Building the Human Cell Atlas: Issues with Tissues

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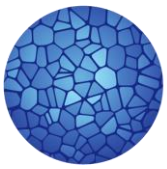

HUMAN CELL ATLAS

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Midway in the journey of our life
I came to myself in a dark wood,
for the straight way was lost.

Ah, how hard it is to tell
the nature of that wood, savage, dense and harsh --
the very thought of it renews my fear!

– Dante Alighieri, *Inferno*, Canto I (trans. Robert Hollander and Jean Hollander)

1. INTRODUCTION

Just as Dante found himself lost in a dark wood, scientists whose research involves human tissue frequently find themselves in a similar position. Dante's wood is the scientist's ever-growing body of norms. Legal norms in the form of laws and regulations. Professional and ethical norms by way of guidelines, policies, and consensus documents. These norms sprout from all levels – from the sub-national to the international. The objective of this article is to help scientists find their way. It is further hoped that through doing so, readers will develop a practical-yet-refined understanding of the role law and ethics play in the acquisition and use of human tissue for research purposes.

Our focus here is the norms governing the collection of and research on human tissue. An expansive concept of human tissue has been taken – from gametes, fetuses, embryos to other tissues from both living and deceased individuals. The article supports and builds upon the work of the Human Cell Atlas (HCA), whose mission is: "To create comprehensive reference maps of all human cells—the fundamental units of life—as a basis for both understanding human health and diagnosing, monitoring, and treating disease."[1] The mission is bold: there are an estimated 37.2 trillion cells in the average human body.[2] Such an undertaking requires that researchers be familiar with the norms that govern the acquisition and use of human tissue. In response to this need, an initial three Tissue Provenance Primers were prepared for the HCA, which dealt with norms governing human tissue research, from gametes to cadavers.[3] This article is a synthesis of the topics examined in those primers.

The article begins with key definitions. A brief overview of applicable international norms from organizations such as Council for International Organizations of Medical Sciences (CIOMS), World Medical Association (WMA), World Health Organization (WHO), the Council of Europe (CoE) and others are then presented. National legal and ethical norms from seven countries – Australia, Canada, France, Mexico, Singapore, the UK, and the US – are discussed with specific attention drawn to the similarities and differences across countries and tissue types. These countries have been selected to represent a range of approaches that can be taken. More concretely, the aim is to familiarize researchers working with human tissue to the central legal and ethical issues regarding its acquisition and use. Accordingly, the article explores consent approaches, including who can consent, what the content of the consent is, the form and procedure the consent

[1] Human Cell Atlas [Internet]. [cited 2019 Jul 4]. Available from: https://www.humancellatlas.org/

[2] Bianconi E, Piovesan A, Facchin F, Beraudi A, Casadei R, Frabetti F, et al. An estimation of the number of cells in the human body. Annals of Human Biology. 2013 Nov 1;40(6):463–71.

[3] The three primers, each individually authored by Sophie Béland, Roxanne Caron, and Seydina B. Touré, are available at https://perma.cc/2XQQ-GUC5.

must follow, etc. There is then a discussion of the recognition of possible "ownership" or "control" interests in human tissue. The varied prohibited acts with respect to the use of human tissue are also explored.

1.1. Methodology

The seven countries under examination in this article were selected to have diversity across geographies, cultures, and regulatory environments in regions of the world with a high output of human tissue research activity. With this in mind, the seven countries are located across North America, Europe, and Australasia. Diversity within each geographical area was also desired, thus multiple countries were chosen within each continent represented. As a result, the selection of Canada, Mexico, and the US aims to showcase the diversity of approaches in one continent, as is the case with France and the UK, as well as with Australia and Singapore.

It is worth noting that, of the seven countries examined, only Singapore, a city-state, is not subject to multiple layers of binding legal norms neither being a federal country[4], nor part of a multinational political union[5]. This is significant because international, national and sub-national (e.g., state, territorial, provincial) legal norms exist concurrently. This article's focus on the high-level ethical and legal norms governing human tissue research. Moreover, a detailed analysis of the interconnections between them is outside the scope of this current work, but links are discussed where possible.

A brief word on citations. Animated by a desire to have a document usable by scientists and other researchers, we have avoided citations of authorities for every proposition. Instead, Table 1 indicates the sources of national norms relied upon in the article. Footnotes with citations are used to bring the reader's attention to literature that further develops topics discussed.

Only foundational legal and ethical normative documents have been examined. "Foundational" here has two meanings, depending on the scale involved. At the international and regional scale, foundational refers to those documents from institutions who shape discourse and policy in the domain of human tissue research. Consequently, norms from organizations such as the WMA, WHO, United Nations Educational, Scientific and Cultural Organization (UNESCO), the European Union (EU), and others have been included. At the national scale, foundational refers to those legal instruments that govern human tissue research and those ethical documents that establish norms upon which access to major research funding is contingent. Accordingly and for example, Australia's *Research Involving Human Embryos Act 2002* and the National Health and Medical Research Council (NHMRC)'s *Ethical guidelines on the use of assisted reproductive technology in clinical practice and research* are included because all human-embryo research in Australia must comply with the former and accessing the NHMRC's crucial funding stream requires compliance with the latter.

[4] Federal countries examined: Australia, Canada, Mexico, and the US. Note that while the UK is formally not a federal country, it resembles one for the purposes of the regulation of human tissue research because norms vary among the four constituent regions of the UK (England, Wales, Scotland, and Northern Ireland).
[5] France and the UK are, at the time of writing, member states of the European Union.

Following the international norms, we turn to an examination of the similarities and differences regarding the legal and ethical regimes governing human tissue research in the seven countries under consideration. In light of this, the following questions guided our research:

- What are the necessary elements in the informed consent standard? (Sections 3.2.1 and 3.2.1.1.)
- Is secondary use for research purposes permitted? If so, under which circumstances? (Section 3.2.1.2.)
- Is broad consent recognized? If so, under which circumstances? (Section 3.2.1.3.)
- Is an "opt-out" model, whereby consent is presumed, recognized? If so, under which circumstances? (Section 3.2.1.4.)
- How are anonymized and coded tissue samples treated within the consent regime? (Section 3.2.1.5.)
- Are consent waivers recognized? If so, under which circumstances? (Section 3.2.1.6.)
- What are the procedural requirements with respect to obtaining consent? (Section 3.2.2.)
- Who can consent to research? (Sections 3.2.3, 3.2.3.1, and 3.2.3.2.)
- How are issues resolved regarding conflicting consent? (Section 3.2.3.3.)
- How can consent be withdrawn? (Section 3.2.4.)
- Are "ownership" or other property-based interests recognized in human tissue? (Section 3.3.)
- Which acts with respect to human tissue are prohibited? (Section 3.4.)

Building upon the answers to these questions, conclusions and recommendations are presented, but first a brief look at definitions.

1.2. Definitions

Definitions are the essential building blocks on which the legal and ethical normative landscape is based. Before deciding what *should* or *must* happen in a given context, terms require definitions to ensure consistent application. The specific definitions given to terms have significant downstream effects, often deciding whether a particular norm is applicable in a certain context. Many of the essential terms treated below have definitions that largely resemble one another across countries. Nevertheless, certain terms, such as fetus and embryo, show considerable variation.

Death

Generally accepted standards of medical practice recognize two methods for establishing death: cardiorespiratory death and brain death. In all countries under examination, both methods for determining death are recognized. As regards brain death, there is no international consensus on whether cessation of functions in the brainstem is sufficient, or whether the whole brain must have ceased functioning.[6] Two related key terms are *antemortem* and *postmortem*, the former meaning preceding death and the latter meaning after death.

[6] Smith M. Brain death: time for an international consensus. *BJA: British Journal of Anaesthesia*. 2012;108(suppl_1):i6-i9. doi:10.1093/bja/aer355

Embryo

It is perhaps unsurprising that the definition of embryo takes various forms in the countries examined. Owing the cultural and ethical sensitivity of embryonic research, countries tend to adopt definitions that suit their specific social and political contexts. Australia, Canada, and Singapore define embryo as a human organism developing for less than eight weeks (56 days) following fertilization or the first mitotic division. Mexico defines embryo as extending to the end of the 12th week of development (84 days). The UK's definition is slightly ambiguous, simply defining an embryo as a "live human embryo", which includes "an egg that is in the process of fertilisation or is undergoing any other process capable of resulting in an embryo". While US federal law does not define embryo, the US National Institutes of Health (NIH) defines the term as "any organism not protected as a human subject…that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells". France notably lacks any definition of the term.

Fetus

Fetus generally lacks a definition in the countries examined. Only Canada, Mexico, and the US define fetus, the former two countries choosing definitions that flow logically from their choice for their chronologically based definition of embryo. Thus, in Canada a fetus is a human organism following the 57th day of its development, and in Mexico a fetus is "the product of conception" from the 13th week of its development until birth. The principal US federal regulations for research on humans, the *Common Rule*, gives an expansive definition of fetus: "the product of conception from implantation until delivery".

Gamete (including ovum, sperm, etc.)

The term is generally not defined in norms, beyond frequently specifying that human gametes are a tissue and thus are a regulated object of legal or ethical norms. Without more, it thus appears self-evident that the biological definition is intended.

Residual (clinical) tissue

Residual clinical tissue refers to tissue that is excised during the course of clinical care and for which there is surplus or leftover material.[7] Because they have already been collected and are already in storage, these tissues are particularly valuable for research, all the more so if other information about the patient can be linked to the tissue. The use of such clinical tissues for research purposes would be considered "secondary use", defined below.

