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Independent Articles

International Ethical Principles for Banking and Secondary Research Use of Human Biospecimens and Associated Data: The Seattle Principles

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Abstract

International access to and sharing of biospecimens is critical to answer important questions about complex diseases, and to ensure the diversity in biospecimen collection necessary to advance science and develop therapies that benefit all. However, many challenges exist. These include the lack of harmonized ethical, legal, and policy frameworks regarding secondary uses of biospecimens and associated data; regulatory and policy hurdles; and differences in cultural perspectives and practices across regional and national jurisdictions.

In this manuscript, a set of ethical principles is presented with the intent to address some of these challenges by ensuring better alignment in ethical practices related to biobanking and the global use of human biospecimens. In addition, these principles could serve as a basis for promoting more consistency among national regulations and policies. The ultimate goal is to develop an international framework for global biospecimen and data sharing.

Keywords: biobanking; biospecimens; research

Introduction

To advance science and develop therapies that benefit all populations, sample sets and their underlying data need to be sufficiently large, appropriately representative, and well characterized. Achieving this often requires international biospecimen and data sharing. However, many challenges exist to such sharing, including the lack of a harmonized international framework. With the goal of addressing these challenges, we are proposing here a set of basic ethical principles for biospecimen research that demonstrate respect for persons and for their rights, welfare, privacy, and autonomy.

Research using human biospecimens and associated demographic, phenotypic, and genomic data has formed the basis for numerous advances in clinical and basic science. This research may be performed by scientists in academic institutions, government and scientific agencies, public health authorities, nonprofit organizations, or private for-profit companies.

Human biospecimens that may be used in research include a wide range of biologic materials, including blood, urine, tissue (such as pathology specimens or research biopsies), cells or cell lines, and components extracted from tissue, such as DNA and RNA. Human biospecimens may be collected as part of an interventional research protocol or as part of a research protocol specifically designed for biospecimen collection and storage. Residual biospecimens that are left over from standard of care interventions or retained after an interventional study can also be stored for future secondary research. Utilizing previously collected biospecimens for such secondary research often allows scientists to avoid additional interventions involving human research participants[1] and maximizes the use of scientific resources.

The collection, retention, and use of human biospecimens are typically regulated by multiple legal and ethical systems, including national laws regarding the delivery of medical care, the privacy of medical information, the practice of pathology, genetic and genomic analysis, policies on retention of human remains, and research involving human participants.

The multiplicity of legal and ethical regimes creates navigational challenges when human biospecimens are collected and used for research projects that span several national jurisdictions, with each jurisdiction having its own specific laws and regulations that are rarely consistent with one another.[2] The "internationalization" of science, with multiple collaborators in multiple institutions across countries, has led to great complexity in ensuring compliance with all applicable laws and ethical principles.[3]

While international nongovernmental entities lack the power or authority to harmonize laws across nations or other jurisdictions, they can play a role in defining the ethical principles that should

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govern and inspire scientific research using human biospecimens. The hope is that the development of principles, with input from multiple stakeholder communities, can lead to the formation of consensus principles that can drive consistent ethical practices across the relevant scientific communities. These principles could also lead to, and form the basis of advocacy for, more consistency across nations in laws and policies regulating the collection, retention, and research uses of human biospecimens. At the same time, widely accepted principles in this field could promote better ethics in science itself and foster and maintain trust among the persons and communities whose biospecimens and data are used for research.

A number of guidelines exist that address ethical issues related to human biospecimen research.[4] However, these guidelines, published over the years, vary in their purposes, scopes and breadths, intended audiences, and levels of specificity. In addition, some are principle based and others are more geared to practical implementation. While many of these guidelines may be considered top-down in nature, the ethical principles we propose here are grounded in a bottom-up approach. They are the product of extensive engagement with a broad spectrum of stakeholders whose voices have been synthesized into a coherent set of principles. In this sense, these principles reflect not only a collective ethical vision but also the current ethical landscape as understood by those directly involved in the stewardship and use of human biospecimens and associated data.

