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Workshop Proceedings: Informed Consent in Biobanking–from the Key Barriers, Challenges, and Perceptions to Digital Innovations

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INTRODUCTION

Biological material of human and nonhuman origin has been collected for decades, creating repositories through the years that serve as source for research and education, with the ultimate goal to establish a high-quality healthcare system on international levels and to introduce novel therapeutic approaches based on personalization.[1] *Biobanking* is a general term used for the collection, storage, and procurement of biological materials, and its standard discipline. Biobanking has evolved from small university-based repositories for specific research to infrastructures that accommodate biosamples for large-scale national and international purposes, annotated with related clinical data and information, essential for fundamental science.[2,3] Collection and utilization of human biospecimen in all kinds of research activities have become a priority to health-related organizations; biospecimens have increased rapidly both in size and in number, leading to new trends and needs in biobanking that must incorporate big data and modern technologies requirements.[4]

As the biobank market grows globally, international collaborations for sample collection and dissemination have expanded. The demand for evolution in biobanking best practices seems to be unavoidable, so as to prevent not only technical issues in biospecimen collection, processing, and storage but also ethical, legal, and social issues arising from the extended use of biospecimens and their primary and secondary data in new research areas.[5,6] For these purposes, standardization of procedures for both biosample and associated metadata management and tracking are essential for current biobank operational systems and biospecimen quality assurance.[7]

Biobanks' organization and operation are based on models of working processes as well as national and international regulatory standards for compliance. These processes ensure, on one hand, the proper biosample handling and link of data, and on the other, donors' autonomous rights and data protection.[8] International best practices and guidelines for biospecimen handling and facilities requirements that can assure certification or accreditation are already implemented in biobanking networks.[9] In addition, inventory database systems for tracking are specifically designed to meet federal requirements related to data privacy and security.[10] Nevertheless, sets of compliance requirements for data protection, seem to be more complicated on international levels, considering the main regulations applied in the European Union and United States.[11,12] Despite their differences, both sets of standards set the same following goals: to protect individuals' privacy by securing and regulating current and downstream data collection, transmission, analysis, and disclosure; and provide them with rights over their biospecimens and sensitive data.[13,14] But, these diverse regulatory schemes and approaches of biobanking governance among countries might lead to significant barriers in biosample export and authorization for worldwide utilization in research activities.[15]

As part of the regulatory schemes that have been set, one of the most important principles in current biobanking and research is the consent procedure by which donors' give their permission for future biosample and data processing.[16] Informed consent is a mandatory part of the donors' welfare system; it is required for any type of research-related activities that use human beings as subjects, combining ethical, legal, and practical implications.[17,18] The main scope of this procedure is to provide information to participants for data disclo-

sure. This information empowers their decision-making and their autonomous choices by providing an adequate understanding beforehand of the research program they're going to be involved in, as well as their current and future rights.[19] Regulations and government standards implied in biobanking compared with other research activities, such as clinical trials, have significant points that should be taken under consideration as biobanks store and manage large amount of biosamples annotated with primary and secondary data for a long period of time.[20] Consequently, samples will be required in new research activities over the years that cannot be predicted or are not planned yet, making the implementation of consent procedure a challenge that should be carefully designed to be complete and valid, protect all parties, and comply with standard requirements.[21,22]

Overviewing biobanking evolution and operational systems, consent modifications over the years have created six different models of consent types that are currently applicable to biobanks.[23] Each of the following consent types described below set and retrieve specific rights to donors and biobanks, respectively, upon biosample and related data, and actually predetermine the future utilization of both[24–28]:

1. Blanket and/or broad consent: participants donate their samples and related data for a broad spectrum of future studies without any restrictions or specific limitations.
2. Study-specific consent: participants donate their biosamples and related data only for a specific research study.
3. Tiered consent: participants donate their biosamples and related data, being enabled to partly tailor their consent preferences, but only for specific study types.
4. Metaconsent: participants donate their biosamples and related data, being enabled to choose their consent options for specific categories of data within different types of research tiers.
5. Dynamic consent: participants donate their biosamples and related data, being enabled to participate in their consent status monitoring and modification associated with research activities of biobanks and other entities.

Within the framework of donors' rights for autonomous choice, they can choose their consent status, which represents their preference for future authorization of biospecimens and linked data given to all subsequent entities involved.[29] More specifically, they choose the appropriate identifiers and/or alphanumeric code that should be linked to their personal data to assure their preferable level of anonymization, data protection, and further contact.[30] In many cases original identifiers are irreversible, having been stripped from identifying data and making it impossible for anyone to link the biospecimens to their sources. Other identifiers are coded, allowing the possibility of eventually finding the original source. The coding actually raises significant questions and issues; for example, what should biobanks do with sufficient data that cannot be used, and/or what should be done in circumstances of possible hidden medical conditions that are accidentally identified during random research?[31]

Addressing such issues and other limitations, barriers, current, and future challenges in research-related activities in biobanking sector, along with the right consent application for the best interest of all parties, was the main scope of the virtual workshop that took place on May 16, 2021, as part of International Society for Biological and Environmental Repositories (ISBER) annual meeting and exhibit event. The 3-hour workshop aimed to introduce all ethical, legal, and practical applications of informed consent according international regulations, following its evolutionary course through the years, and representing future perspectives and applications based on novel technologies in the era of digitalization. Twenty-three representatives from the biobanking and scientific sector gave their opinions and insights on the current operational strategies and consent options applied in biobanks and discussed the perspective of implementation of novel procedures that could cover technological evolution and set universally accepted principles. Based on potential real-time scenarios and survey questions, the final part of the workshop aimed to create an indicative point of view on how biobanks apprehend the present system, and what are the levels of readiness and/or willingness to change, by implementing novel technologies and giving donors total control over their biospecimens and related data.