Secondary use

Secondary use is frequently undefined, its definition seemingly taken as self-evident. The *Tri-Council Policy Statement* (*TCPS2*), Canada's leading ethical norms for research involving humans, defines secondary use as "refer[ing] to the use in research of human biological materials originally collected for a purpose other than the current research purpose". As such, secondary use may refer to either human tissue initially collected for a separate research purpose than that

[7] Giesbertz NAA, Bredenoord AL, van Delden JJM. Inclusion of Residual Tissue in Biobanks: Opt-In or Opt-Out? *PLOS Biology*. 2012;10(8):e1001373. doi:10.1371/journal.pbio.1001373

for which its use is currently sought or to tissue initially collected for clinical care, whose use is now sought for research purposes.

Tissue

The approach adopted in defining tissue generally seeks to take an expansive definition and then carve out exceptions. For example, Singapore has defined human tissue as "any human biological material" but then provides a list of excluded human biological materials, e.g., hair shafts and nail plates. This approach facilitates an expansive approach to the regulation of human tissue research while allowing for considered exceptions. Where reproductive materials are regulated separately, as in the UK, gametes and embryos outside the human body are excluded from the definition of human tissue.

2. INTERNATIONAL AND REGIONAL NORMS

This section provides an account of those international and regional norms that govern human tissue research. At the outset, it should be noted that the individual from whom tissue derives should be considered as a research participant. That the primary material used in the research is human tissue excised from the body, rather than an individual human *per se*, does not generally change the protections and rights afforded to research participants. The discussion begins with an introduction to international norms, their characteristics, and their relationship to national norms. It then proceeds to give an overview of the aspects of human tissue research these international and regional norms seek to govern. The fundamental concepts in human tissue research that these norms introduce are explained more fully later in this article, where the specificities of national norms are explored. Annex 1, an edited compilation of key excerpts of international norms, should be consulted to better understand the substantive content of international norms governing human-tissue research.[8]

2.1. Overview of the Sources of International and Regional Norms

International norms must be distinguished from regional norms. International norms for the purposes of this article are norms created by global organizations. International norms intend to govern activities globally, whether research is done in remote parts of rural China or in Brussels. In the absence of Treaties or Covenants, international norms are generally professional or ethical norms. As such, they are commonly considered guidelines, which do not have the "force" of law and, without more, no penalties flow from their non-observance.

Regional norms, for the purposes of this article, are specific to European norms. The common European normative space is particularly well developed in large part to the work of the Council of Europe (CoE) and the European Union (EU). France and the UK, both examined in this article, are members of both the CoE and EU. The CoE's 47 member states include all of Europe, except Belarus and Kosovo. Three types of regional normative instruments from the CoE are included in this article: recommendations, conventions, and protocols to conventions. Recommendations reflect a consensus position from the member states and recommend the enactment of legislation in each member state. Even if not binding, the recommendations are nevertheless heavily relied upon for pan-European research. Conventions and their protocols thereto are binding – the member states are under an obligation to uphold the principles expressed therein. Two types of EU normative instruments are included in this article: opinions

[8] Annex 1 is accessible at http://bit.ly/2LtHbpe.

and regulations. Opinions, in this article, are those from the European Group on Ethics in Science and New Technologies (EGE), which inform policy-creation by the EU's executive body, the Commission. Regulations are the "hardest" kind of EU normative instrument, applying exactly as written within each member state.

Both international and regional norms are indispensable in setting standards for research globally. These norms have particular significance for researchers working in large research consortia, clinical trials, or in countries with insufficiently comprehensive domestic norms. In the context of the seven countries under study, these international norms provide the scaffolding upon which much of the domestic norms are built. International norms tend to be less specific than domestic norms, often allowing flexibility in the way they are implemented at the national level. For example, Mexico's principal ethical guidelines for research involving humans, the *Guía nacional para la integración y el funcionamiento de los Comités de Ética en Investigación*, directly quotes and builds upon principles derived from international and European norms.

2.2. Shaping Tissue Research: What the International and Regional Norms Establish

Free, informed consent is the guiding principle in international norms regarding human tissue research. In pursuance of conditions that makes such consent possible, researchers are under a duty to disclose sufficient information, in intelligible form, to research participants and tissue donors. Even where postmortem tissue donation is in issue, norms from the International Society for Biological and Environmental Repositories (ISBER) and the Council of Europe (CoE) specify that consent from the deceased, their next of kin, or other legal representative is primordial.

Certain guidelines, notably the World Medical Association (WMA)'s *Declaration of Taipei*, the Council for International Organizations of Medical Sciences (CIOMS) / World Health Organization (WHO)'s *International Ethical Guidelines for Health-related Research Involving Humans*, the EU's *General Data Protection Regulation* (*GDPR*), and the CoE's *Recommendation CM/Rec(2019)2 of the Committee of Ministers to member States on the protection of health-related data* recognize informed broad consent to research under certain conditions, e.g., on-going governance and the research involves no more than minimal risk of harm. Perhaps unsurprisingly, other norms originating from these bodies also explicitly recognize consent waivers and opt-outs (presumed consent or notification).

In addition to foundational aspects of consent, many international norms also emphasize the need for researchers to ensure the confidentiality and privacy of donor-participant information. Privacy interests may be assimilated to other kinds of participant interests such as bodily integrity. As such, risks of privacy-related harms should be proportionate to the aim pursued, as is done with other risks.

There is also a consensus that participant-donors should not be compensated for their tissue, aside from reasonable out-of-pocket expenses or for time and inconvenience. Such a position seeks to prevent the commodification of human tissues and to protect certain vulnerable groups from exploitation. In a similar vein, norms from the International Society for Stem Cell Research (ISSCR) and the International Federation of Gynecology and Obstetrics (FIGO) emphasize the need for additional protections for oocyte and embryo donors, preventing undue influence and coercion, and thus allowing free and informed consent to research participation.

3. NATIONAL NORMS

For all tissue types, national norms complement the above.[9] These national norms can be divided into two broad categories – legal and professional/ethical. This section provides a brief description of each category of norms before giving country-specific overviews of the key legal, professional and ethical instruments that create such norms.

Legal norms are rules enacted by governments, often in the form of either legislation (statute) or regulations. Within a single country, there are often sub-national entities that may also generate legal norms, e.g., states, provinces, and territories in Australia, Canada, Mexico and the US, and the devolved regions of the UK. A comprehensive review of the norms originating from all sub-national bodies is outside of the scope of this article. Accordingly, researchers should seek out further resources to determine whether there are additional norms to which their research will be subject.

Professional and ethical norms are primarily created by professional associations, panels, and other bodies. Oftentimes governmental agencies or funding bodies may also create ethical norms, as is the case with the UK's Human Tissue Authority's *Codes of Practice* and the US's NIH *Grants Policy Statements*. Even though these norms do not have the same "force" as their legal counterparts, they can nevertheless have great influence on the conduct of research because access to funding is contingent upon research conforming to these norms.

Both legal and ethical/professional of norms must be consulted to determine the proper methods for tissue collection and use. While many legal norms aim to be comprehensive, they nevertheless leave much discretion to researchers. As such, professional and ethical norms often complement legal norms by filling lacunae.

3.1. Overview of National Legal and Ethical Norms

Turning to the varied legal and ethical norms governing the collection and use of human tissue for research purposes in each of the seven countries, this section complements Table 1 through a discussion of the norms listed therein. Each country is considered separately, giving an overview of its respective national normative landscape. The next section then explores and compares the substantive similarities and differences among the seven countries' normative frameworks for human tissue acquisition and use for research purposes.

3.1.1. Australia

In Australia, only embryonic tissue, and for certain purposes, human oocytes, are the subject of national ("Commonwealth") laws. Specifically, the *Research Involving Human Embryos Act 2002*, its accompanying *Research Involving Human Embryos Regulations 2017*, and the *Prohibition of Human Cloning for Reproduction Act 2002* govern the collection and use of embryos and oocytes. These laws work in tandem with two sets of ethical guidelines from the National Health and Medical Research Council (NHMRC): the *Ethical guidelines on the use of assisted reproductive technology in clinical practice and research* and the *National statement on ethical conduct in human research* ("*National statement*"). This former set of guidelines covers

[9] For a more comprehensive treatment of the relationship between international and national legal and ethical norms, see Campbell A, Glass KC. The legal status of clinical and ethics policies, codes, and guidelines in medical practice and research. *McGill LJ*. 2000;46:473.

the use of gametes, embryonic, and fetal tissue for certain research purposes. It works in tandem with the *National statement* to create a comprehensive regime of ethical guidelines. The *National statement* is a more general, foundational document, specifying the ethical guidelines for research involving humans (and human tissue) in general. Notably, legislation often refers to the *National statement* for defining such things as "proper consent". Because Australia is a federal country, the laws of the Australian states and territories also have an important role to play. Each state and territory has their own similar and nationally consistent laws to the two 2002 Commonwealth Acts, as well as *Human Tissue Acts*, which govern other types of human tissue.

3.1.2. Canada

Similar to Australia, the only national, or "federal", law applicable to research on human tissue are the *Assisted Human Reproduction Act* and its *Assisted Human Reproduction (Section 8 Consent) Regulations SOR/2019-195*. The primary set of professional and ethical norms are the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans 2014* (*TCPS2*), developed by Canada's three federal funding agencies: the Canadian Institutes of Health Research (CIHR), the Social Sciences and Humanities Research Council (SSHRC), and the Natural Sciences and Engineering Research Council (NSERC). The guidelines are comprehensive, covering all types of human tissue. Due to Canada's federal structure, provincial and territorial laws govern the collection and use of human tissue. These sub-national laws work in conjunction with the *TCPS2*.

