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Legal and Ethical Challenges of International Direct-to-Participant Genomic Research: Conclusions and Recommendations

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Abstract

Direct recruitment of participants using the internet has proven to be an effective strategy for increasing the number and diversity of participants in genomic research, especially research on rare diseases. Institutional review boards and research ethics committees (RECs) have approved this strategy for domestic research, but they have been reluctant to approve it for international research because they do not know whether it is legal to use direct recruitment in other countries without obtaining approval from an REC in each country from which participants may be enrolled. To inform this question, we obtained legal and ethics opinions from experts in 31 diverse countries, and their responses to our standard questions are separately published in this symposium. Although none of the countries has a law specifically addressing this emerging issue, it appears that local ethics approval would be required in many countries. This article presents the argument that single-site ethics review in the researcher's country will facilitate this valuable research while still protecting the welfare and interests of participants and their countries.

I. Introduction

Direct-to-participant (DTP) recruitment and enrollment via the internet has proven to be an effective way of conducting genomic research, especially research on rare diseases. Although this novel manner for researchers to interact with prospective and enrolled participants has been approved by institutional review boards (IRBs) and research ethics committees (RECs)[1] for domestic research, some IRBs and RECs have been reluctant to approve it for international research because of concerns about its legality in other countries. Thus, the threshold question is whether it is legal for a researcher in one country to recruit and enroll participants in another country when there has not been an ethics review in the participant's country. This determination is crucial because separate ethics reviews in numerous countries to obtain a small number of participants in each country would be extremely burdensome and greatly delay the research or preclude it entirely.

To answer the question of whether international DTP genomic research is legal we enlisted expert collaborators from 31 countries, and their country reports are published separately in this symposium. Using the country reports as a starting point, this concluding article discusses the legal, ethical, policy, and practical ramifications of extending the DTP methodology to worldwide genomic research.[2] Our example or "use case" for the entire article is genomic research on rare diseases, including rare cancers. It is one of the first applications of international DTP genomic research, and using a specific use case helps bring greater clarity to the range of difficult issues addressed in this article. In addition, researchers, patients, and their family members understand that new methods of scientific discovery are needed for rare diseases. According to a recent article from the International Rare Diseases Research Consortium and the Global Alliance for Genomics

and Health: "The singularity and diversity of rare diseases, combined with the small number of patients for each disorder, effectively precludes conventional research discovery approaches. . . ."[3]

The analyses and recommendations in this article are solely those of the authors, and they do not necessarily represent the views of the authors of the country reports or others with whom we have consulted. In fact, all authors of this article do not necessarily agree with all of the analyses and recommendations.

II. Balancing the Scientific Imperative with Ethical Considerations

DTP research is on the rise among both academic and commercial researchers.[4] Its appeal is largely attributable to the opportunity it presents for enhanced recruitment capacity across large geographical areas. By replacing traditional local recruitment, as well as in-person consent and study procedures, with decentralized efforts that leverage social media, internet-based advocacy communities, electronic consent, and sample collection kits sent by mail, DTP projects ameliorate some of the most logistically challenging elements of research study operations.

Although regulators are already fairly accustomed to the use of internet recruitment via Facebook postings and the like, electronic consent remains a source of unease for some IRBs and RECs. Online consent protocols range from highly interactive apps with built-in quizzes to simple electronic versions of the paper consent. Most involve breaking traditional consent form information into short sections that must be read and clicked through before advancing. Other alternatives to in-person consent include videoconferencing and consent by phone.

There are reasonable concerns about the potential drawbacks of some of these newer forms of consent. The ability to accurately assess competency, for example, has been questioned. One DTP study addressed this concern by using video conference sessions instead of online consent

forms to allow for more interactive assessments. Another concern, in the case of a fully online consent, is verification of the identity of the prospective participants. Depending on the level of concern about potentially fraudulent study enrollment, identity verification may be as simple as a follow-up email confirmation, or as complex as the use of online verification services, secure transmission of images from government-issued identification, and even biometrics such as fingerprinting.