METHODS

Workshop Organization

Occasioned by the ISBER virtual annual meeting and exhibits, an educational workshop with the title "Informed Consent in Biobanking; from the Key Barriers, Challenges and Perceptions to the Digital Innovations" was conducted by Metabio's executives, following the mission of ISBER as a global biobanking organization that represents global interest on ethical biobanking and the universal interest on informed consent. The workshop took part virtually via Zoom and was divided into four separate sections.

Section 1

A poll survey consisted of 21 questions. Before all presentations 20 participants were asked to complete the poll survey, by answering consent-specific questions, addressing both current systems and future perspectives. The main scope of the survey was to investigate what present procedures are followed by the industry in research-related activities; how satisfactory are they; if they provide standard principles on international level; if they are easily implemented in scientific procedures

Scenario 1:

Adult female with diabetes type II has provided permission for biosample donation and subsequently usage in broad research spectrum, through a broad consent type. In downstream research analysis, mutations in BRAC1 and BRAC2 have been identified, increasing her susceptibility for breast cancer development.

Scenario 2:

Adult male provided consent for research activities upon his biosamples and associated data. Family history assessment and monitoring showed the appearance of hereditary genetic factor associated with specific disease development and family members showed 25% risk to develop the disease.

Scenario 3:

During a sudden novel pandemic outbreak (e.g. Covid-19), hospitalized patients with severe symptoms have been treated with non-standardized methods. Biosample and data have been collected for studying patient's treatment under mechanical support. After patients' stabilization, healthcare providers inform them that their biosamples and associated data have been already used, but they refuse to follow-up and want to withdraw.

Figure 1. Real-life scenarios included in workshop activity.

and provide effectiveness in patient or donor follow-up; the willingness and/or the need for innovative technologies in future biobanking considering the rapid evolution in technology and research; and how familiar participants are with different consent-related options and/or donors' rights before the main detailed presentations.

Section 2

Section 2 explored the evolution of informed consent and a complete description of current and future needs, covering topics such as informed consent requirements, historic background, different regulations, challenges and barriers, consent types, and statuses available. The main scope of this first presentation was to introduce all consent applications and options as part of innovation and progress accessible, and to attract attention to a largely undisclosed problem within the community, by presenting main issues and limits in international networking.

Section 3

A detailed description of novel digital applications for donors' and/or patients' engagement by introducing the Real-time Dynamic Tiered e-consent tool and addressing modifications and system biobanking requirements for its integration were discussed in Section 3. The main scope of this second presentation was to provide all information for innovative technologies in consent sectors and answer the following important questions: Do biobankers really want it? Can it really be applied? What are the advantages and disadvantages of digitalized consent forms, and how ready is the current system to incorporate these novel technologies globally?

Section 4

During the final part of the workshop activity, three different use cases (Fig. 1) of potential real-life scenarios were presented. Having all scenarios in mind, different options and types of informed consent were discussed, scenario-related questions were also discussed, and the group came to a consensus for the best consent type for patients or donors, as well as decide which is for the best interest of biobanks and which could combine both interests. Participants were separated into subgroups, by joining randomly created breakout rooms and in the end one representative from each group cited the main discussion points. The primary scope of these use cases was to present difficult research-related circumstances, raise concerns to informed consent implementations, search for balance between regulations, patients' or donors' rights, and ethical issues, and conclude if there is one consent type that could protect all parties and comply with all standard requirements, covering needs of both biobanks and individuals. One primary question arising from these scenarios was whether or not the patients' or donors' decisions via their informed consent can be set aside for the common good, or the possibility to prevent future disease outcome through random research findings. What should entities do if they do not have the legal right to communicate further with an individual, but they have strong evidence-based findings that they and/or a family member not included in the consent procedure would eventually develop a specific disease? Is there a consent type that could prevent such circumstances? Who informs individuals of research-related results?

In addition, subgroups brainstormed the topic of consent management and dynamic e-consent requirements in current systems, addressing the possible implications and potential applications when the usage