This paper offers up a set of principles shaped by discussions at numerous meetings of the International Society for Biological and Environmental Repositories (ISBER), Public Responsibility for Medicine in Research (PRIM&R), the 2024 UN General Assembly Science Summit, and other public and scientific fora, such as the Asian-Pacific Open Forum in 2023. These principles are intended to establish common ground for all interested, including relevant stakeholders such as scientists, biobankers, ethics review committees, regulators, policymakers, and the public.

The principles presented herein, intended for a broad international audience, are offered in this context and with these goals. The principles should be read as a whole and interpreted in conjunction with one another.[5]

1. Principle of Transparency to Participants

> Information about the practice of collecting, retaining, and using biospecimens for research should be made available to those from whom biospecimens are collected (herein referred to as "participants").[6] In the cases of biospecimens collected as part of an interventional research protocol or a research protocol specifically designed for biospecimen collection and storage, informed consent of participants should be sought and obtained. That information should, as a routine matter, include whether there is a possibility of biospecimens and associated data being shared with researchers in other countries or with for-profit entities engaged in research and development, and, if so, whether the biospecimens may be used to develop treatments and diagnostics.

Discussion

It is a foundational element of clinical practice that a patient should be informed of, or at least have ready access to, information about the circumstances and consequences of any clinical procedure they may be undergoing. Similarly, if, at the time a patient's biospecimens are collected for clinical purposes, it is known that scientists may use the biospecimens for research purposes, the patient should also be offered information about possible future use. In this situation, informed consent should be obtained whenever feasible, even though, as in some Nordic countries, a notification process with an opportunity for the patient to opt out of research participation may be sufficient to protect the autonomy interests of participants. In planned interventional clinical research, or in research that is designed as a prospective collection of biospecimens for future research use, the research team should obtain informed consent from the research participant, with reference to anticipated future research uses of the biospecimens.

The importance of transparency and informed consent for the research use of biospecimens has been highlighted by the cases of Henrietta Lacks[7] and the Havasupai tribe,[8] and by several court cases in the US,[9] as well as incidents[10] and widely publicized situations in other countries.[11] Some studies indicate that, when asked, most participants are willing to share their health data and biospecimens with researchers if they will be used for the advancement of scientific knowledge.[12] However, studies have also indicated that individuals are somewhat less willing to share their biospecimens with for-profit entities or with researchers in other countries.[13] Thus, it is important to disclose this information to potential research participants as a routine matter in the informed consent process, and to provide them with information about the categories of researchers and entities with which they consent to share their biospecimens and data.

2. Principle of Respect for Consent of Participants

> Participants should be able to give their consent, freely and without coercion or deception, to the collection and research uses of their biospecimens. The breadth and terms of consent sought and given may depend upon a wide variety of factors. For example, some researchers may seek, and participants should be free to give, broad consent regarding permissible future research purposes in order to maximize use of scientific resources and facilitate future research uses and scientific advances. Consent should be recognized as effective for the duration defined in the consent, even past the life of the participant. If consent has been obtained for collection, retention, and future research uses of human biospecimens, governance mechanisms (as described herein) should consider the proposed research uses with respect to the terms and conditions of that consent, including consent that has been broadly given for future research uses.

Discussion

Respect for participants' consent is fundamental to respecting their autonomy and requires consideration of participants' reasonable expectations for the uses of their provided biospecimens. However, it is inherently challenging to anticipate all future research questions that any single biospecimen might inform. As scientific knowledge progresses, new research areas emerge that scientists could not have reasonably foreseen. Similarly, future research purposes may arise that physicians and researchers cannot now anticipate or describe to participants in order to obtain specific consent for those future uses.

Moreover, given the potential risks that biospecimen collection imposes on patients, there is an ethical obligation to value this resource. Consents that use a broad description of future research aim to maximize the uses of these valuable resources by allowing for important future research that may not have been specifically anticipated at the time consent was given. Broad consent is intended as consent that describes the types and scopes of future uses for which specimens may be used, without returning to the participant for a specific consent for each new research study. Unlike a "blanket consent" that would allow anyone and everyone to use biospecimens for any purpose, a broad consent typically includes use restrictions