3.1.3. France

The bedrock to France's normative fabric is Chapter 2 of Title 1 of Book 1 of the *Code civil*, which establishes key concepts for the respect of the human body. Building upon these concepts, the *Code de santé publique* presents a comprehensive normative structure that governs all aspects of human tissue research within Metropolitan France. Moreover, the Comité consultative national d'éthique pour les sciences de la vie et de la santé (CCNE) plays a central role in France's normative space by guiding much of the public debate preceding revisions to France's bioethics laws. Notably, a major revision to the bioethics provisions to the *Code* concerning, among other things, the regulation of ART and embryos, is expected later in 2019. As a member of both the EU and the CoE, the norms emanating from these bodies also feature prominently in the national normative landscape.

3.1.4. Mexico

In Mexico, the *Ley General de Salud*, and its accompanying *Reglamento de la Ley General de Salud en Materia de Investigación para la Salud*, *Reglamento de la Ley General de Salud en Materia de Control Sanitario de da Disposición de Organos, Tejidos y Cadáveres de Seres Humanos*, and *Norma Oficial Mexicana NOM-012-SSA3-2013* work together to create a comprehensive legal framework for the collection and use of human tissue. The Comisión Nacional de Bioética's *Guía nacional para la integración y el funcionamiento de los Comités de Ética en Investigación* builds upon the principles developed in these legal documents. Missing from Mexico's normative fabric is the use of embryos – there is no definitive legal or ethical guidance concerning the use of embryonic tissue for research purposes. As a response to this, the ART community in Mexico has turned to self-regulation, issuing a national consensus document. As another federal country, state laws may also be applicable.

3.1.5. Singapore

Singapore has two comprehensive laws governing the collection and use of human tissue for research purposes. For tissues derived from living individuals, including gametes and embryos, the *Human Biomedical Research Act 2015* and its two accompanying regulations, the *Human Biomedical Research (Restricted Research) Regulations 2017* and the *Human Biomedical Research (Exemption) Regulations 2018* apply. For tissues from deceased individuals, including fetal tissue, the *Medical (Therapy, Education and Research) Act* applies. The *Human Cloning and Other Prohibited Practices Act* also establishes a variety of prohibited acts involving certain uses of gametes and embryos. The Bioethics Advisory Committee (BAC)'s *Ethics Guidelines for Biomedical Research* establish ethical norms concerning research on human tissue and work in concert with the *Human Biomedical Research Act 2015*.

3.1.6. United Kingdom

The UK has three principal laws governing the use of human tissue for research purposes. The *Human Tissue Act 2004* governs the storage and use of tissues from living and deceased individuals for certain research purposes in England, Wales, and Northern Ireland. The *Human Tissue (Scotland) Act 2006* only governs the use of human tissue from deceased individuals. The *Human Fertilisation and Embryology Act 1990* applies throughout the UK, and governs the collection and use of gametes and embryos. The common law, which governs the removal of tissue, works in tandem with these statutes. As regards ethical guidelines, the Human Tissue Authority (HTA)'s *Codes of Practice and Standards* create a comprehensive ethical framework that works with the *Human Tissue Act 2004* and the common law to govern the collection and use of human tissue from living and deceased individuals, to the exclusion of gametes and embryos. Also relevant for tissue for deceased individuals is the Nuffield Council on Bioethics' ethical framework in their *Human Bodies: Donation for Medicine and Research*. Finally, the Human Fertilisation and Embryology (HFEA)'s *Codes of Practice* complete the normative puzzle, working alongside the *Human Fertilisation and Embryology Act 1990* and the common law to govern the collection and use of gametes and embryos. As is the case with France, the UK's membership to both the EU and CoE means that regional European norms influence the national normative landscape.

3.1.7. United States

In lieu of governing human tissue research *per* se at the federal level, the US's regulatory approach governs access to federal funding for research. That is, research funded through other means is not subject to many federal regulations. The principal legal norms governing the collection and use of human tissue for research purposes are set out in part 46 of title 45 of the Code of Federal Regulations (45 CFR part 46). Subpart A of the regulations constitutes the *Federal Policy for the Protection of Human Subjects*, better known as the *Common Rule*. The *Common Rule* establishes a baseline of protections for human participants in research conducted, funded, or regulated by any of the 20 US federal agencies who have adopted it. Subparts B, C, and D supplement the *Common Rule* by providing additional protections for certain vulnerable population groups, e.g., pregnant women, incarcerated individuals, and children. Notably, however, the *Common Rule* does not apply to research concerning deceased individuals. Furthermore, the *Public Health Service Act* governs, among other things, research on the transplantation of human fetal tissue funded by the Department of Health & Human Services. The collection and use of tissue from deceased individuals is primarily a question for state law.

At the time of writing, all states, except Florida and New York, have adopted the *Revised Uniform Anatomical Gift Act* (*UAGA*). The *UAGA* creates a comprehensive legal framework for tissue donation for deceased individuals. References to US legal norms governing tissue from deceased individuals are to the *UAGA*.

A panoply of ethical norms complement these legal norms. The use of embryonic tissue for stem cell research is subject to a variety of ethical guidelines, including the American Society of Reproductive Medicine (ASRM)'s *Donating embryos for human embryonic stem cell (hSEC) research: a committee opinion*, the NIH's *Guidelines for Human Stem Cell Research*, and the National Academies' *Guidelines for Human Embryonic Stem Cell Research*. For tissue from deceased individuals, key ethical guidelines include the American Association of Anatomists (AAA)'s *Body Donation Policy* and the Consensus Panel on Research with the Recently Dead (CPRRD)'s *Ethics Guidelines for Research with the Recently Dead*. Much like Australia, Canada, and Mexico, the federal structure of the US means that many states have their own laws regarding human tissue research.

3.2. Consent Approaches

Legal and ethical norms in all countries examined require that consent be obtained for the use of tissue in research. Consent is grounded in the concept of individual autonomy; individuals have the right to decide whether or not to participate in research, and this applies with equal force to the use of their tissues. This section gives an overview of the varied consent approaches in the seven countries under study. The section is divided into four sub-sections: the standard and content of consent (3.2.1), procedural requirements with regard to consent (3.2.2), who must give consent (3.2.3), and withdrawal of consent (3.2.4). Table 2 provides a high-level summary of the recognition of consent approaches in the seven countries under study.

3.2.1. Standard and Content of Consent

The consent standard gives substance to the concept of individual autonomy mentioned above. Researchers are under a duty to provide sufficient information so that an individual participant is able to look after their own best interests, however defined. If norms require that a research participant be aware of, e.g., the potential harms that may flow from participation, it is the researcher's duty to ensure that sufficient information is given about potential harms.

The sub-sections that follow will deal first with the required elements of the informed consent standard. Related concepts such as secondary uses, broad consent, and opt-out / presumed consent are then discussed. Finally, the circumstances in which consent may not be required are treated, viz., where tissue samples are anonymized or coded, or where a consent waiver is sought.

3.2.1.1. Elements of Consent

Consent must be informed. This goes to the content of the consent – to what uses or purposes are tissue donors consenting? Requirements as to the content of consent impose duties on the researcher to disclose sufficient information to the participant so that the participant understands the nature, purpose, and implications of their participation. While the specific language may differ across countries, some general propositions may be distilled for all tissue types, except for tissue derived from deceased individuals (more below).

Unsurprisingly, it is a universal requirement that the nature and purpose of the intended research should be explained to the prospective participant. Even where broad consent is sought, some description of the general purposes or fields is required. (For more on broad consent, see section 3.2.1.3.) Risks and benefits of participation should also be discussed. Information about confidentiality is another common requirement, whereby researchers must explain the measures taken to protect participant privacy. All countries, except France and Mexico, also have specific provisions for the disclosure of information regarding storage and/or disposal of the collected biospecimens. Canada and the US supplement this disclosure requirement to include the expected duration of storage. What to do with incidental findings are also frequently the subject of research norms. Australia, Canada, Singapore, and the UK all require researchers to have considered the possibility of incidental findings and inform participants about the potential of such findings, along with the established procedure for their handling.

Norms frequently aim to ensure participants are aware of any implications due to peculiarities in the consent regime itself. For example, in Singapore researchers must inform participants about the conditions under which they are able to withdraw consent and the potential that research data generated prior to withdrawal may still be used. Another example of this is in the US *Common Rule*, where researchers must explain to participants that if biospecimens are de-identified, they may be used for future research projects without additional informed consent. Such requirements further the purpose of information-giving, namely to ensure the participant understands the implications of their choice prior to consenting.

Information that must be disclosed to participants may also vary according to certain kinds of sensitive research. For example, norms from Australia, Canada, the UK and the US have special requirements for research on biospecimens from which human stem cell lines may be derived, as well as for genomic research. Such requirements should be understood as part of lessons learned from past research projects such as the HeLa stem cell line, where the lines were created without the tissue donor's consent.[10] Researchers must tell participants that human stem cell lines derived from their tissue donations may be used indefinitely, and that while resulting discoveries may have commercial potential, participants will not benefit from such potential. As regards genomic research, researchers are to provide additional information about the implications of such research to participants.