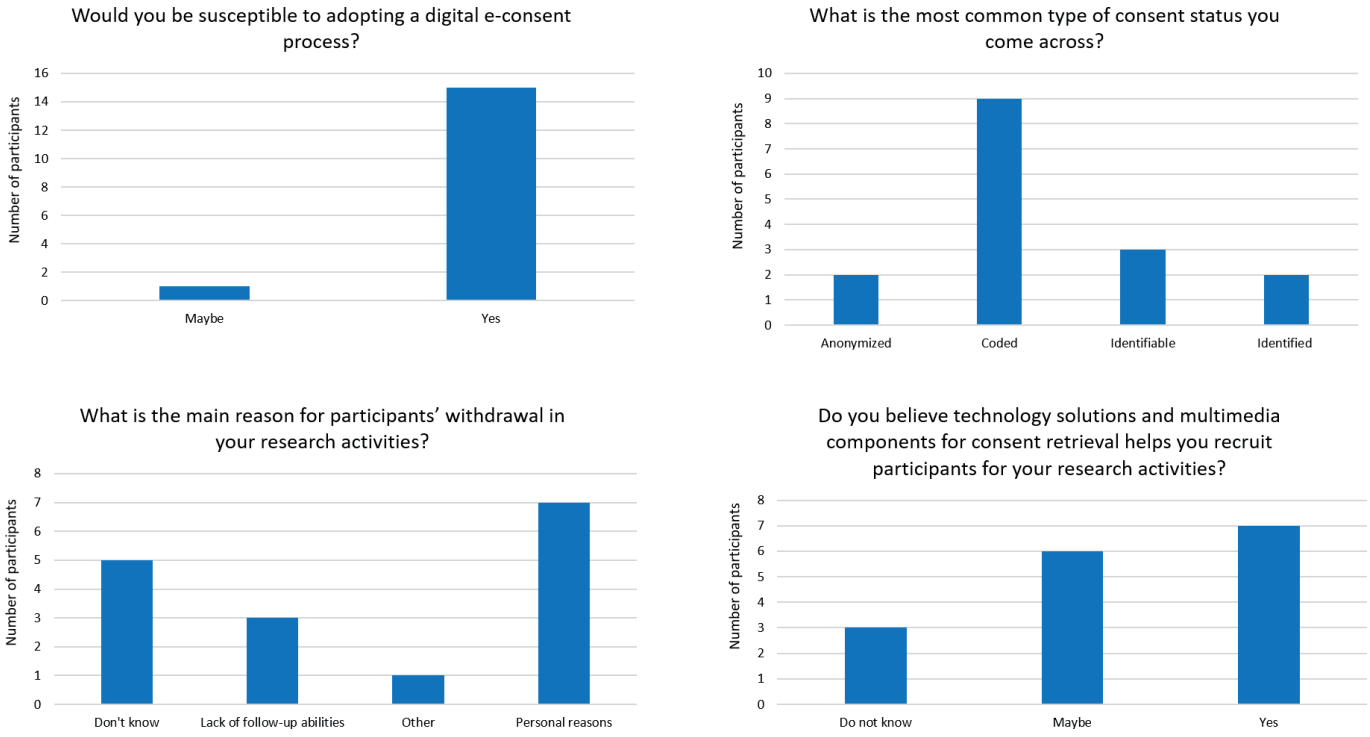


Figure 2. Questions 1 through 4.

chain of biosample and associated data is managed 100% by the donor.

RESULTS

Poll Survey

The poll survey results are represented below, divided into the following three separate question packs: (1) Questions 1 through 10 in Figures 2, 3, and 4; (2) Questions 11 through 19 in Figures 5, 6, and 7; and (3) Questions 20 and 21 in Figure 8.

Questions 1 through 10

Sixteen participants completed the question pack from questions 1 through 10. Participants were asked about their susceptibility to implement novel digital consent types in their current system, as well as questions about potential issues associated with both donor's participation and biosample utilization and/or dissemination. According to responses, it seems that the most common type of consent status they come across in their organization is coded (56%), followed by anonymized, identifiable, and identified with mean value of 16%. The majority of participants (> 40%) believe that multimedia and novel technologies might help toward patients' or donors' participation increase in research-related activities; however, they seem to be susceptible to adopting e-consent processes in their current system (94%), due to legal, ethical, and standard principals (44%), followed by the lack of human involvement and the need for familiarization and training with equality of 19%. Some also considered the big change in requirements in current processes (13%) and the increased cost (6%). Of participants, 31% had experienced inability of biosample sourcing and/or procurement due to data transmission issues related to consent-related legislation inconsistencies, and 13% had participated in research-related activities that actually failed due to consent procedures. Considering patient or donor participation and their right to withdraw as participants for selected personal reasons was the leading cause of withdrawal (44%); 19% selected inability to follow-up; and 31% did not know the actual reasons. For questions related to the main procedures used in organizations to evaluate patients' or donors' voluntariness, competence, and comprehension of the "Use of statement of agreement included already in the informed consent" was selected by 44% of participants; it was followed by "Other" or "Face-to-face interaction" chosen by 25% in both instances. Random research findings associated with patients' or donors' well-being were not reported to individuals according to one-fourth of participants; on the other hand, 75% of participants agreed that they actually communicate with patients in such circumstances in person, via telephone, or with other procedures, not involved in the present survey as an option. When asked about the primary reason they believe re-consent should be required, half of participants selected the answer "If data and biosamples will be used in unrelated research fields" and the other half the answer "Implementation of novel technologies and research activities" and "Do not know" together.

Questions 11 through 19

Sixteen participants completed the question pack from questions 11 through 19. The second pack of questions were set to investigate the current consent type implemented in organizations and if it covered needs both on local or international levels. Barriers for the establishment of international standard principles were also brought up, along with the main reasons participants believed patients; or donors' influence their decision to be enrolled in research-related activities. The majority of participants represented the biobanking sector. According to their opinions and personal experiences, there was more than one reason that prevented individuals from donating and/or participating in research, including their cultural background, friends, and family and lack of trust in related procedures. Currently, most of the organizations, based on participants' answers, seemed to use blanket and/or broad consent models (69%) followed by study-specific models (19%). Dynamic and tiered consent were used by a minority of the participants (6%). More than half of participants were satisfied with the current consent type implemented within their organizations (69%). On the other hand, no consensus was observed if the current consent types used addressed the need for cooperative partnership within an international network research system; 31% of participants believed it did, 31% believed it did not, and 38% selected the "Partially" or the "Do not know" answer. Even so, it seems that if they had to choose the fit for purpose consent type to be used in the future, no big changes