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and terms of oversight, such as ethics committee approval, for the future research uses of biospecimens. Many study populations and ethicists consider such broad consent to be ethically acceptable when used in conjunction with ongoing oversight of subsequent future research uses.[14] Broad consent has also been found to be acceptable by international policy documents, such as the Council for International Organization of Medical Sciences' *International Ethical Guidelines for Health-related Research Involving Humans*. However, broad consents may not be acceptable to some populations or in some jurisdictions. For example, the European Union, in its General Data Protection Regulation, requires researchers to obtain specific research participant consent for use of clinical data in research.[15] Additionally, a specific research consent may be more appropriate in some research contexts: for example, if additional uses of the biospecimens are precluded by consent terms that restrict further sharing. Nonetheless, as a normative matter, the abilities of individuals to give broad consent for future research uses is to be preferred, in that it maximizes the efficiency and opportunity for valuable scientific research, while also providing individuals an initial informed choice as to the future research uses of their biospecimens.

The concepts of this principle are also intended to apply in the case of biospecimen collection and secondary uses when the participant is a child or individual who lacks consent capacity. In those instances, consent is to be obtained from a legally authorized representative consistent with applicable laws. For new research uses of the participant's identifiable biospecimens, some national laws or research ethics committees may require the minor to reconsent at the time they reach legal maturity. On the other hand, in some jurisdictions, an ethics review committee may find a waiver of consent acceptable in these circumstances.

In some countries, national laws or local norms may require the consent of family members (for example, the eldest male in the household) or tribal or group elders; if so, consent must be sought from the participant first, and subsequently also from these other individuals. The use of biospecimens of deceased persons in some jurisdictions may require the consent of surviving next-of-kin or of the estate administrator, if the participant did not consent before death, and those laws must also be respected when applicable.[16] Consent at the population or community level is discussed in Principle 5, Safeguarding the Welfare of Specific Communities.

3. Principle of Respecting the Scope of Consent

> The secondary use of stored biospecimens in specific research projects should be allowed only if (a) that use falls within the scope of research uses identified in an informed consent process (which may include a specific or a broad consent process) as part of a study or biobanking protocol approved by a competent and appropriate research ethics committee, or (b) that use has been approved by a competent and appropriate research ethics committee that has considered the possible benefits of such research use, as well as any foreseeable detriment or harm to participants from that use (see Principle 6).

Discussion

When consent has been given for future research uses of biospecimens, researchers and research institutions, including commercial entities, have an ethical obligation to examine the content of that consent and to consider the context in which consent was given, in order to ensure that the terms of that consent allow specific intended uses. Compliance with the substance of consent is essential in safeguarding the rights and interests of participants and, at the population level, in maintaining social trust in the research enterprise.

In some cases, it may not be clear whether a specific secondary research use falls within the scope of an original consent. Importantly, resolving this is a context-specific determination that must consider the nature of the proposed secondary research; whether the secondary research could reasonably be understood to fall within the scope of the research described in the original consent; whether the secondary research includes new or significantly heightened risks, including privacy risks, that were not described in the original consent; and whether the participant population has known concerns about the specific intended secondary use.[17] One approach would be to deploy a "tiered consent," in which research participants are allowed to choose among a list of options for future research uses of their biospecimens and data. However, the use of such tiered consent carries an obligation to adhere scrupulously to the parameters of the consented uses for as long as the biospecimens and data are retained for research. Further, meeting this obligation requires appropriate IT or human infrastructure to track and respect such choices. The various types of consent for the use of biospecimens and data and their advantages and disadvantages have been discussed previously in the literature.[18]

When clinical biospecimens have been collected during clinical care and are considered for secondary research without consent for future research use, it should be required that a research ethics committee review and approve proposed uses. In that process, a research ethics committee should consider, among other factors, the nature of the proposed use, its reasonable acceptability to the participant population, and the benefits and risks to the participants, including any group harms.

4. Principle of Respecting Withdrawal of Consent for Future Research

> Collection and storage of biospecimens as part of an interventional protocol or a protocol specifically designed for the collection of biospecimens should allow for participants to request later that their biospecimens will not be used for new research, if it is reasonable and practicable to identify these biospecimens at the time of request. At the same time, it is allowable for custodians to refrain from destruction of biospecimens, associated data, and/or newly derived research data in these cases, based on compelling and legitimate purposes, such as research integrity or to allow an ongoing study to be concluded. Any such limitations on the withdrawal of consent should be clearly explained in the informed consent process.