Perhaps the most oft-cited source of uneasiness about online consent is participant comprehension.[5] Although the research community largely agrees that paper consent forms burdened by up to 30 or 40 pages of complex medical and legal language do not lend themselves to optimal comprehension, there remains something reassuring about the image of a research professional at the participant's side, helping to navigate and translate these complexities, and pledging to safeguard the welfare of the participant in accordance with the research protocol. However, published research indicates that information recall scores for online consent are typically consistent with and sometimes better than those using traditional methods.[6]

Two well-known DTP research projects that have enrolled substantial numbers of participants are the "Count Me In" and "All of Us" research programs. Both recruit from across the United States, using an online consent process. Count Me In (CMI) is a non-profit cancer research organization, stewarded by the Broad Institute, Dana Farber Cancer Center, Emerson Collective, and the Biden Cancer Initiative. As described on its website, CMI "enables interested patients to share their saliva, blood, stored tumor samples, clinical information, and experiences to help researchers detect new and important patterns in cancer progression and response to treatment across large numbers of people."[7] CMI began its work with a single metastatic breast cancer study, but it has since expanded to include prostate cancer, angiosarcoma, esophageal and stomach

cancer, osteosarcoma, and brain cancer. In a review of the angiosarcoma (AS) project, CMI researchers reported that 120 patients with this rare cancer registered in the first post-launch month and 338 patients registered within 18 months. The authors explained that "this represents not only a significant proportion of people living with this disease in the U.S., but also a substantially increased pace of enrollment compared to previous efforts (with the largest previous AS study having collected clinical data from 222 patients treated over 14 years)."[8] They attributed the study's success to "a patient-partnered approach that leverages social media."

All of Us (AoU), by contrast, does not focus on a specific disease, but instead seeks to enroll one million participants from across the United States in an NIH-sponsored longitudinal cohort study.[9] Prospective participants consent online via the study's website, or by downloading a smartphone app. AoU opened for enrollment in May 2018, and as of July 2019, more than 230,000 participants had enrolled. Of those, 175,000 participants had contributed biospecimens. The research team reported that "more than 50% of these participants are from groups that have been historically underrepresented in biomedical research."[10]

AoU recruits exclusively in the United States and is approved by a single IRB, established specifically for the program, at the NIH. CMI has Dana-Farber/Harvard Cancer Center IRB approval to recruit in the U.S. and Canada. The increased diversity of subjects and enhanced statistical power increase the likelihood of successful outcomes from these studies and suggest that international DTP genomic studies can be fruitful.

It is important to note that CMI and AoU are only used as examples of successful DTP recruitment. Contrary to most international DTP genomic research and this article's use of research on rare disorders, CMI and AoU utilize multiple data sources (and possibly biospecimens). They are designed to have ongoing data collection and support diverse research projects.

As discussed in greater detail below, international DTP genomic research presents minimal risks and potentially high scientific benefit to both participants and society at large. An important, often-overlooked benefit is supporting the autonomy of research participants to make informed decisions about whether and how to participate in research.[11] According to the Belmont Report:

> An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect autonomy is to give weight to autonomous persons' considered opinions and choices while refraining from obstructing their actions unless they are clearly detrimental to others. To show lack of respect for an autonomous agent is to repudiate that person's considered judgments, to deny an individual the freedom to act on those considered judgments, or to withhold information necessary to make a considered judgment, when there are no compelling reasons to do so.[12]

Although the Belmont Report was written for the United States, the notion of autonomy extends beyond any single nation's borders. Just as people around the world engage in the global economy as online consumers, so too should those who learn of a research study via the internet or international advocacy groups be permitted to choose whether to participate, provided the research has been approved by an REC.

Even though access to the internet is increasing around the world, a digital divide still persists in some countries and in some communities, which could be an obstacle to the democratization of access to research. In addition, some individuals may lack autonomy due to diminished capacity caused by age, health status, limited language fluency, or social circumstances

such as culturally based gender roles. Consequently, constraints on enrollment might interfere with the exercise of autonomy and any benefits derived by participation in genomic research on rare disorders.

Scientific research also can provide benefits to society as a whole, and this possibility supports the advancement of international DTP genomic research.[13] Expanding enrollment in genomic studies across borders enhances the diversity of research findings. This differs from the past, where scientific research often targeted, and therefore benefited, a small proportion of the world's population, typically those residing in affluent countries near large academic medical centers. By democratizing access to research participation through remote consent and streamlined procedures for biospecimen collection, there is an opportunity to equalize research participation. No longer do prospective participants need to live in a particular geographic area or have a direct connection to an investigator to take part in research. Instead, they may learn about and enroll in studies through social media or other decentralized means, consent from their own home, and participate by sending a collection kit back to the researcher by mail.