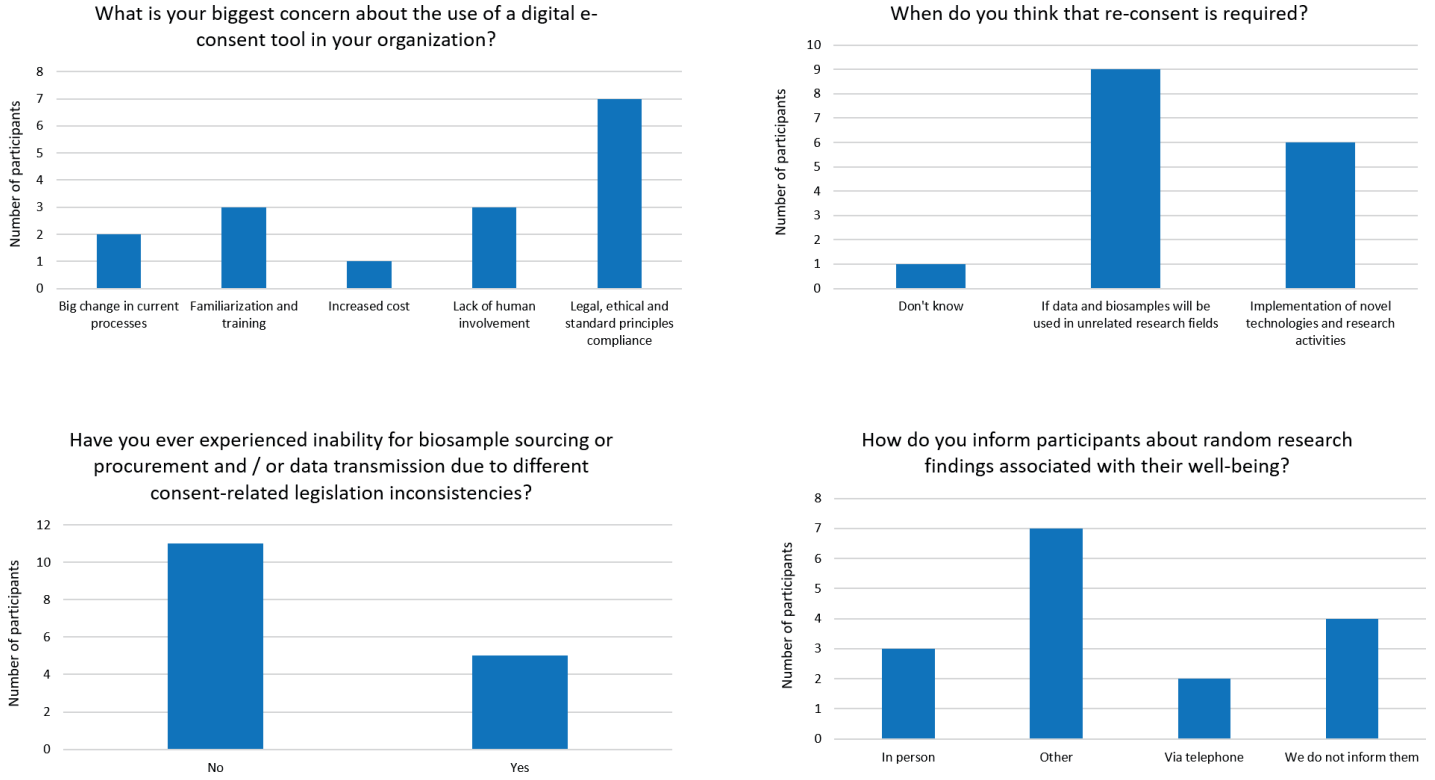


Figure 3. Questions 5 through 8.

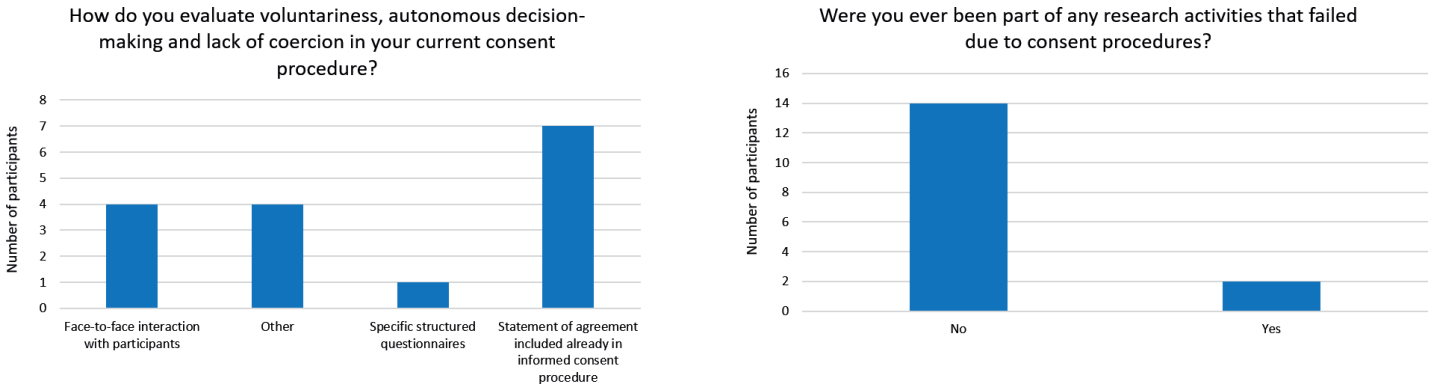


Figure 4. Questions 9 and 10.

would be made, having blanket and/or broad consent as the major preference. According to participants' opinions, the main barrier for global consent consensus were both the lack of international standard principles and language. In addition, participants were asked how easy it was to obtain consent and to define the average time of the total procedure; answers were controversial, with 44% claiming that there were difficulties and 51%