Discussion

Respect for individual participants and their autonomy must also include their right to withdraw consent. Researchers should inform participants that they are free to withdraw consent at any point and for any reasons, including for future use.[19] However, in some circumstances, it may not be feasible to cease research activities already involving the biospecimens[20] or withdraw data points if the research has already been published. Also, it may not be possible to reidentify the biospecimen provided by a specific participant or retrieve biospecimens already distributed by a biobank for a research study. In addition, biospecimen-related data for research regulated by the US Food and Drug Administration, among others, may need to be maintained for study integrity, or in the interest of public health and safety, despite the withdrawn consent of a research participant.[21] Therefore, it is critical for researchers and biobanks to communicate clearly with participants about any limitations on withdrawal of consent.[22]

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5. Principle of Safeguarding the Welfare of Specific Communities

> Consideration should be given to possible positive and negative benefits to participants and their communities from use of biospecimens from participants in specific self-defined groups, with the goal that both burdens and benefits are equitably allocated in the collection, retention, and research uses of biospecimens. In cultural and religious contexts in which a self-defined community[23] has historically been at some enhanced risk of social harms, those who seek to collect, retain, and use human biospecimens for research should, of course, seek consent from individual potential participants, but should also consider the value of consulting with representatives of the participant communities whose members are significant sources of the biospecimens, or at least making those representatives or community institutions aware of the proposed collection and storage. Scientists planning to establish biobanks of human biospecimens for research purposes should strongly consider proactive engagement with participant communities and their representatives in order to ensure awareness regarding biobanking activities, to understand and mitigate the risk, if any, to participant communities, and to build trust. In addition, the views of those communities in designing critical features of the biobank should be accommodated to the extent reasonably possible, including, for example, perspectives regarding informed consent practices, privacy practices, methods of considering and approving specific future research uses of retained biospecimens, and final disposition of biospecimens.

Discussion

In addition to respecting individual autonomy in biospecimen research, it is also important to consider the perspectives and values of the study population and associated self-defined communities in the design and conduct of the research. Specific communities may have religious or cultural norms related to biospecimen research (or research more generally) that should be respected.[24] Some cultures prioritize communal rights with respect to decision-making and individual autonomy:[25] for example, by requiring community consent, consent from tribal leaders or a participant's relatives. Additionally, some communities may have requirements for burial or other disposition of unused biospecimens donated for research, such as their return to the individual or tribe.[26]

In order to establish and maintain the trust of participants and associated self-defined communities, the religious perspectives and cultural norms and values of these communities should be considered and integrated into the research design and conduct. Historical context, community structure, and vulnerability, particularly in relation to Indigenous communities, should be considered, and, ideally, an enduring partnership formed.

Data sovereignty, or the authority and right of a population to govern data generated within a given jurisdiction, is a key consideration for biospecimen research involving indigenous communities.[27] Indigenous data sovereignty should be considered before the use of specific data in research proposals, and may require further guidance from the community. Guidelines for research practices and the reporting of research on indigenous populations have been published.[28]

In addition to individual risks, consideration should be given to the benefits and risks to communities of biospecimen research. Communities may benefit or be harmed by certain types of research, such as research on stigmatizing conditions, even when individually identifiable information is not released. Some types of research, such as ancestry studies, may not be acceptable to some communities.[29] The Havasupai and San cases[30] provide examples of dignitary harm resulting from biospecimen research in which researchers used biospecimens, without a discrete population's prior knowledge and consent, for purposes that the population found objectionable, including studies of schizophrenia, inbreeding, population migration, dietary history, and marriage practices.