Casting a wide net is particularly important in the study of rare genetic diseases and rare cancers, a major focus of DTP genomic research and the use case for this article. It is now well-recognized that errors in the interpretation of the genetic variants causing rare disease, even in the most well-studied populations, have resulted from a lack of data from less represented populations.[14] Furthermore, researchers who seek to advance our scientific understanding of rare diseases cannot rely on traditional recruitment and enrollment methods. Small patient populations are scattered around the globe, and therefore finding an adequate number of participants in a single researcher's own country is rarely possible. An alternative is to identify research collaborators in other countries who might be willing to submit applications to their own ethics committees to

recruit study participants in their respective localities. However, the administrative, financial, and regulatory burdens associated with initiating a new protocol at numerous international sites makes this path forward impractical, particularly when only a few participants (or even a single participant) might be eligible at each site.

We are aware that equalizing research participation is quite different from equalizing access to health care services that might develop from the research. This is a concern in high income as well as low and middle income countries (LMICs), although the history of research exploitation of residents of LMICs requires additional consideration. Thus, in the informed consent process for international DTP genomic research, claims of direct benefit to participants ought to be extremely modest, and the main motivation for most participants is likely to be altruism.

Physical risks associated with genomic research are minimal, as they usually involve only saliva collection and possibly sharing information from one's medical records. The privacy risks to both individual participants and their biological relatives are of greater concern, and they merit careful description in the consent process and thoughtful consideration by both prospective participants and researchers. Among the key privacy-related issues are whether data are in identifiable form, whether stigma or other social harms may result from participation in research, and whether legal protections are in place to prevent discrimination in employment, insurance, or other areas. A detailed discussion of all these issues is beyond the scope of this article.

The focus of much DTP genomic research on rare diseases, the principal use case of this article, should not convey the impression that the research will have a limited effect on health. In the U.S., a rare disease is defined as one that affects less than one in 200,000 persons.[15] The World Health Organization (WHO) estimates that there are about 5,000 to 8,000 rare diseases, most with a genetic basis.[16] Worldwide, rare diseases affect about 400 million people, including 25 million

in the U.S alone.[17] Scientific advances developed to prevent, diagnose, and treat rare diseases also may be applied to other, more common, diseases. Therefore, existing legal restrictions in many countries on international DTP genomic research have major implications for population health.

III. Legal Analyses from 31 Countries

An initial, critical question for this overall research project is whether international DTP genomic research is currently lawful in countries around the world. To answer this question the investigators identified experts in research laws from a diverse sample of 31 countries. The list of countries and legal experts appears in Appendix 1. The procedures we followed in devising the questions, including obtaining input from varied stakeholders and experts, is discussed in the introduction to the country reports in this symposium.[18] The complete set of questions appears in Appendix 2. In this section we review some of the most important findings.

Questions 4 and 7 are extremely revealing.

4. Assume that a researcher from outside your country wants to conduct DTP genomic research in your country:

A. Would it be lawful for the researcher to do so without Human Research Ethics Committee (HREC) approval in either the researcher's country or your country?

B. Would it be lawful for the researcher to do so if the research were approved by an IRB/REC in the researcher's own country, but was not submitted for approval in your country?

C. Would the external researcher be required to have a collaborator in your country?

D. Would it matter whether the external researcher is based at a commercial, governmental or academic entity?

7. Does your country have laws, policies, or guidelines dealing with genetic or genomic research or genetic or genomic privacy that would apply to international DTP research? Do your national laws on these issues apply outside of your country when residents or citizens of your country enroll in a DTP study conducted abroad?

Legal experts were given three options to respond to question 4: "Yes," "No," and "Unsure/Other." They also had an opportunity to describe the bases for their answers. Question 7 was open-ended and allowed for more nuance and variation in the responses. From the responses to these two questions we tried to draw conclusions concerning international DTP genomic research's likely legality and determine whether there are any general trends. In some cases, however, responses to some of the components were given without elaboration or explanation.[19] In these circumstances, we sought clarification or referred to other sections of the reports to understand the basis upon which the responses were given. We point out the circumstances in which we were unable to infer how the country experts arrived at their responses. Furthermore, because these are novel legal issues, it was not surprising to see that many of our respondents chose "unsure/other" as an answer, which sometimes limited our ability to find commonalities between their responses.