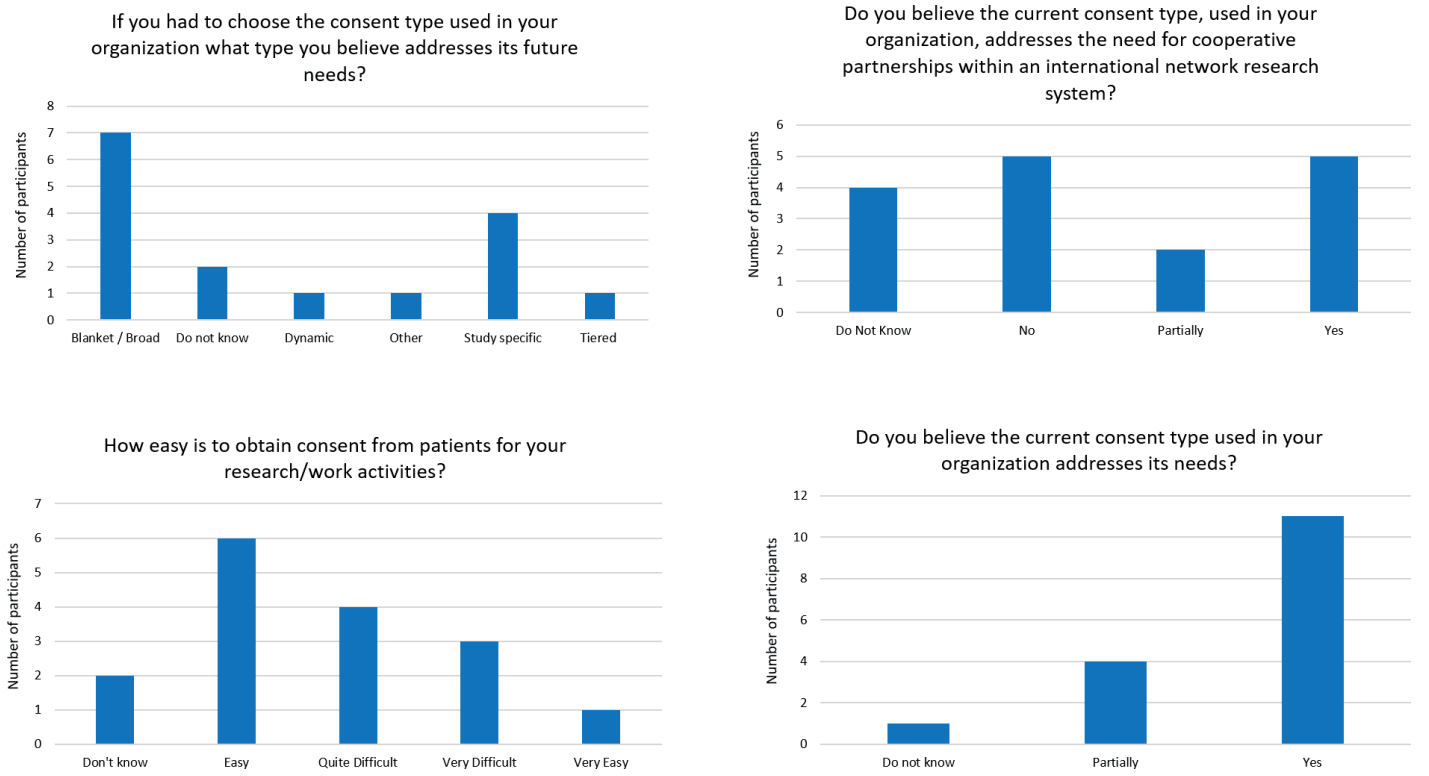


Figure 5. Questions 11 through 14.