The informed consent standard for tissues that will be excised and used in research only after death is generally less stringent. Certain elements of informed, specific consent are not applicable. For example, the specific research project is frequently impossible to know when consent is sought as the donor's time of death is unknown. Typically, donors must only specify which tissues are to be donated, e.g., eyes, kidney, whole body, etc., and the general purpose for which the tissue is being donated, e.g., teaching, research, etc. Ideally, consent to tissue donation and use after death should be obtained during the prospective donor's lifetime. Even though additional information-giving is not required in the strict sense, as much information as is practicable should be given. In particular, it is a best practice to discuss potential benefits and harms with prospective donors whose tissues will be used after their death, especially where the research will involve genomics as such research may have implications for relatives.

[10] For an overview of the history of the HeLa cell line, see Masters JR. HeLa cells 50 years on: the good, the bad and the ugly. *Nature Reviews Cancer*. 2002;2(4):315-319. doi:10.1038/nrc775.

3.2.1.2. Consent to Secondary Uses

Consent for secondary use must be distinguished from consent for primary use. Where an individual consents to specific research or to clinical use of their tissue, this consent does not extend to other, so-called "secondary" uses. In the research context, secondary use denotes a use of biospecimens or data that is distinct from the initial research purpose for which the biospecimens or data were collected. Likewise, in the clinical setting, where tissue is excised for diagnostic or other care-related purposes, the patient's consent typically does not extend to research uses of such tissue. Uses such as quality assurance and teaching generally fall under the umbrella of clinical care and do not require separate consent.

Certain countries, e.g., Singapore and the Canada, recommend that consent for research be separate from consent for clinical care, prioritizing the latter. While Singapore's BAC recognizes that "every effort should be made" to use surplus clinical biospecimens for research uses, they nevertheless say that consent to research should be obtained only after consent to clinical care has been made. Canada, on the other hand, recommends a "clear distinction" between consent to clinical and to research uses but leaves leeway as to how this is to be achieved in practice. Others, such as the UK and Australia, permit consent to research to be sought in the clinical context, but specify that some degree of separation between clinical and research consent is required for gametes and embryos. Specifically for the UK, consent is not required for the use of already stored tissues for a non-scheduled purpose under the *Human Tissue Act 2004*, such as for public health monitoring. The US's *Common Rule* acknowledges the possibility of using surplus clinical biospecimens, but it is silent on whether any distinction or separation of clinical and research consent is necessary. Mexico's norms are silent on the issue of secondary use. France notably follows an opt-out approach to residual clinical tissue. Patients are provided with a notification that the tissues left over from their clinical care will be used in research, unless the patients object. (For more on opt-out approaches to consent, see section 3.2.1.3.) Despite the differences in approach, there is general consensus that research on fetal or embryonic tissue requires that consent to research be separate from consent to any clinical care.

Alternatively, under limited circumstances, a consent waiver may be sought. Generally, waivers for the research use of residual tissue may only be obtained where researchers cannot, without undue burden, contact the individuals concerned. Such is the approach in Australia, Canada, and France. (For more on waivers, see section 3.2.1.6.) The UK requires consent for use of residual tissue unless the researcher is not in the possession of information that can identify the person from whom the tissue originated and the tissue is released by a licensed tissue bank with "generic ethical approval" from a research ethics committee (REC) for research that is within the ambit of the approval, or where the tissue is destined for a specific, REC-approved research project.

3.2.1.3. Broad Consent

Recognized in all countries under study except Mexico[11], broad consent is a model in which research participants are informed that, subject to governance, their data and samples will be used for unspecified future research. Broad consent may also be referred to by other names. UK norms frequently refer to such consent as "generic" consent. Australia notably draws a

[11] While not explicitly recommended in the *TCPS2*, researchers working with population cohorts over the last decade in Canada have used broad consent. For further information, see Allen C, Joly Y, Moreno PG. Data sharing, biobanks and informed consent: a research paradox. McGill JL & Health. 2013;7:85.

distinction between “extended” consent and “unspecified” consent. The former refers to consent that encompasses future research that is closely related to the original project or in the same area of research, such as cancer research. The latter is a more far-reaching consent that encompasses use for any future research.

Best viewed an extension of the informed consent standard, broad consent does not amount to a carte blanche for researchers. Where researchers seek broad consent, they should discuss the general nature of the envisioned research, as well as the manner in which tissues will be conserved, data will be protected, and the established governance structures for access. Broad consent usually includes provisions for ongoing monitoring and ethics approvals. Beyond merely recognizing broad consent, norms from the UK’s Human Tissue Authority and Medical Research Council encourage broad consent to be sought, and the former body’s guidelines stipulate that researchers should discuss with research participants the benefits giving broad consent may have.

Despite wide recognition, broad consent is not considered appropriate for all tissue types. Namely, embryonic tissue research generally requires consent to a specific research project. However, France expressly recognizes broad consent for embryonic tissue research, and US norms generally stress the need for embryo donors to be aware of the implications of human stem cell research, rather than knowledge of the specific research project.

3.2.1.4. Presuming Consent: Opt-out vs Opt-in

Traditional consent models are “opt-in”, that is, individuals must give their consent to the use of their tissues. In an “opt-out” model, by contrast, individuals are considered to have consented to the use of their tissues for research, unless, after notification of the research, they “opt out”. For example, an opt-out approach would ensure that an individual giving tissue for clinical care would be provided with notice that their tissue will be used for research purposes and that they have the right to withdraw their consent to the use of their tissue for research purposes.

The distinction between research and therapeutic or transplantation purposes is especially important when considering an opt-out model. Only France follows an opt-out model for postmortem organ donation for research purposes but still requires opt-in for whole-body donation. Whereas Singapore and the UK, except Northern Ireland, have followed opt-out models for postmortem organ donation for therapeutic purposes, donation for research remains subject to a traditional opt-in model.

France has the most extensive opt-out approach to consent for research purposes. Founded on the notion of “national solidarity”, the use of postmortem tissue for research purposes and use of residual clinical tissue for research purposes is subject to an opt-out model. France’s robust opt-out system does, however, have two important caveats. The opt-out model does not apply to gametes collected for research purposes nor to umbilical cord and placenta tissue collected for clinical use.

Australia is the only other country under study whose norms expressly permit an opt-out approach regarding research samples under limited circumstances: the REC must have approved the use of the opt-out, the research must be low-risk, the research’s integrity relies on a near-complete rate of participation, etc. The circumstances in which an opt-out approach may be implemented may be limited to certain kinds of research. For example, Australia’s ethical guidelines do not permit an opt-out approach to be used for genomic research.

3.2.1.5. Anonymized or Coded Samples

Frequently, it is the possibility or reasonable likelihood of identifying an individual from biospecimen data that prompts the application of research norms. Thus, research on anonymized or coded samples may not require the consent of the individual from whom the tissue was derived. Roughly speaking, the anonymization of samples consists in irreversibly removing any data from samples that could lead to a reasonable likelihood of re-identification of an individual from whom those samples derive. Related to anonymization is coding. Where data undergo a coding process, data that would enable someone to readily identify the individual from whom a sample or data are derived are replaced with a code or pseudonym. Re-identification is then made possible via access to the key that links the codes to an individual.

The distinction between anonymized and coded samples is important for the applicability of certain norms. For example, the US *Common Rule* does not apply to coded biospecimens, or the data generated therefrom, provided that such biospecimens were not first obtained through direct researcher-participant interaction, as is the case for secondary uses. That is, in the US, tissues and associated data may be anonymized and then used in other research without again prompting consent requirements. In the UK, consent is not required where tissue samples have been coded, the researcher does not have access to the identification key, and the research project has been approved by a National Health Service Research Ethics Committee (NHS REC). Another example of consequences flowing from the distinction between identifiable and de-identified data (certain identifiers removed) is the ambit of Singapore's *Human Biomedical Research Act 2015*: where biospecimens, excluding human gametes and embryos, have been de-identified, the Act does not apply. That anonymized embryos and gametes remain subject to consent rules is not unique to Singapore. In a similar vein, Canada's recently amended *Assisted Human Reproduction (Section 8 Consent) Regulations SOR/2019-195* require researchers to obtain a signed document, which confirms consent to research, from the gamete donor, before the donor is anonymized. Nevertheless, it is important to note that even where consent is not required, ethical guidelines generally still recommend obtaining it whenever practicable.

3.2.1.6. Consent Waivers

Waivers enable researchers to forego certain requirements of the informed consent standard. Issued by a REC, research ethics board (REB), institutional review board (IRB), or other analogous body, a consent waiver permits researchers to forego either substantive or procedural consent requirements for the collection and use of samples for initial research, or for a use that is different from the initial research purpose. For example, a REC may determine that no additional consent must be sought, or may determine that consent, which is normally obtained in writing, may be obtained orally. Where recognized, consent waivers generally apply to both primary- and secondary-use samples.

Waivers are more broadly recognized than opt-out approaches. All of the countries examined, except Mexico[12], recognize consent waivers in certain circumstances. Of these, all but

[12] In 2014, the Mexican federal government amended *the Reglamento de la Ley General de Salud en Materia de Investigación para la Salud*, derogating from provisions that allowed researchers to seek a consent waiver from ethics boards. Nevertheless, the *Norma Oficial Mexicana, NOM-012-SSA3-2013*, still permits a waiver to be sought. Those conducting research to which Mexican norms may apply should seek additional advice regarding the suitability of waivers.