Because DTP research is a relatively recent phenomenon, it is also unsurprising that none of the 31 selected countries had specific legislation regulating international DTP genomic research. Accordingly, the experts in these countries responded in one of two ways: (1) through extrapolation or analogy to existing legislation (statutes or regulations) in related fields, such as genetics, research involving human participants, and health privacy; or (2) through reference to other normative instruments, such as policies or guidelines (soft law). In some circumstances, the experts referred to both legislation and soft law. As a result, the responses reflect the opinions of

the legal experts based on related or broader norms in the absence of specific legal provisions. From these opinions, we determined the likely legality (or more accurately, the permissibility) of international DTP genomic research in the current global landscape.

4A. Would it be lawful for the researcher to do so without HREC approval in either the researcher's country or your country?

Generally, a researcher who wants to conduct DTP genomic research in a foreign jurisdiction will have to obtain either external or local HREC approval, as 22/31 of our selected legal experts considered such research to be unlawful without external or local HREC approval (Table 1).[20]

Table 1:

Would it be lawful for the researcher to do so without HREC approval in either the researcher's country or your country?	
Yes	1 (3.2%)
No	22 (71%)
Unsure	5 (16.1%)
Other	3 (9.7%)
Total	31

Legal experts in 12 out of these 22 countries based their responses solely on legislation that explicitly requires either local or external ethical approval for the conduct of research activities (Table 2).[21]

Table 2:

Normative Requirements for External and Local HREC Approval	
Legislation	12 (54.5%)
Soft Law	9 (40.9%)
Both Legislation and Soft Law	1 (4.6%)
Total	22

As previously stated, these conclusions derive from related legislative norms. In the absence of express legislative guidance, 9 of the 22 countries referred exclusively to soft law documents, such as policy statements or guidelines, in their responses (Table 2).[22] None of the 10 countries had any

specific documents in place that explicitly addressed international DTP genomic research. Legal experts therefore drew upon related norms pertaining to research conduct, as was done within the legislative context. Nigeria drew upon both legislative and soft law documents. As with prevailing legislative norms, policy statements and guidelines generally require that research projects be reviewed and approved prior to commencement. While these documents are not legally binding, they are an expression of best research practices. Moreover, as they are more flexible than legislation, they may be more readily amended to account for new research developments. As a result, they may be consulted as authoritative normative frameworks potentially applicable within the context of international DTP genomic research.

Legal experts in 5 out of 31 countries responded "unsure" as they were either unsure of the applicability of their countries' current legislation to international DTP genomic research or stated there was no legislation applicable to international DTP genomic research (Table 1).[23] Legal experts in the remaining 3 of 31 countries responded "other," stating that the applicability of current legislation would vary depending on the circumstances of the research (Table 1).[24] Germany is the only country where external or local HREC approval is not required in all cases, including DTP genomic research. In Germany, however, health research is regulated at a professional and institutional level, and ethics approval is required where a licensed medical practitioner is involved or in other narrow regulatory circumstances.

In brief, a survey of our legal experts' reports indicates that the requirement for HREC approval is a well-established principle in the conduct of various forms of research. Pending specific legislation, it is apparent from existing norms that in most cases either external or local HREC approval will be required for international DTP genomic research projects.

4B. Would it be lawful for the researcher to do so if the research were approved by an IRB/REC in the researcher's own country, but was not submitted for approval in your country?

Of the 22 countries in which our legal experts stated it would be unlawful to conduct DTP genomic research with neither external nor local HREC approval, the majority (17/22) considered it would also be unlawful to carry out the research without local HREC approval, even if external approval had been obtained.[25] We include Peru within this grouping despite an "unsure" response. This observed trend outlines the prevalence of local HREC approval over approval given by a foreign HREC. As a result, for the majority of countries (17/31) DTP genomic research without local HREC approval will be proscribed (Table 3).

Table 3:

Would it be lawful for the researcher to do so if the research were approved by an IRB/REC in the researcher's own country, but was not submitted for approval in your country?	
Yes	5 (16.1%)
No	17 (54.8%)
Unsure/Other	9 (29%)
Total	31

Of the 17 countries that stated that it would be unlawful to conduct DTP genomic research without local HREC approval, 11 based their responses solely on legislation (Table 4).[26]

Table 4:

Normative Requirements for Local HREC Approval	
Legislation	11 (64.7%)
Soft Law	5 (29.4%)
Both Legislation and Soft Law	1 (5.9%)
Total	17

The remaining 5 out of 17 based their responses solely on soft law documents (Table 4).[27] As noted earlier, Nigeria drew upon both categories of norms.