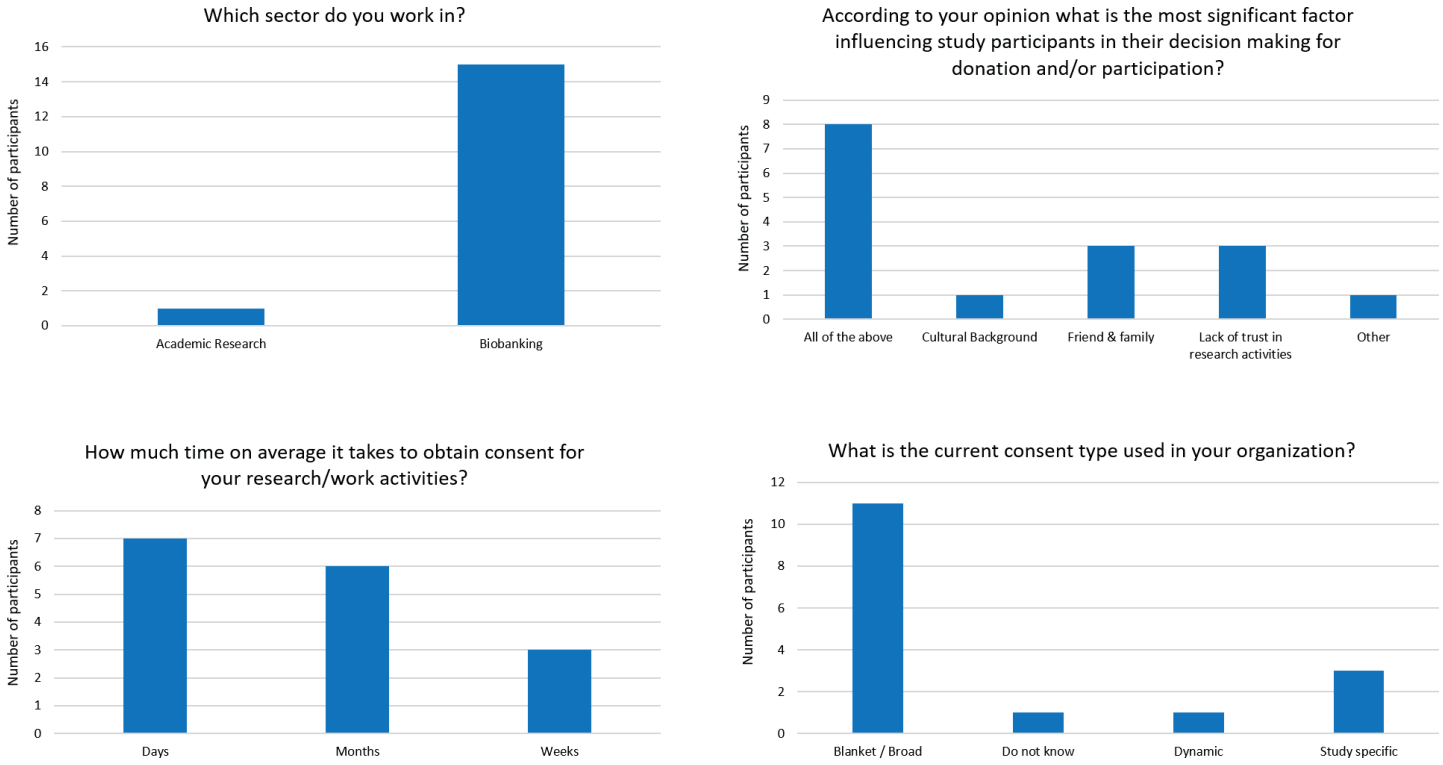


Figure 6. Questions 15 through 18.

claiming it was an easy procedure. The average time was also different in ranging from days (44%) to months (38%).

Questions 20 and 21

Twenty participants completed the question pack with questions 20 and 21. Participants were asked about the kind of donation control patients or donors should have as well as their willingness to provide patients total control over their biosample donation and associated data. Most of the participants selected the option "All of the above," regarding the first issued raised from question 20, including control over both biosamples and associate data, communication, research findings, and research field in general. Of participants, 15% selected the option "None of the above." Controversy was observed among participants for question 21, related to patients' or donors' total control over their donations. Of the participants, 40% were not amenable to giving total control over biospecimens and related data to patients or donors. Nearly 50% of participants responded positively to the prospect of providing individuals with total or partial control.

Workshop Activity: Real-life Scenario Remarks

Workshop participants presented their leading discussion points over informed consent types and real-life scenarios, considering all parties. There was consensus that research findings might be essential for patients' or donors' well-being; however, there was controversy if those research results should be returned to individuals if that option was not mentioned in their consent status. Representatives from US–based biobanks reported that in such circumstances, educated staff with high expertise

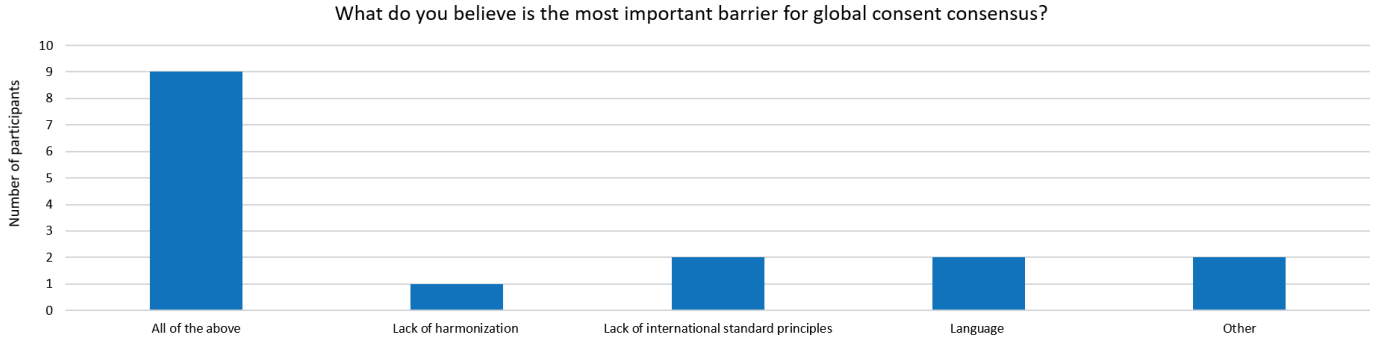
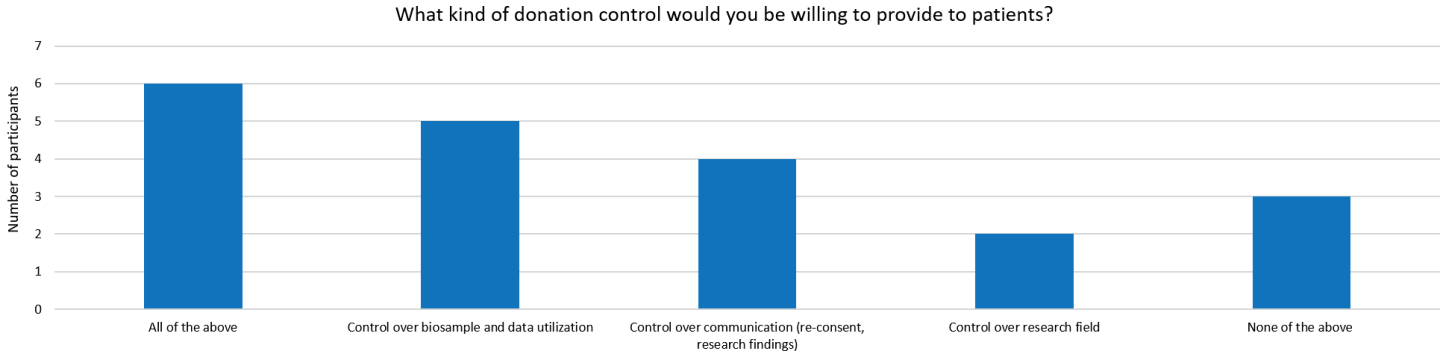


Figure 7. Question 19.