To promote trust and avoid harm to communities, researchers should make a good faith effort to engage with self-defined communities as early as possible in the study design stage. The research should be relevant to the study population and their communities, and research without meaningful engagement should be avoided.[31] To the extent feasible, research benefits to the community should be maximized. Research co-design maximizes study value and participation while minimizing potential harms to the community. Engagement can demonstrate respect for a community's values, culture, and traditions. By building trust, researchers may also be better able to perform long-term studies and conduct follow-ups when necessary. However, in some circumstances, researchers may struggle to determine which self-defined groups are part of a study population, who speaks for the community, or which community engagement approaches are feasible and appropriate for the proposed work. Guidelines related to these issues have been published by H3Africa.[32]

The need for and type of community consultation will depend on the study population, the type of research and downstream assays and research questions, and cultural sensitivities regarding the research. In addition, feasibility and available resources need to be considered. Possible strategies may include engagement with community leaders, surveys, focus groups, and deliberative democracy approaches involving the study population and associated communities. Community representatives may serve, as appropriate, on biobank governance/advisory boards such biospecimen utilization access committees and ethics review boards. In addition, in certain circumstances, it may be appropriate to establish community advisory boards to provide ongoing advice on issues related to community perspectives regarding the design and operation of a biobank and/or associated research.[33]

6. Principle of Human and Community Welfare Protection

> In their planning and deliberations, researchers and research ethics committees should consider possible injuries to participants' reputation and welfare, or that of their descendants and/or self-defined communities, that could potentially result from future uses of their biospecimens. These considerations would be particularly acute if the majority of biospecimens to be used in a proposed research project are drawn from persons who are vulnerable (e.g., those who may have difficulty providing voluntary informed consent or who may be at a greater risk of harm or exploitation) and/or part of discrete and insular disadvantaged population groups. In all cases, researchers planning projects and cognizant research ethics committees considering proposed projects must balance these interests against the promise of gain of scientific or medical knowledge that could enhance human welfare and well-being, with the goal of allowing the production of such knowledge while protecting participants and relevant communities from any significant harm.

Discussion

Research uses of biospecimens and associated data that have been primarily or largely gathered from one defined population have the potential to result in published findings that may be perceived as adversely characterizing that population. In this context, one should be cognizant of the risk of populations being characterized in research findings as possessing inherited genetic traits suggesting suboptimal health outcomes, experiencing heightened incidence or prevalence of specific illnesses, or adversely affected by dietary

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habits or environment. The historical example previously mentioned, of the use of biospecimens and health information from members of the Havasupai tribe to study incidence of mental illness, is cautionary in this regard.

In considering possible adverse impacts of research findings on a specific participant population, one must balance the need for scientific impartiality and objectivity with predictable negative impacts on that participant population. This principle is not intended to discourage publication of research findings for fear of offending a participant population, but is intended to caution scientists who are downstream users of previously collected biospecimens and data, and the ethics committees that review proposed research, to be aware of these possible effects and to seek to design and publish their studies, not by disguising results, but by carefully qualifying findings and suggesting consideration of any alternate explanations.

7. Principle of Participant Privacy

> Identifiable data not required for future research uses or for management of collected biospecimens (e.g., quality control, participant follow-up, possible return of research results) should be removed. The process used to remove identifiable data from stored biospecimens, and the extent of that removal, may appropriately differ among collections of biospecimens.

Discussion

Biospecimen research on important scientific and health issues frequently benefits from significant amounts of linked data, such as clinical, phenotypic, and genotypic data. As more information is collected, the risks of reidentification and possible discrimination against research participants and associated groups, such as their geographic, racial, or ethnic communities, also arise. It is therefore important to remove identifying information not needed for anticipated downstream uses to protect the privacy of participants and the confidentiality of their data.

Protecting the privacy interests of participants and maintaining the confidentiality of their associated health data is not only ethically appropriate and legally required; it also promotes participation in research if individuals feel confident that their privacy is safeguarded throughout the research process.

Internationally, the regulatory landscape regarding biospecimen use, data protection, and individual privacy is fragmented. Many countries and jurisdictions have implemented legislation on the collection of data, and, in particular, the international sharing of data. Currently, 172 countries have enacted data privacy laws, and others are considering bills or draft laws. While these are not specific to participant privacy in research, they do encompass such uses and have a resounding effect on research.[34]

Considerable variation exists in terminologies related to identifiability. These terms include identified, de-identified, tokenized,[35] coded, pseudonymized, anonymized, and anonymous biospecimens and data, all of which have implications on the levels of privacy and protection afforded. The US Food & Drug Administration and European Medicines Agency have adopted International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use E15 definitions to define these categories for genomic data.[36] The European Data Protection Board has also issued guidelines on pseudonymization for data used in research.[37]

Researchers should develop and institute explicit policies and procedures to protect the privacy of participants and the confidentiality of their data. These policies and procedures should include specific data encryption methods, coding practices, access controls, agreements not to release code keys or attempt reidentification of individuals from de-identified data, and the use of nondisclosure agreements when appropriate. The risks of reidentification and associated harms to participants and implemented mitigation processes should be discussed during the informed consent process.