France, have national guidelines specifying factors to take into consideration where a waiver is sought. While such conditions vary by country, some general principles can be distilled. The research should involve minimal risk to the research subject, and the use of the tissues in question must be essential to the completion of the research. Other factors include the fact that obtaining consent would be impracticable, e.g., due to the age or quality of contact information, and that the individual from whom the tissue derives did not previously object to the purpose for which the researchers now seek to use the tissue.

Despite wide recognition, there are a few circumstances in which waivers may not be suitable. These specific exclusions are in addition to the general requirements that the proposed research be low risk, etc. France, for example, does not permit waivers where the research involves gametes. Additionally, the US Common Rule does not permit a waiver if broad consent was offered and declined. The limited number of these exclusions suggests that the decision to grant a waiver is a richly contextual one for an REC to make, rather than one suited to bright-line rules.

3.2.2. Procedural Requirements with Respect to Consent

The previous section has dealt with the substantive aspects of consent, primarily the *content* the consent must have and when the typical informed consent standard may be departed from. In addition to the content of consent, there are frequently procedural requirements governing the taking of consent. Rather than answering *for what* consent is given, procedural requirements answer *how* consent must be given. Procedural requirements often assist in providing evidence of informed consent, or afford participants additional opportunity to reflect on their decisions regarding research participation.

Aside from consent needing to be given prior to research starting, the most common procedural requirement with respect to consent relates to written consent. Across the countries examined, there is general consensus that mere oral consent is insufficient. Most frequently consent must be written, but oral consent may be permitted where it is documented in writing or given in the presence of a witness. This latter requirement is specific to postmortem tissue donation. Such a procedure recognizes the possibility that an individual may wish to consent to tissue donation during a final illness where written procedures could be unduly burdensome. Norms in Australia, Canada, Singapore, the UK and the US all allow for these approaches. [13] Mexico, however, has rigid requirements for postmortem organ donation – such consent must be in writing, attested to by two witnesses, or done in the presence of a public notary.

The UK is the only country examined with legal and ethical norms specific to human tissue that do not require written consent, provided the research does not involve tissue from deceased individuals or any reproductive materials such as gametes, embryos, etc. Nevertheless, these UK norms still recommend that a record of consent be kept. France and Mexico require written consent for all tissue types. Australia, Canada, Singapore, and the US have norms that permit oral consent, but these norms are not specific to human tissue research. Rather, they are norms that govern any research involving human subjects. In light of this, it is recommended that, where possible, consent be obtained in writing, even where norms may permit otherwise.

[13] Because France follows an opt-out model for postmortem tissue donation, no additional procedural requirements exist as consent is presumed. For Australia, Canada, and the US, postmortem tissue donation is an issue for the states, provinces, and territories. As such, slight variations may exist but the consensus position stands.

Procedural requirements are most prevalent in the context of fetal and embryonic tissue research. As with other requirements seen regarding the use of fetal and embryonic tissue, these procedural requirements can be seen as reflecting the sensitivity of the issues surrounding the use of such tissue for research. Of the countries examined, there is consensus that consent must be obtained in writing. Moreover, there is consensus that the research consent process should be separate from the clinical care process for both IVF embryos and fetal tissue. The required level of separation does, however, vary by country. For example, Singapore's *Human Biomedical Research (Restricted Research) Regulations 2017* give a bright-line ban on the fusion of the role of researcher and clinician – the researcher cannot be involved in the clinical care of the donor of either embryos or oocytes. By contrast, Canada's ethical guidelines state that members from the clinical team may obtain the initial research consent from embryo donors, but should not be the ones to seek re-consent.

Beyond the separation of consent processes, "cooling-off" periods are frequently required for embryonic and fetal tissue research. A cooling-off period provides a time lapse between when information is given and when consent is obtained, or when consent is obtained and research begins. The former approach allows research participants to reflect on their choice before giving consent, while the latter affords participants the opportunity to withdraw consent before the tissues are used. For both embryos and oocytes, Singapore requires that consent to research donation be obtained only after eight days following the disclosure of all relevant information. France requires initial consent to be re-confirmed by writing after three months for embryonic research, except for research involving embryos of poor quality that cannot be implanted and those having been used for pre-implantation diagnosis (PGD). Canada's ethical guidelines in *TCPS2* specify that for human embryonic stem cell research, consent must be sought again from the appropriate parties prior to commencing research. In a similar vein, Australian guidelines require that embryo-destructive research not commence until at least two weeks after consent was given, allowing for the relevant parties to withdraw their consent before research commences.

3.2.3. Who Must Give Consent

The previous two sections analyzed the substance consent must have and the procedure the taking of consent must follow. This section builds upon these topics and considers *who* is able to consent to research in particular contexts. Three subsections will follow, which examine consent from the tissue contributor (3.2.3.1), substitute consent (3.2.3.2), and resolution of consent conflicts (3.2.3.3).

3.2.3.1. Consent from the Tissue Contributor (First-Party Consent)

Across the seven countries, the general position is as follows: where the individual from whom the tissue derives is a living, mentally competent adult, consent must be sought from that individual. This is the position for all tissues, including gametes. However, where embryonic or fetal tissue is in issue, there are some complexities owing to the fact that the tissue derives from two individuals and may have even been created for the reproductive purposes of still other individuals.

For embryonic tissue research, there is consensus that, at minimum, consent is required from the individual(s) from whom the embryo originates. Where the embryonic tissue is from surplus embryos after the cessation of ART, the unanimous consent of the couple who sought

ART is required. Where a couple who sought ART has used gametes donated by other individuals for the creation of embryos, the consent picture can get complex. For example, Australia's *Research Involving Human Embryos Act 2002* requires consent for the use of excess ART embryos to be sought from each gamete-provider and their partner (if any) at the time of donation, as well as the woman for whom the embryo was created and her partner (if any) at the time the embryo was created. Such an approach potentially implicates the consent of six individuals where embryos were created from the gametes of two individuals, both of whom have partners, for another couple. A similar, but less expansive approach is found in Canada's *Assisted Human Reproduction Act*, which requires consent to be sought from the couple for whom the embryo was created, as well as gamete-providers, if they are different individuals. The UK's *Human Embryology and Fertilisation Act 1990* notably only requires the consent of gamete-providers with respect to research on embryos. Norms in France and Singapore require the consent from the members of the couple from which the embryo originates. Ethical norms in the US show a variety of approaches: while the American Society for Reproductive Medicine requires the joint agreement of the partners, the National Academies recommend consent from gamete-providers. Mexico notably does not have any federal regulations on the use of fetal and embryonic tissue for research. [14]

As regards fetal tissue, consent is generally only required from the woman whose pregnancy was terminated. While fetal tissue donation is governed by the laws of Australian states and territories, Australia's National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* recommends that consent be sought from the woman. The US has a similar position, with issues regarding fetal tissue being largely a question of state legislation. For fetal tissue transplant research funded by the US Department of Health and Human Services, consent is to be sought from the woman whose pregnancy was terminated. An outlier is Singapore's *Medical (Therapy, Education and Research) Act*, which allows for either "parent", presumably those individuals whose gametes combined to create the fetus, to consent to the use of its tissue for research.

3.2.3.2. Consent on Behalf of Another (Substitute Consent)

In certain circumstances, others may be able to consent on behalf of an individual from whom a tissue derives. This may also be called substitute, or third-party, consent. The circumstances in which substitute consent may be recognized are based on the status of the person from whom the tissue originates and may be divided into three categories: minors, adults lacking capacity, and deceased individuals. The first two will be dealt with together.

Special regimes apply to minors and adults lacking capacity. The latter group frequently includes the elderly or other populations who are particularly vulnerable owing to their mental

[14] As of June 2019, Mexico still does not have a federal law governing the use of embryos and stem cells for research, despite repeated calls from the medical and scientific communities. See, e.g., Mansilla-Olivares A, Rojo J, de Jesús Medina M, et al. Posición de la Academia Nacional de Medicina de México con el fin de regular el uso de células troncales y de embriones humanos para fines terapéuticos o de investigación. *Gaceta Médica de México*. 2018;154:729-731 and Kably Ambe A, Ortiz CSL, Serviere Zaragoza C, et al. Consenso nacional Mexicano de reproducción asistida. *Revista Mexicana de Medicina de la Reproducción*. 2012;4(2):68-113.

state. As a general proposition, minors and adults who lack capacity cannot consent on their own. This idea is rooted in the idea that meaningful consent is only possible where the consenting individual has the capacity to understand the implications of research participation and to look out for their best interests.

For minors and adults lacking capacity, consent must be obtained from a designated third party, e.g., a parent or legally authorized representative, who has the authority to do so. However, guardians or representatives cannot necessarily consent to the same research activities as adults with full capacity. France's *Code de la santé publique*, for example, specifies that embryonic and fetal tissue from a woman who is a minor or under guardianship cannot be used for research, other than for an investigation into the reason for which there was a miscarriage or stillbirth. Similarly, Canadian legislation only allows for the collection of gametes from minors for their own future reproductive use and not for research purposes.

