did not involve confidential data or intervention. Page 8 line 4 indicates that participants were asked about demographic data and religion, and page 7 line 5 indicates that they were all patients. Both data about religion and health is often considered sensitive data. On page 7 line 17 it says that the verbal consent was documented (How? Recording? Please explain). In the table on page 9, 25.5% of the participants are described as illiterate, and this may help explain the choice of consent method. I assume that the procedure chosen is in line with Egyptian legislation. I would like to see more thorough information about the Egyptian legislation here and some information about how the rights of particularly the illiterate adult patients who participated in the study were ensured. Please also add information about how data protection was ensured.

• We considered approval of participation as a verbal consent. The first question in the form was "Do you agree to participate in this research? The application form didn't contain a section for the name, so the participant couldn't be identified. Moreover, this statement is present in the methods section" Participants were de-identified using a unique code, which was coded to the individual's demographic form.". Concerning regulations, when an illiterate person is asked to participate with his samples at the Egypt National Cancer Institute biobank, there is an SOP to regulate this. This paragraph is copied from the SOP "If the subject/representative cannot read an impartial witness to be present during the entire consent discussion to attest that the information in the consent form and any other information provided was accurately explained to, and apparently understood by the subject/representative, and that consent was freely given. The witness may be a family member or friend. "This applies to other biobanks in Egypt as well.