Of the initial 22 countries that stated it would be unlawful to carry out DTP genomic research without local or external approval, 4 stated that such research would be lawful with

external HREC approval, even without local approval: Australia, Canada, Japan, and Spain. These responses are not definitive, however, as there may be certain circumstances where local HREC approval will be required.[28] The responses for Australia, Canada, and Japan were based mainly on soft law documents, whereas Spain drew on legislation.

Legal experts in 9 out of 31 countries were "unsure" as to whether DTP genomic research could be conducted solely with external HREC approval (Table 3).[29] This was due either to lack of explicit legislation or soft law (Jordan, France, Greece, Singapore, South Korea), or variability in the applicability of existing norms (Finland, United States).

The report for Germany stated it would be lawful to conduct DTP genomic research solely on the basis of external HREC approval. However, as previously stated, this would depend on whether HREC approval would be required in the researcher's home country. Moreover, German HREC approval may be required if the research forms part of a clinical trial in Germany.

In sum, the majority of legal experts consider it to be unlawful for a researcher to conduct DTP genomic research in their respective countries without local HREC approval, even if the research had received external HREC approval. Even in cases where legal experts responded "unsure" or "yes," there may be cases where local HREC would be required.

4C. Would the external researcher be required to have a collaborator in your country?

Legal experts were divided on whether external researchers would be required to have local collaborators in their respective countries when conducting DTP genomic research. Twelve out of 31 experts stated that the presence of a local collaborator would not be required, 9 out of 31 stated that it would be required, and 10 out of 31 were unsure (Table 5).

Table 5:

Would the external researcher be required to have a collaborator in your country?

Yes	9 (29%)
No	12 (38.7%)
Unsure/Other	10 (32.3%)
Total	31

Of the 12 experts who stated that the presence of a local collaborator would not be required where foreign researchers conducted DTP genomic research in their respective countries, 4 stated that existing legislation did not explicitly require the presence of a local collaborator.[30] Four of the 12 experts stated that soft law norms did not mandate that external researchers have a local collaborator.[31]

Out of the 9 experts who stated that external researchers would be required to have a local collaborator in their respective countries, 5 derived their responses from legislative sources.[32] The remaining 4 out of 9 experts relied on existing soft law norms.[33] Ten out of 31 legal experts were unsure whether external researchers would require a local collaborator. Of these 10 experts, 4 stated that, despite not being required by legislation, the presence of a local collaborator would be required as a matter of practicality.[34] Two of these 10 countries did not have any explicit statements in legislation or soft law addressing the need for a local collaborator, and therefore legal experts were unsure if it would be a requirement. In 2 of these 10 countries, the requirement for a local collaborator depended upon the context of the research.[35]

Thus, despite several legal experts responding that a local collaborator is not explicitly required in their home countries, the possibility for local collaboration cannot be ruled out. Altogether, in addition to the 9 legal experts stating that it would be required, an additional 6 stated that it would be necessary either as a practicality or in certain circumstances.[36] Therefore, according to our experts, most of the countries studied would require the presence of a local collaborator when conducting international DTP genomic research.

4D. Would it matter whether the external researcher is based at a commercial, governmental or academic entity?

External researchers' institutional affiliations do not generally affect the legality of the conduct of their research, with 25 out of 31 respondents replying that it would not matter if the researcher were based at a commercial, governmental, or academic institution (Table 6).[37]

Table 6:

Would it matter whether the external researcher is based at a commercial, governmental or academic entity?	
Yes	25 (80.6%)
No	4 (12.9%)
Unsure/Other	2 (6.5%)
Total	31

In 13 of these 25 countries, the insignificance of an external researcher's institutional affiliation derived from legislation,[38] 9 of the 25 countries drew from soft law documents,[39] and Nigeria drew from both legislative and soft law sources.[40]

Four of 31 legal experts stated it would matter whether the external researcher were based at a commercial, governmental, or academic entity (Table 6).[41] However, this may not always be determinative. In China, for instance, academic-based research projects are more easily approved than commercial- or government-based projects. In India, the importance of the researcher's affiliation will vary depending upon the type of research project and its objectives. Two out of 31 legal experts were unsure whether the external researcher's affiliation would have an impact upon the lawfulness of the research (Table 6).[42] This is due to lack of explicit legislative or soft law guidance. In sum, researchers of various categorizations may engage in international DTP genomic research subject to requirements for ethics approval. The overall irrelevance of institutional affiliation, when viewed in light of the global requirement for ethics approval,

indicates that ethics approval remains the basic consideration in the context of international DTP genomic research.