8. Principle of Specific Consideration of Genetic/Genomic Research

> When genetic and/or genomic sequencing will be undertaken as part of a specific research use of retained human biospecimens, this should be specifically addressed in any applicable informed consent process, as well as in the proposed uses to be considered as part of ethics committee review. Researchers should seek to remove other identifiable information and should be specific in their proposal to the cognizant ethics committee about any intent to share or not share genomic sequences with other researchers, and how participant privacy and welfare will be safeguarded if such sharing occurs.

Discussion

The issue of privacy is particularly pertinent to genetic/genomic research data derived from biospecimens. Genetic and genomic data are unique to an individual and can have downstream implications for the individual, their family, and community members. There are possible negative consequences of the intended or unintended release of genetic/genomic data, including discrimination for life and health insurance or employment due to certain genetic characteristics that may be perceived as undesirable.[38] There are also concerns regarding potential uses of these data by law enforcement agencies.[39] By the very nature of genetic and genomic data, de-identification of these data cannot completely guarantee sustained privacy. This situation is further exacerbated by increasing requirements to make such research data available through genetic and genomic databases and supplemental data to scientific publications.[40]

Some jurisdictions may have regulations with specific requirements to protect genetic and genomic data. For example, the European General Data Protection Regulation considers genomic and genetic data a special, protected category of data, requiring rules regarding the processing and sharing of this data, particularly with entities outside of the regulatory jurisdiction.[41]

Studies indicate that participants surveyed are concerned about the possibility of identification and, while willing to share their data, require assurance that it will be shared with reputable entities in a secure and protected manner[42] and governed by a trustworthy body with the power to enforce regulations of processing and sharing.[43] Therefore, participants should be informed about potential uses of their biospecimens in genomic and genetic research. This information should be included in the informed consent process, along with details about any future sharing of these data and a discussion of risks and measures being taken to ensure the privacy and confidentiality of the participant at each phase of biospecimen and data use and sharing.

Finally, there are situations in which researchers seek to perform genetic or genomic analysis on biospecimens originally collected without explicit participant consent for such future genetic or genomic research. In these cases, researchers should first make reasonable efforts to select biospecimens that were originally collected with consent for future genetic and genomic research. If such resources are not practicably available, it is essential that the researcher gain ethics committee approval for the proposed research uses, and that the review process include particularly

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rigorous consideration of the factors embedded in these Principles, including privacy and respect for human and community welfare. Further, any approvals should be specific to the study presented and not generic in nature, so as to permit repetitive reuse of biospecimens.

All reuse ideally should be approved by the authorized research ethics committee most closely affiliated with the origin of the biospecimens and, where appropriate, through consultation with the communities from which the biospecimens were collected. This would avoid situations like that of the Havasupai, in which de-identified biospecimens were repeatedly shared downstream without reference to the initial representations made to participants and their communities when the biospecimens were first gathered.

9. Principle of Returning Research Results

> Research using human biospecimens may yield meaningful (e.g., prognostic or diagnostic) information that could be of benefit to individual participants. In many studies, participants may be unidentifiable; in other studies, in which participants are identified or reasonably identifiable, researchers and ethics committees must consider whether and how any validated, clinically actionable or otherwise significant results should be returned to participants. For this purpose, they must take into account the feasibility of returning results and the direct value, if any, to participants of returning results, recognizing that in some cases, return of results may not be feasible, the results may not be analytically valid, or the results may lack significance to participants. Researchers must anticipate these issues by establishing and proposing an ethically defensible plan regarding the return (or non-return) of any research results and incidental findings to identified or reasonably identifiable participants. That plan should be reviewed and approved by a competent ethics committee. If human biospecimens are obtained pursuant to an informed consent process, the researcher's intent to return results to participants (or not to return results to participants), and the participant's options in this regard, if any, should be discussed during the informed consent process.