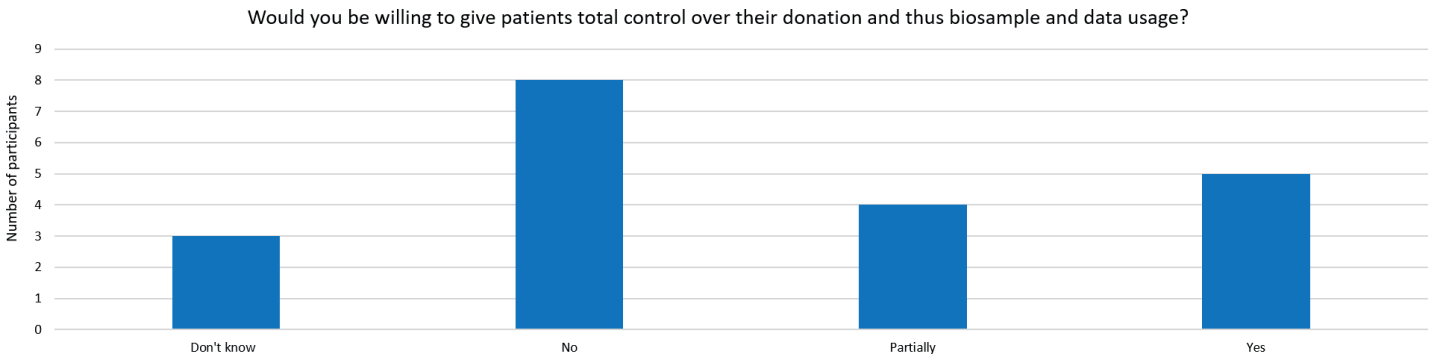


Figure 8. Questions 20 and 21.

undertook the procedure to inform patients or donors in potential health-related results. Most of the participants agreed that by using broad consent, their organization was legally covered to use data and metadata without the need to consider re-consenting for follow-ups. According to group members' feedback, there was not such a consent type in most organizations that included patients' or donors' personal agreement for further contact; usually, following broad-consent methodology, associated hospitals or research centers decided further communication contextually and continued taking patients' or donors' associated metadata.

The same controversy was apparent regarding third parties, such as family members. On the one hand, participants believed that family members were already involved in research-related activities and were covered by the given informed consent signed from an individual because they provided their family history to all entities. On the other hand, susceptibility was observed about the right to use and share data associated with family members, as well as the spectrum of research-relative activities in which these data can be used in the future.

DISCUSSION

The informed consent doctrine, first introduced in the late 20th century, has gone through many stages of development and evolution over the past decades, not only historically based but also technologically, addressing the needs of each era in regulation, science, research, and healthcare in general.[32–35] Although these changes are incorporated in informed consent procedures and principles, so as to assure individuals' rights over their donation and data and provide them with autonomy, many issues and challenges still remain and might became more complicated as the evolution of current research and innovation processes increase rapidly.[36] Informed consent requires many modifications in the era of "omics" and "big data" on national and international levels, by setting regulations and standard principles for harmonization among countries, to cover main areas of concern and pitfall points in the global biobanking network.[37,38] The lack of harmonization, standardization, and common language were the main barriers according to the workshop's poll participants for global consent consensus.

Language is not only a barrier for biobanks and other health-related entities that share data and information, but also leads to inadequate understandings from patients or donors.[39] Alongside religious influence, cultural background, false patient perceptions about research procedures, and potential family influence, many individuals refuse to participate in clinical trials and/or donate biospecimens and related data.[40–42] According to poll participants and their personal experiences, cultural background, friends, family, and lack of trust in related procedures were all significant factors contributing to patients' or donors' final decision-making for donation and participation in research activities, emphasizing more on friends and family influence and/or the lack of trust in such procedures, regardless of the cultural background.

The lack of harmonization and standard consent type in the biobanking industry and other health-related sectors, create a large gap in informed consent requirements because some of the consent types used do not adhere to its main principles, such as broad consent.[43] Donations using broad consent, from a sample cohort that can be used in any research type, although the current broad consent type cannot be described as adequately informed from a patient perspective, which means that one of four major criteria that is considered for the process of informed consent to be complete and valid is not.[44,45] Despite that, broad consent was not only majorly used in the present biobanking industry but also was preferable for future needs according to the poll survey answers, followed by that of study specific consent, mostly as part of a clinical trial. Of note, more than half of the participants feel that the current consent type addresses the needs of their organizations but does not completely address the needs for future cooperative partnerships within an international network research system. Taking into account the workshop's results from The National Institutes of Health Clinical Center Department of Bioethics in 2013,[46] it seems that broad consent is preferable by both researchers and patients. From the scientists' perspectives the lack of extra burden to seek individuals' permission each time new research is conducted is a priority and from the patients' perspective the need to sign up only once and not be further contacted is preferable. Patients also agreed that an optimal and ethical permissible broad consent should consist of the following three main components: initial broad consent, procedure of approval of future research related-activities, and an ongoing process for donors follow-up and communication.