7. Does your country have laws, policies, or guidelines dealing with genetic or genomic research or genetic or genomic privacy that would apply to international DTP research? Do your national laws on these issues apply outside of your country when residents or citizens of your country enroll in a DTP study conducted abroad?

The majority (26 out of 31) of legal experts reported that their respective countries had existing legislation and/or soft law documents dealing with genetic or genomic research or genetic or genomic privacy (Table 7).

Table 7:

Does your country have laws, policies, or guidelines dealing with genetic or genomic research or genetic or genomic privacy that would apply to international DTP research?	
Yes	26 (83.9%)
No	5 (16.1%)
Total	31

Fifteen of 31 legal experts reported having legislation and/or soft law in their countries dealing expressly with genetic or genomic research or genetic or genomic privacy.[43] This finding can be illustrated through the GDPR, which protects genetic data as a special category of personal data. In the absence of specific normative guidance relating to genetic or genomic research or genetic or genomic privacy, legal experts in 11 of 31 countries reported legislation and/or soft law in related domains that could be applicable to international DTP research.[44] Such domains include general privacy norms, health laws, and norms regulating the conduct of research involving human participants. Legal experts in 5 of 31 countries reported a lack of legislation or soft law in their respective countries regarding genetic or genomic research or genetic or genomic privacy.[45]

Concerning the application of local norms to residents or citizens enrolled in DTP genomic studies conducted abroad, national laws are generally territorial and do not apply outside their respective jurisdictions. This, however, is subject to certain exceptions. Legal experts in 10 out of 31 countries stated that national norms could apply extraterritorially to DTP studies under certain circumstances (Table 8).[46]

Table 8:

Do your national laws on these issues apply outside of your country when residents or citizens enroll in a DTP study conducted abroad?	
Yes	10 (32.3%)
No	4 (12.9%)
It depends	10 (32.3%)
Unsure/Did not respond	3 (9.7%)
No applicable norms	4 (12.9%)
Total	31

Several legal experts noted this was the case where recruitment of citizens or residents took place within their respective jurisdictions or where there was a substantial connection between the study and the country.[47] An additional 10 of 31 legal experts stated that national norms in their respective countries applied extraterritorially (Table 8).[48] It should be noted here that the majority of these 10 countries are member states of the European Union and referred to the GDPR as being applicable in their responses,[49] even where local norms did not apply extraterritorially.[50] The GDPR applies extraterritorially to entities that process the personal information of EU residents, whether these entities are European-based or not. Four out of 31 legal experts stated that their national norms did not apply extraterritorially[51] and 3 out of 31 were either unsure as to their application or did not address the issue of extraterritoriality (Table 8).[52] The remaining countries reported not having any norms relating to genomic or genetic research or genetic or genomic privacy, thus the issue of extraterritoriality was neither raised nor relevant to the discussion.[53]

Although international DTP genomic research has yet to be addressed by legislators or policymakers in our selected 31 countries, genetic or genomic research or genetic or genomic privacy have been addressed, either explicitly or indirectly, in existing legislation and soft law documents. In the absence of express normative guidance, these frameworks may be applicable to international DTP genomic research.

Our survey represents an attempt to discern the legality of conducting international DTP genomic research based on the opinions of legal experts in 31 countries. Because it is a recent development, DTP genomic research has not been regulated by specific legislation. Consequently, legal experts referred to existing legislation pertaining to related subject matters or, where applicable, to soft law documents, such as guidelines or policy statements. From these norms, our legal experts formulated reasoned opinions on the legality of international DTP genomic research through extrapolation or analogy.