Of particular import is that even in countries with national ethical guidelines that govern research on tissues obtained from minors or adults lacking capacity, sub-national laws may further specify the conditions under which such research must be conducted. For example, Canada's *TCPS2* works in tandem with Article 21 of the *Civil Code of Quebec* to create a comprehensive consent regime for minors and adults lacking capacity. However, a detailed overview of the varied regimes for tissues derived from minors and adults lacking consent is outside of the scope of this article.[15]

The issue of third-party consent is most evident in the context of tissues derived from deceased individuals. In most of the countries studied[16], the unambiguous antemortem objection of the deceased will preclude family members from authorizing the donation of the deceased person's tissue, organs or whole-body. Some countries also forbid tissue donation if there is the reason to believe that the deceased *would have* objected to the donation, even if they have not done so expressly. In most Canadian provinces and US states, law expressly precludes the possibility of family members or other legal relations of the deceased overriding or 'vetoing' antemortem consent/objection to the use of tissues, organs, or whole body for research purposes. Put simply, the antemortem consent/rejection of the deceased is binding. Pending no evidence of the deceased's objection, however, family members are permitted to consent on the deceased's behalf. It should nevertheless be considered a best practice to seek the consent of individual donors while capable if practicable.

Finally, where a cadaver remains unidentified, a separate consent regime may apply owing to the fact that the wishes and next of kin of the deceased may be impossible to ascertain. For example, in Singapore, where a body has not been claimed within 24 hours of death, the Director of Medical Services may authorize its use for research. Mexican federal law similarly specifies that the normal regime for postmortem tissue donation does not apply to unidentified cadavers, such use needing to be authorized by the Minister of Health.

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[15] For a more thorough treatment of issues of capacity in biomedical research, see Dalpé G, Thorogood A, Knoppers BM. A Tale of Two Capacities: Including Children and Decisionally Vulnerable Adults in Biomedical Research. *Frontiers in Genetics*. 2019;10:289. doi:10.3389/fgene.2019.00289

[16] Mexican law does not specify if the donor's antemortem objection or consent is binding and would disallow family members from affirmatively or negatively consenting on their behalf.

3.2.3.3. Resolution of Disputes as to Consent

Permitting consent to be sought from multiple individuals opens the door to having conflicts over consent. One involved party may consent while another does not. Across the countries studied, the regimes for resolving conflicts as to consent are piecemeal. Certain countries require unanimous consent, giving each interested party a veto over the use of tissue for research. Such an approach may be understood as privileging choices to not participate in research on tissue. This is generally the approach taken for research on embryonic tissue – the unanimous consent of the involved parties is required. A noteworthy approach is found in Canada's *Assisted Human Reproduction Act.* Any use of excess IVF embryos requires unanimous consent from both partners, giving any partner a "veto" over the use of the embryo. However, where one member has contributed gametes while the other has not, the gamete-contributing partner has the exclusive right to make decisions regarding the use of the excess embryos when those individuals are no longer in a partnership and the embryos have not yet been used.

Sometimes disputes as to the use of excess IVF embryos upon partnership breakdown have reached courts of law. The only cases reported are those that involve disputes about the use of excess embryos for procreational ends – no case regarding the use of embryos for research has yet reached courts. Canadian[17] and UK[18] courts have chosen to rely on the notion of continuing consent from both partners enshrined in the applicable national legislation to settle the disputes. On the other hand, some courts in the US, in absence of the separating couple having recorded their mutual wishes for the fate of the embryos, have engaged in a multifactorial analysis that seeks to balance the two sides of procreational autonomy – the right to reproduce and the right to avoid reproduction.[19] In response to disputes over the use of embryos, the US State of Arizona has enacted legislation that compels courts to award embryos to a member of a couple who wants to use them for procreational ends.[20]

Without any specific norms on this point, it remains an open question whether the decision-making control awarded over embryos for reproductive use by a court should itself be sufficient to use any embryos for research purposes if the reproductive project for which the embryos were awarded has since ended. Relying on the general norms, it would appear that consent should still be sought from the other member of the couple. Losing procreational autonomy should not also entail the loss of the ability to decide whether embryos should be used in research, especially in the context of the generation of human stem cell lines, which can last indefinitely.

Any disagreements as to consent for postmortem tissue donation are generally resolved by a legally defined list of individuals who can consent and the priority their consent receives. Typically, the spouse or partner of the deceased has first priority, with either the children or parents of the deceased having the next priority in decision-making. For example, the spouse of the deceased would have final say in the decision regarding postmortem tissue donation.

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[17] *SH v DH* (2019 ONCA 454) [Canada]

[18] *Evans v Amicus Healthcare Ltd* [2004] EWCA Civ 727 [UK] (See also *Evans v United Kingdom* (Application No. 6339/05) 7 March 2006, the European Court of Human Rights rejecting an appeal of the decision.)

[19] See, e.g., *Davis v Davis*, 842 S.W.2d 588 (Tenn. 1992) [US]; *In re Marriage of Rooks* (2018 CO 85) [US]

[20] Ariz. Rev. State. Ann. § 25-318.03 (2018).

3.2.4. Withdrawal of Consent

With the key aspects of consent now dealt with, we turn our attention to withdrawing consent. Free consent implies the ability to withdraw consent. Just as with other research involving humans, individual tissue contributors should be able to withdraw consent to participate so long as it is possible to do so. This is the general position across all countries and tissue types.

While withdrawal is available in principle, the actual effect of withdrawal may not necessarily accord with the tissue contributor's expectations, which often envisage the removal of any data derived from their tissues. Where data has been anonymized, such removal may be impossible. Bearing this in mind, ethical guidelines generally advise researchers to inform participants about what can be expected where consent is withdrawn, which is akin to an 'informed withdrawal'.

Notably, norms governing embryonic tissue research across the countries examined generally specify that after embryos have begun to be used in the research process, consent may no longer be withdrawn. Such an approach balances the varied procedural requirements with respect to embryonic tissue donation examined in the previous sections. The procedural requirements ensure the bona fide nature of the donors' consent while the specified cut-off time for withdrawal safeguards researchers' expectations regarding the security of their access to the tissues

For embryonic tissue, Canada and the UK are the only countries whose norms specify that withdrawal of consent be in writing. For fetal tissue, norms and guidelines generally do not specify a time nor method by which participants can withdraw, with the exception of Singapore, the latter requiring withdrawal to be in writing. Any consent given to postmortem tissue or body donation for research may be revoked during the donor's lifetime. In France, the only country under examination with an opt-out approach to postmortem tissue donation, withdrawal of consent is done through the Registre national des refus, administered by the Agence de la biomédecine.

3.3. Ownership and Control Interests in Tissue

Beyond the crucial aspects of consenting to the use of tissue in research, legal developments in other areas also may affect the use of tissue. In particular, whether tissue constitutes "property", conferring an "ownership" interest, as well as autonomy / privacy issues, i.e., "control", are particularly pertinent.

Generally speaking, common law countries may recognize ownership interests in tissues, while civil law countries do not, seeing excised tissues as an extension of the human body itself, therefore not capable of being "owned".[21] Hence, such countries use the language of "control" that is, the exercise of a personal autonomy right. Of the countries examined in this article, Australia, Canada (except Quebec), Singapore, the UK, and the US have common-law based legal systems. France, Mexico, and Quebec have civil-law based legal systems.

[21] For a more comprehensive treatment of the debates surrounding the recognition of "property" and "ownership" interests in human tissue, see Gold ER. *Body Parts: Property Rights and the Ownership of Human Biological Materials*. Georgetown University Press; 1996.

There is a growing body of case law in Canada and the US that tissue samples are the "property" of the institution that stores them.[22] In these cases, tissue has been assimilated to medical records. The property right recognized in these cases is a limited one that usually excludes other rights commonly incidental to property, such as the right to use for other purposes, transform, or sell. The institutions who "own" these tissues nevertheless remain bound by the same consent approaches for their use. Being declared an "owner" of tissues does not replace the need to seek re-consent, waiver, etc. if the use of the tissue has changed. Moreover, the individuals from whom the tissues were derived also maintain rights of reasonable access and withdrawal.

Case law in Canada and the UK has also recognized that gametes and embryos can be considered "property" in certain contexts.[23] These cases all treated either sperm or embryos as property for dispute-settlement purposes. That is, the context-specific nature of these decisions is primordial, and their applicability to other situations is an open question. Remarkably, two of these cases sought to resolve a dispute over whether cryopreserved, stored sperm and embryos could be used for reproductive means, even when neither party had contributed the reproductive material in issue. [24]

As stated above, the approaches in France, Mexico, and Quebec do not recognize the human body or any tissues derived therefrom as property. For example, in the context of divorce proceedings, a Quebec court found in favor of a woman seeking to retain two placentas in her possession.[25] Rather than applying a property-based analysis, the court opted for a multifactorial analysis that included interests of dignity, autonomy and privacy. Moreover, Mexico's *Ley General de Salud* expressly prohibits the recognition of property interests in human cadavers, emphasizing the need to treat them with respect and dignity. A similar approach is found in France's *Code civil*.

It is advised that while "property" or "ownership" may be recognized for human tissues, the notion of individual autonomy that informs the consent process nevertheless should be at the forefront of considerations in research design and implementation. The 'no property' rule in many civil law countries also may pose its own issues. For example, French biobanks find themselves in an ambiguous position regarding the legal status of their holdings if the samples do not constitute property.[26] Generally then, the right of control of the donor can be considered a limited property right or an extension of an autonomy interest.