Discussion

Despite cultural and socioeconomic factors influencing expectations and the value placed on accessing results,[44] there is a notable societal trend toward expecting access to individual results.[45] Returning individual results is increasingly viewed as a manifestation of respect for study participants, grounded in the principle of reciprocity. Participants contribute valuable information to research for societal benefit and thus have an implied right to access their personal health information, which should be honored whenever possible.

Generally, the demand for returning individual results is highest for validated research methods from certified laboratories and for results that are clinically urgent and actionable. Conversely, concerns about returning results arise when results are not fully validated, their health implications are unclear, their value in clinical decision-making is limited, or the information is complex. In such cases, questions about the data's meaning and usability for participants should be considered to avoid confusion and anxiety in participants.

The legal and regulatory frameworks governing the return of individual results from biospecimen research to research participants vary significantly across jurisdictions and types of research results.[46] These frameworks vary from mandates to return individual results under certain conditions to provisions that address conditions for participant access to such data.

Returning individual results is not always possible, particularly in secondary research, where personal identifiers are typically removed and participants' identities are encoded or anonymized. This is further complicated with the passage of time. In secondary research conducted years after biospecimen collection, contact information may be lost or outdated.

Respecting participants requires that results be returned in an ethically appropriate manner that accommodates the diverse needs and preferences of specific communities and type of information.[47] Depending on the results' implications, a trusted individual able to interpret the results should be identified, ideally a known health care professional or counselor who can discuss the findings in a contextually and culturally appropriate way. This necessitates careful planning and allocation of costs.

10. Principle of Ensuring Responsible Use of Biospecimen Resources

> Those who collect and/or use human biospecimens for research have a presumptive obligation, having undertaken a collection or study, to ensure responsible accessioning, handling, and use of biospecimen resources. This includes trustworthy stewardship to maintain biospecimen and data quality and integrity, as well as to ensure effective biospecimen tracking and utilization. The responsibility includes avoiding collecting and retaining biospecimens and data that have no realistic prospect of future research use. This is necessary to prevent wastage of human biospecimens and frustration of the intent of participants. Further, after completing a study using stored human biospecimens, researchers have an ethical responsibility to publish their research findings and methods in a forum reasonably available to the public and to peer scientists, unless there is a compelling reason not to do so. The data should be shared with other scientists to facilitate other research and increase overall benefits to participants, their communities, and the general public. Those who have collected biospecimens and associated data in a systematic way, with an intent to aid research, should be acknowledged in publications and presentations of results from the analysis of those data.

Discussion

The responsible use of biospecimens is critical to maintain the trust of research participants, research sponsors, and the public. Individuals who donate their biospecimens for research often contribute their biospecimens for altruistic purposes, and they expect them to be well utilized to advance scientific discovery and improvements in health care. Also, while risks to participants from biospecimen research are generally low, participants may undergo invasive procedures for the collection of those biospecimens, and biospecimen use may pose risks to particpants' privacy. Consequently, those who collect or use biospecimens for research have an obligation to ensure the responsible use of biospecimens and data, including ensuring biospecimen quality and fitness for intended purposes and sharing biospecimens to facilitate research that may potentially benefit research participants and society.

Underutilization of biospecimens collected in research has been identified as a significant ethical issue.[48] Studies have shown that those who collect and store biospecimens for research have concerns about underutilization of biospecimens in their collections.[49] Factors affecting utilization include findability, the availability of other sources of biospecimens, the choice of collection model, strategic planning, and other important factors, such as the availability and nature of informed consents.[50] Using informed consents with broadly stated permissible future research uses (see Principle 2) and minimizing restrictions in the consents can help maximize the use of biospecimens.

Appropriate stewardship of the biospecimen is a critical component in the effort to enable responsible use. Responsible stewardship must also include protection of the privacy of research participants (see Principle 7), the confidentiality of their data, and

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appropriate uses of their biospecimens, including good governance (see Principle 11).

Ensuring responsible use of biospecimens also includes the ethical disposal of biospecimens when they are no longer useful. There may be local, legal, or biosafety rules for the disposal of human biospecimens. Additionally, as noted previously, certain populations may require return of any unused biospecimens for burial and/or religious ceremonies (see Principle 5).