The follow-up procedure was not always feasible (19%), according to the poll survey, and wass actually one of the causes for patients' or donors' withdrawal. On the other hand, considering the option of anonymity for increased protection of individuals' identity (from the ethical point of view) makes further communication with individuals extremely difficult or not possible at all.[47] Anonymized samples arise a major barrier in longitudinal data collection and partially limits research activities in biobanks as the big data collections cannot be sufficiently used and distributed among other research-related entities.[48] In many instances of substantial changes in initial consent, further communication between investigators and individuals is essential for future research activities, leading to the need for re-consent procedures.[49] The poll participants selected the following two main reasons that re-consent is needed: if data and biosamples will be used in unrelated research fields, and in the case of implementation of novel technologies and research activities.

A mandatory challenge arises in the implementation of informed consent; the evaluation of individuals' comprehension, voluntariness, and autonomous decision-making, which are not standardized among entities and countries.[50] Asking poll participants how they assess these procedures, variability was observed including face-to-face interactions, structured questionnaires, and statement of agreement included in informed consent procedures. Thus, lack of clarity in potential future utilization of their biospecimens and concerns about the security, privacy, and disclosure of their sensitive data, increase the lack of public trust and may lead to failure of healthcare-related programs, emphasizing patients' or donors' desire for greater transparency and engagement in research.[51] Of the survey participants, 13% have experienced research failure due to consent procedures.

Introduction of dynamic consent options as a solution for patients' or donors' engagement through interactive interfaces seems to respond more effectively to these challenges, as it has the potential to accommodate different consent approaches in biobanking and healthcare in general, protect donor's interests over time and contains all the range of characteristics to enable individuals' incorporation as "equal" partners in research-related activities and enrollment in the usage chain of data use.[52,53] Dynamic e-consent is a promising innovative tool for both patients and biobanks and/or other health-associated sectors, based on its potentials, including the ability for major longitudinal studies on targeted population cohorts; establishment of novel clinical research international networking; supporting of large-scale cross-border data sharing and ongoing communication between all stakeholders; and the ability of an effective and easy future way for follow-up. Thus, solving most if not all the issues raised by survey participants.[54–56] Despite that, dynamic consent models were not the first choice for future use by the poll participants, but the susceptibility for adopting an electronic digital consent was observed by an impressive majority of 94%. Although most of the executives and scientists within the workshop agreed that a novel technical solution for consent processes might help in patients' or donors' recruitment for research, their biggest concern was associated with legal, ethical, and standard principles for compliance. Some of the participants considered also the technical competence of the staff members, including the need for familiarization and training, alongside the lack of human involvement. A few more issues were raised in the subject, such as the possible increased cost of the implementation of these novel technologies and the big changes in current systems although preferable. These concerns come to consensus with previous reviews addressing the challenges, limits, and future needs for electronic consent implementation in current systems, supporting the requirements for both technical infrastructures set up and standard polices and guidance establishment within national and international frameworks.[57–59]

A key role in healthcare quality and personalized medicine affects patients' partnership in research-related activities; thus, patient-centric approaches and strategies are developed to support enrollment and giving patients more information and control over donation.[60] Building trust and relationships between biobanks and patients is mandatory for future research development.[61] According to the survey results, half of the participants would give patients/donors control over their donation and associated data either totally or partially. On the other hand, 40% of the participants are not willing to give them total control over their biosample and data usage. Asking them what kind of donation control would they be willing to provide to patients, the following three main areas were selected: control over biosample and related data utilization; control over future communication for re-consent and research findings; and control over research field, related to their donation. It is critical to note that 15% of participants were not willing to give any of the above types of control to participants.

Sheehan et al[62] previously published some of the main points of criticism related to the implementation of dynamic consent and the right it gives to patients, emphasizing the concerns for patients potentiality to interfere with the research processes and their ability to express their preferences in related activities, which subsequently might affect the final research conduction. Criticisms for the implementation of dynamic consent, being an extra burden to current and future processes in biobanking activities has been reported by Steinsbekk et al[63] as well. Despite that, the majority of the biobanking representatives in the poll survey were willing to incorporate patients in research and give them authority to more research-related outcome disclosure.

These workshop results and conclusion remarks have certain limitations considering the very small number of participants and the lack of diversity background among them. In addition, large-scale focus groups, including participants from different fields, such as biobanking, research institutes, healthcare providers and pharma, alongside a group of patients or donors, might give more representative insight of current and future needs and considerations in the field of informed consent and best practices requirements for both patients and other stakeholders' rights. Some very mandatory pitfalls in biobanking and informed consent were discussed, giving a boost for brainstorming and food for thought to achieve a global informed consent type consensus in healthcare and biobanking industry.

CONCLUSIONS

As the nature of healthcare changes in the era of large-scale studies and big data analytics, biobanking evolution and incorporation of computing and networking

technologies might be unavoidable so as to create harmonized and standardized procedures for patients' engagement and consent consensus on international levels. From past to present, via the ISBER virtual annual meeting and exhibits, an educational workshop was conducted to inform participants about consent evolution, challenges, issues, barriers, regulations, and novel technological options. Possible implications and potential applications are raised when the usage chain of biosample and associated data is managed totally by the donor, as well as considerations of novel technologies incorporation in the current system. The main consent-related issues deal with organizations' present and future perspectives. According to survey results, biobank representatives seem to realize the gap in current operational systems and come to consensus with previous reviews about the main issues and barrier in obtaining consent from participants and the need for harmonized standard polices for international networking, along with practical ways for patients' enrollment in research. Although willingness levels from close to the half of participants to give patients total control over their biospecimens and related data were observed, some considerations for the implementation on these novel technologies and big changes in current systems still remains. Further exploration is needed by focusing on more a diverse, large-scale group of participants to have more information on current issues and the initial steps needed to achieve the best quality in future global healthcare.

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