3.4. Prohibited Acts

Certain uses of human tissues may be prohibited. The choice to prohibit, rather than to regulate, generally reflects a belief that a particular act challenges some fundamental value in a

[22] See e.g., *Piljak Estate v Abraham* 2014 ONSC 2893 [Canada]; *Washington University v Catalona,* 490 F.3d 667 (8th Cir. 2007) [USA].
[23] *SH v DH* 2019 ONCA 454 [Canada]; *Lam v University of British Columbia* 2015 BCCA 2 [Canada]; *JCM v ANA* 2012 BCSC 584 [Canada]; *Yearworth and Others v North Bristol NHS Trust* [2009] EWCA Civ 37 [UK].
[24] *JCM v ANA* 2012 BCSC 584 [Canada]; *SH v DH* 2019 ONCA 454 [Canada].
[25] *Droit de la famille – 061409* 2006 QCCS 7871 [Canada].
[26]Commin V. Legal issues surrounding French research-focused biobanks. In: Human Tissue Research [Internet]. Oxford: Oxford University Press; 2011. Available from: https://perma.cc/5HQR-5JF4

society, such as human dignity or the sanctity of (human) life. For example, the belief that life begins at conception animates a large part of the recent prohibitions on fetal tissue research in the US, which is further discussed below.

It is important to distinguish an act that is prohibited due to lack of consent from an act that is prohibited *per se*. In the former case, the act is permitted so long as proper consent has been obtained. In the latter case, individuals cannot consent to these activities because the activities themselves are prohibited, often by way of criminalization. This section is concerned with this latter category of acts.

Owing to their sensitivity, most prohibited acts in the seven countries under study concern embryonic and fetal tissue. For embryonic research there is consensus regarding the 14-day rule – embryos must not be used in research that are more than 14-days old (not including the time in which its development may have been suspended) or after the formation of the primitive streak.[27] There is moreover consensus that embryos upon which research has been conducted should not be implanted into a human. Only Singapore and the UK permit the creation of embryos for research purposes. Australia and Canada do not permit the creation of embryos for research purposes, except if it is for training or research on ART procedures. France does not permit the creation of embryos for any research purpose, all research relying exclusively on surplus IVF embryos. Mexico notably does not have any federal legislation dealing with prohibited acts for fetal and embryonic tissue.

With its quickly changing normative landscape, the US merits a separate, but brief, discussion. As already mentioned, US federal law only generally regulates which research is eligible for federal funding, rather than regulating all research, irrespective of funding source. Thus, for the purposes of our analysis, "prohibited acts" at the federal level in the US only describes those acts which are ineligible for federal funding. Notably this includes the creation of embryos for research purposes. Accordingly, only surplus IVF embryos may be used. As regards fetal tissue research, neither fetal tissue that was purchased nor that which originated from a pregnancy whose purpose was to provide such tissue may be used in research funded by the Department of Health & Human Services. Moreover, the current administration has announced a "comprehensive review" of human fetal tissue research, ordering the NIH to stop procuring new human fetal tissue. At the state-level, certain acts have been prohibited by way of criminalization. Since just 2016, research on tissue from elective abortions has been criminalized in six states, with further examples of such legislation in the pipeline.[28]

All of the countries examined, except Mexico, have norms addressing human cloning, all of which prohibit human reproductive cloning. Australia, Singapore and the UK permit non-reproductive cloning while Canada, France, and the US prohibit any form of human cloning.

As regards the creation of organisms that are part-human and part-animal, also known as part-human chimeras or cytoplasmic hybrids, a range of approaches emerges with variable specificity. Only Australia and the UK allow for the creation of part-human chimeric embryos,

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[27] For recent discussion surrounding the potential need to revisit the 14-day rule, see Hyun I, Wilkerson A, Johnston J. Embryology policy: Revisit the 14-day rule. *Nature News*. 2016;533(7602):169.

[28] Wadman M. University fights restrictive law on fetal tissue research. *Science*. 2019;363(6434):1376. doi:10.1126/science.363.6434.1376.

but the development of such embryos beyond 14 days is prohibited in both countries. Australia's legal norms are silent on the introduction of human stem cells into an animal embryo and the UK's appear to permit the creation of a part-human chimeric embryo so long as its DNA is predominantly animal. Canada finds itself in a unique position: while the *Assisted Human Reproduction Act* appears to allow the creation of part-human chimeric embryos whereby human cells are introduced into animal embryos, the *TCPS2* prohibits the creation of any part-human chimeras. As is the case with its other norms, the US federal government does not legally prohibit the creation of part-human chimeras. The NIH has a moratorium on funding any such research but did unveil a draft framework, seeking public comment in 2016, without any apparent further developments.[29] France expressly prohibits the creation of any chimeric or "transgenic" embryos. Singapore's legal norms are silent on the issue, but the Bioethics Advisory Committee (BAC) in 2010 recommended that research involving part-human chimeras should be permitted and tightly regulated. Mexico has no legal or ethical norms on the point.

There is consensus in the countries under study regarding the prohibition of commerce in human parts. Prohibiting the trade and sale of human tissues can be broadly seen as protecting the human body from potentially degrading treatment. As such, all seven of the countries studied have legal norms that either restrict or prohibit the sale or purchase of organs and other human tissue. In Canada, Mexico, France and Singapore, the sale of organs and tissues is illegal. In the USA and the UK, those acts are prohibited if the tissue or organs are destined for transplant or therapy. Nevertheless, legislation in Australia, Singapore, the UK, and the US, permits the reimbursement of reasonable expenses incurred in the holding, processing, etc. of human tissues. The distinction is an important one – only allowing for reimbursement of reasonable expenses preserves the notion that the tissues themselves are not being purchased.

4. CONCLUSION AND RECOMMENDATIONS

And then we came forth, to see again the stars.[30]

Our tissues are the building blocks to the bodies we inhabit, which in turn are sites of expression of the characteristics that distinguish us as humans. Our bodies are vehicles for the exercise of our autonomy and loci of our inherent dignity as humans. The panoply of norms, both international and national, examined in this article have at least one structuring characteristic: they seek to protect the human research subject from potential violations of personal interests, such as security of the person, privacy, autonomy, etc. Observing norms ensures the safety of research participants, which consequently supports the continued legitimacy of scientific and biomedical research.

The way in which the interests of research participants are protected, as well as their level of protection are culturally specific and vary across countries. For example, the universal requirement of free, informed consent ensures that research respects individual autonomy and choice. Nevertheless, how this essential requirement is satisfied varies across the seven countries under consideration. This is well illustrated in Table 2, which gives an overview of the recognition of alternative approaches to the traditional "opt-in" model to free, informed consent,

[29] Request for Public Comment on the Proposed Changes to the NIH Guidelines for Human Stem Cell Research and the Proposed Scope of an NIH Steering Committee's Consideration of Certain Human-Animal Chimera Research, 81 Fed. Reg. 51921 (published August 5, 2016).
[30] Dante Alighieri, *Inferno*, Canto XXXIV (trans. Robert Hollander and Jean Hollander).

viz., consent to secondary uses, broad consent, presumed consent (opt-out), and waivers. Certain approaches, such as secondary use and waiver receive wide recognition, while broad consent and presumed consent are relatively less well recognized. Even where there is high-level consensus, key differences remain that are specific to types of tissues and of research.

All seven countries examined have unique approaches to the regulation of human tissue research. The normative fabrics of France and Mexico, however, have consistently been outliers in the analysis. Mexico's norms governing human tissue research generally lack consideration of many of the issues examined in this article. There is no clear recognition of any of the four alternative approaches to informed consent and fetal and embryonic tissue research operates in a grey zone, lacking normative consideration. On the other hand, France recognizes all four of the alternative approaches, including opt-out for residual clinical tissues, and even follows a broad consent model for research on embryonic tissue. The UK's overall approach seems to be one of permitting research but with regulation. The *Human Tissue Act 2004* and *Human Fertilisation and Embryology Act 1990*, combined with their respective regulatory bodies, the Human Tissue Authority and the Human Fertilisation and Embryology Authority, have developed a comprehensive, considered approach to all aspects of human tissue research this article has examined, even permitting the creation of embryos for research purposes and of part-human chimeras. Australia, Canada, Singapore, and the US find themselves somewhere in the metaphorical middle: each country has sophisticated, detailed normative frameworks but does not consistently present themselves as outliers.

Despite the differences, some key similarities have emerged. The core content of consent tends to be the same across countries: researchers must inform tissue donors about the nature and purpose of the intended research and participant confidentiality must be discussed. Genomic research and research on biospecimens from which human stem cell lines may be derived also generally trigger additional requirements for researchers specific to the implications of each category of research. The use of formalities, such as written consent and cooling-off periods, are seen in most countries whose norms govern research on embryonic tissue. These same formalities tend to be relaxed in cases of organ and tissue donation during a last illness, which protects a dying individual's final wishes from being stifled or overridden by the need to comply with certain formalities. The suitability of waivers is generally seen as a context-specific question for RECs, rather than one for bright-line rules. What's more, the use of anonymized or coded samples affects consent requirements. There is also broad consensus that there should not be a free market for human parts, with each country's norms protecting the human body from market pressures in some way. And the similarities continue, with substitute consent broadly recognized from family members for postmortem tissue donation, and obtaining consent from the woman whose pregnancy was terminated for fetal tissue research, to name a few.

It is hoped that researchers working in transnational contexts such as international research consortia will see that there are more similarities than differences when it comes to these norms. There is even a commonality to some of the differences. Differences generally are in relation to particularly sensitive aspects of human tissue research, such as research on embryonic and fetal tissue. Accordingly, each country's norms have sought different ways of governing this type of research in a way that accords with their society's beliefs and mores. Furthermore, the diversity between and among the countries under consideration suggests that the fruits of the analysis may be transferrable. The answers to the research questions should be able to guide researchers

working in other countries in understanding the general contours of the normative landscape in which human tissue research is situated. There is more holding us together than driving us apart.