Research data sharing is an ethical obligation that allows other scientists to verify the study's results, reanalyze the data, reach new conclusions, or explore new research questions. Such sharing is required by funding agencies or research sponsors, for example by the National Institutes of Health.[51]

To facilitate transparency (see Principle 1), researchers may also consider sharing general information about the research uses of biospecimens in their collections by sending newsletters to participants or creating a publicly available website.

11. Principle of Governance and Oversight

> Human biospecimens retained solely and specifically as a resource for future research purposes should be subject to a biobanking protocol reviewed by a competent research ethics committee convened by an institution, entity, or government. For this purpose, competence should be gauged by knowledge of relevant ethical standards; reasoned, independent application of those standards to the proposed biobanking protocol; and consideration of the abilities of the researchers to undertake the studies they propose. Proposed uses should be evaluated by consideration of scientific merit, ethics principles, and reasonable expectations of participants. Consultation with representatives of primary participant self-defined communities is desirable and may be implemented by including such representatives on the ethics committee or by obtaining a consultation from one or more participant community representatives. There should be continued oversight of the implementation of approved research to ensure accountability and this should include required ethics committee review and approval of specific new research uses of the biospecimens.

Discussion

Governance and oversight of the collection, storage, distribution, and use of human biospecimens is critical for ensuring that biospecimens are collected and used in ways that are ethically and scientifically sound. It is also important to earn and maintain the trust of participants and the public.[52] The importance and components of good governance in the use of human biospecimens have been addressed in a number of international ethical guidelines.[53]

As noted in these guidelines, good governance includes transparency, accountability and stewardship of biospecimens (see Principle 10). Governance and oversight are especially important where no consents are available, or consents are used that are broad in their nature with regard to future research uses.

To provide appropriate oversight, a competent research ethics committee should review protocols for the collection, storage, distribution, use, and disposal of human biospecimens in compliance with relevant national and local regulations and policies. The research ethics committee should have knowledge of regulatory and ethical standards relevant to the proposed biobanking protocol. Any proposed specific research uses of the biospecimens should be evaluated by the research ethics committee to determine whether their intended use is ethically appropriate, whether the samples are suitable, and whether the researchers are able to undertake the proposed work. Furthermore, the ethics committee must consider the protections in place for the privacy of participants and the confidentiality of their data, whether the use is consistent with the expectations of participants expressed through consent, and whether any potential group harms have been considered and addressed, particularly for international sharing where regulations and cultural norms may differ.

Good governance is particularly important for biobanks, because biobanks can serve as surrogate decision-makers/caretakers for biospecimens and data, particularly when a broad consent is used for future research uses. Biobanks may establish a governance plan consisting of the set of authorities, processes, and procedures guiding key operational decisions made within the resource. Such governance plans should also include legacy or contingency plans to mitigate the risks to biospecimens in cases of management change, funding termination, or completion or discontinuation of research participation. In addition to oversight by research ethics committees, biobanks may use a variety of other governance and oversight committees to provide guidance and oversee operations. Finally, as previously mentioned, good governance and oversight should also involve community engagement when feasible and appropriate (see Principle 5).

Conclusion

It is challenging to identify and articulate principles that facilitate science yet are culturally sensitive to individuals and communities across diverse global settings. We believe that the eleven principles outlined herein represent foundational, universally applicable benchmarks that generally reflect a consensus among the relevant research community. The intention of the principles is to provide an umbrella ethical framework that addresses, and can inform the resolution of, the challenges of an often-fragmented regulatory global landscape. While our hope is that these principles will stand the test of time, we recognize that as new technologies emerge and mature, the principles may require revisiting. For example, these principles do not specifically address the implications of artificial intelligence for biospecimen research, although we believe that the fundamental principles presented herein are valid and pertinent in that regard. We hope these principles can serve as a catalyst for the development of a better-aligned and ethically grounded international framework for the sharing and secondary uses of biospecimens and associated data. Such a framework should not only facilitate important international research that leads to advancements in science and health care benefiting all populations, but also promote high ethical standards in research involving human biospecimens and associated data.

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