To conclude, we offer the following recommendations, which bear the results of the analysis in mind:

- When obtaining consent, researchers must discuss the nature and purpose of the intended research, the potential risks and benefits flowing from participation, and the measures taken to protect participant privacy.
- Where "ownership" or property-like interests are recognized, consent from the participant generally remains primordial.
- Consent may be withdrawn so long as it is possible to do so, e.g., before data / samples are anonymized or destroyed.
- While consent for the use of tissue after death from living individuals generally needs only specify which tissues are being donated and for which general purpose, additional information should be given so far as is practicable.
- Where there is clear evidence that the deceased objected or consented to certain uses of their tissues, this expression of will is binding and cannot be overridden by next of kin.
- The further use of already anonymized or coded samples may obviate the need to obtain consent, but generally still requires approval from a competent research ethics committee.
- Without an opt-out, secondary use of non-anonymized, clinical tissue samples will either require re-consent or a waiver from a research ethics committee.
- Where broad consent is appropriate, additional governance structures such as access controls/committees should be in place.
- Research for which waivers are sought must generally involve, among other things, no more than minimal risk to the participants; the tissues should be essential to the completion of the research; and re-consenting is impracticable. The decision for granting a waiver is context-specific and ultimately rests with the competent research ethics committee.
- When seeking consent to use gametes and embryos from a donor who is also a patient, some degree of separation between the clinical and research context is required.
- Embryonic tissue research often requires obtaining consent from multiple individuals. As such, national and sub-national legal and ethical norms should be consulted to determine from whom consent must be obtained and whether there is a set priority of decision-making authority in particular circumstances.
- At this time, where permitted, embryonic tissue research is generally limited to 14 days. This applies equally to part-human chimeric embryos, where their creation is permitted.
- For embryonic or fetal tissue research, researchers should consult their jurisdiction's legal and ethical norms to ensure compliance with additional formalities.
- Human reproductive cloning is prohibited.
- Special consent regimes apply when using tissues from minors, incompetent adults, or members of other vulnerable populations.
- Researchers working in federal countries should consult both national norms as well as the legal norms from their state, province, or territory.

Table 1. ***Selection of National Legal and Ethical Norms***

	Legal Norms	Ethical Norms
Australia	*Research Involving Human Embryos Act 2002* (Cth), 2002/145 [as amended 2016] *Research Involving Human Embryos Regulations 2017* *Prohibition of Human Cloning for Reproduction Act 2002* (Cth), 2002/144 [as amended 2017] State and territorial *Human Tissue Acts*	*National statement on ethical conduct in human research* (National Health and Medical Research Council) [2007, updated 2018] *Ethical guidelines on the use of assisted reproductive technology in clinical practice and research* (National Health and Medical Research Council) [2017]
Canada	*Assisted Human Reproduction Act*, SC 2004, c 2 [as amended 2012] *Assisted Human Reproduction (Section 8 Consent) Regulations SOR/2019-195* Provincial and territorial *Human Tissue Gift/Donation Acts*	*Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (Canadian Institutes of Health Research (CIHR), Social Sciences and Humanities Research Council (SSHRC), Natural Sciences and Engineering Research Council (NSERC)) [2014]
France	Chapter 2 of Title 1 of Book 1 of *Code civil* (Article 16 *et seq.*) [as amended 2019] *Code de la santé publique* [as amended 2019], especially: Title 2 of Book 1 of Part 1 of *Partie legislative* (Article L1121 *et seq.*) Titles 1-6 of Book 2 of Part 1 of *Partie législative* (Article L1211 *et seq.*) Titles 1-4 of Book 1 of Part 2 of *Partie législative* (Article L2141 *et seq.*) Book 2 of Part 1 of *Partie réglementaire* (Article R1211 *et seq.*)	Various opinions (“avis”) and other advisory documents issued by the *Comité consultatif national d'éthique pour les sciences de la vie et de la santé* (CCNE), especially : *Avis N° 52 : Avis sur la constitution de collections de tissus et organes embryonnaires humaines et leur utilisation à des fins scientifiques* [1997] *Avis N° 58 : Consentement éclairé et information des personnes qui se prêtent à des actes de soin ou de recherché* [1998]

Mexico	*Ley General de Salud*, Diario Oficial, 1984-02-07, N. 27 [as amended 2018] *Reglamento de la Ley General de Salud en Materia de Control Sanitario de da Disposición de Órganos, Tejidos y Cadáveres de Seres Humanos* [as amended 2014] *Reglamento de la Ley General de Salud en Materia de Investigación para la Salud* [as amended 2014] *Norma Oficial Mexicana NOM-012-SSA3-2013, Que establece los criterios para la ejecución de proyectos de investigación para la salud en seres humanos* [2013]	*Guía nacional para la integración y el funcionamiento de los Comités de Ética en Investigación (6th ed.)* (Comisión Nacional de Bioética) [2018] Ambe AK et al. *Consenso Nacional Mexicano de Reproducción Asistida*. Rev Mex Med Repro (2012); 4.5 (2)
Singapore	*Human Biomedical Research Act 2015* (29/2015) [as amended 2019] *Human Biomedical Research (Restricted Research) Regulations 2017* (S 622/2017) *Human Biomedical Research (Exemption) Regulations 2018* (S 734/2018) *Medical (Therapy, Education and Research) Act* (Chapter 175) [as amended 2014] *Human Cloning and Other Prohibited Practices Act* (Chapter 131B) [as amended 2005] *Human Organ Transplant Act* (Chapter 131A) [as amended 2012][31]	*Ethics Guidelines for Human Biomedical Research* (Bioethics Advisory Committee) [2015]

[31] Establishes an opt-out approach to organ donation for therapeutic purposes but not for research purposes.

United Kingdom	*Human Tissue Act 2004* (UK), c 30 [as amended 2019][32] *Human Tissue (Scotland) Act 2006* (Scot) ASP 4 [as amended 2019][33] *Human Transplantation (Wales) Act 2013* (Wales) NAWM 2 [as amended 2015][34] *Human Fertilisation and Embryology Act 1990* (UK), c 37 [as amended 2019]	*Codes of Practice and Standards* (Human Tissue Authority) [2017] *Code of Practice (9th ed.)* (Human Fertilisation and Embryology Authority) [2019] *Human Bodies: Donation for Medicine and Research: An Ethical Framework* (Nuffield Council on Bioethics) [2011] *Human Tissue and Biological Samples for Use in Research: Operational and Ethical Guidelines* (Medical Research Council) [2014]
United States	45 CFR Part 46 Subparts A, B, C, and D [as amended 2017], with Subpart A constituting the *Federal Policy for the Protection of Human Subjects* ("*Common Rule*") *Public Health Service Act*, 42 USC 241 *et seq.* [as amended 2018] *Revised Uniform Anatomical Gift Act* [2006] *Uniform Determination of Death Act* [1980]	*Body Donation Policy: The Donation of Bodies for Educational & Biomedical Research* (American Association of Anatomists) [2009] *Donating embryos for human embryonic stem cell (hESC) research: a committee opinion* (American Society of Reproductive Medicine) [2013] *Ethics Guidelines for Research with the Recently Dead* (Consensus Panel on Research with the Recently Dead) [2005] *Guidelines for Human Embryonic Stem Cell Research* (National Academies) [2010] *National Institutes of Health Grants Policy Statement* [2018]

[32] The *Organ Donation (Deemed Consent) Act 2019* amends the *Human Tissue Act 2004*, creating an opt-out approach to organ donation for transplantation purposes in England but not in Northern Ireland. The amendments are expected to come into force in 2020.

[33] The *Human Tissue (Authorisation) (Scotland) Bill*, which passed Scottish Parliament in June 2019 and has yet to receive royal assent, amends the *Human Tissue (Scotland) Act 2006* and establishes opt-out consent to organ donation tissue donation for transplantation purposes.

[34] Establishes an opt-out approach to organ donation for transplantation purposes but not for research purposes.

Table 2. ***Recognition of Consent Approaches***

	Secondary Use	Broad Consent	Presumed Consent (Opt-Out)	Waiver
Australia	Recognized for both research and clinical tissues. If tissues are not anonymized, re-consent or waiver must be sought.	Recognized.	Recognized for research purposes, but not for genomic research.	Recognized.
Canada	Recognized for both research and clinical tissues. If tissues are not anonymized, re-consent or waiver must be sought.	Recognized.[35]	Not recognized.	Recognized.
France	Recognized for both research and clinical tissues. Opt-out approach followed for secondary research use of clinical tissue. If research tissues are not anonymized, re-consent or waiver must be sought.	Recognized.	Recognized for the use of residual clinical tissue for research purposes.	Recognized, but not for research on germ cells.
Mexico	Not recognized.	Not recognized.	Not recognized.	Ambiguous.[36]
Singapore	Recognized for both research and clinical tissues. If tissues are gametes, embryos, or are not anonymized, re-consent or waiver must be sought.	Recognized, but not for research "deemed to be sensitive", such as research on gametes and embryos.	Not recognized.	Recognized.
United Kingdom	Recognized for both research and clinical tissues. If tissues are neither coded nor anonymized, re-consent or waiver must be sought.	Recognized.	Not recognized.	Recognized.
United States	Recognized for research tissues. If tissues are neither coded nor anonymized, re-consent or waiver must be sought.	Recognized.	Not recognized.	Recognized, but not suitable where broad consent was offered and declined.

[35] See footnote 11.

[36] See footnote 12.