Overall, the majority of legal experts responded that either external or local HREC approval would be required to conduct DTP genomic research in their home countries. Moreover, the majority stated that local HREC approval would be required. In addition to local HREC approval, the presence of a local collaborator is generally required. In the majority of countries, there are no restrictions on the conduct of international DTP genomic research based on the researcher's institutional affiliation. Additionally, the majority of countries already have legislation in place dealing with some aspects of genetic or genomic research or genetic or genomic privacy that may be applicable to international DTP genomic research. Finally, in answering question 10, a majority of legal experts stated that they were unsure whether their respective countries' legislation or soft law would change in the next 5-10 years because of increasing international DTP genomic research.[54]

IV. International Restrictions on Research

International DTP genomic research requires that biospecimens or the resulting genetic data cross state and national borders. As the preceding section makes clear, however, International DTP genomic researchers must navigate a daunting combination of national and international law. And given the global trend toward more stringent data protection laws, the legal landscape governing scientific research, including international DTP genomic research, will likely become even more complex in the coming years. In this section, we explore several recent developments that serve as case studies of the current complexity and uncertainty facing international DTP genomic researchers, as well as some consequences of legal restrictions on scientific research.

United States

Given the lack of comprehensive data privacy legislation in the United States, scientific research and the flow of genetic information are governed by a patchwork of federal and state laws.[55] There are currently over 200 statutes in effect in 49 states and the District of Columbia that implicate genetics and genomics in a variety of contexts, including ownership of genetic data, employment and insurance discrimination, health insurance coverage, privacy, research, and the use of residual newborn screening specimens.[56] For example, some states have deemed genetic information to be the property of the individual being tested[57] and/or impose informed consent requirements for genetic testing and analysis.[58] States may also regulate the retention of biospecimens and the resulting data in healthcare and research,[59] impose security requirements for genetic data or other health records,[60] or convey additional protections to research participants (e.g., applying Common Rule protections to all human subjects research).[61]

The diversity of state laws poses challenges for researchers seeking to recruit subjects from jurisdictions across the country. These challenges may be heightened in the context of research that relies on the DTP model, as such efforts have the potential to implicate laws in multiple jurisdictions (e.g., laws in place in the state where either the researcher or participants reside, or both). Such laws might vary considerably with respect to the protections afforded participants or the restrictions placed on researchers (and in some cases they may be in direct conflict). Although state laws that conflict with federal law may be preempted in certain circumstances, many existing federal statutes (e.g., Health Insurance Portability and Accountability Act (HIPAA), Genetic Information Nondiscrimination Act (GINA), and Clinical Laboratory Improvement Amendments (CLIA)), permit states to adopt more protective laws.[62]

In the absence of congressional action, more comprehensive data privacy laws are being enacted and implemented at the state level. For example, the California Consumer Privacy Act of 2018 (CCPA),[63] effective on January 1, 2020, is leading the way, with other states likely to enact similar legislation.[64] This legislation and pending bills vary in their scope and whether they explicitly address research or genetic information, but, like the European Union's General Data Protection Regulation (GDPR), commonly grant access and correction rights to individuals and impose restrictions on the use and sharing of personal information without explicit consent. It remains to be seen whether the United States will adopt comprehensive data privacy legislation, and if it does, whether Congress will preempt state laws in favor of a more uniform law.

Europe

Legal uncertainty is not confined to jurisdictions like the United Sates that lack comprehensive privacy legislation, a fact illustrated by the GDPR.[65] Implemented in May 2018, the GDPR is a sweeping law imposing restrictions on the processing of personal information of individuals

residing in the European Economic Area (EEA) and grants numerous rights to data subjects. Because the GDPR applies to any entity that targets EEA residents, regardless of whether the entity has a presence in Europe, the effects of the GDPR are being felt worldwide and will likely affect researchers engaged in DTP genomic research. In addition, the GDPR has served as a model for similar legislation in other, non-EU jurisdictions.[66]

The GDPR designates genetic data as a "special category of personal data,"[67] processing of which is generally prohibited unless "the data subject has given explicit consent to the processing of those personal data for one or more specified purposes."[68] However, the GDPR contains several provisions designed to facilitate scientific research. For example, although the GDPR typically prohibits further processing of data in a manner that is incompatible with the "specific, explicit, and legitimate purposes" for which it was initially collected (i.e., "purpose limitation"), this requirement is relaxed if carried out "for purposes in the public interest, scientific or historical research purposes or statistical purposes."[69] Similarly, the GDPR permits storage of data for research purposes for longer periods than would otherwise be permitted under the regulations in most circumstances ("storage limitation").[70]

The GDPR defers to the law of the EU or Member States in several key areas that could have a dramatic impact on scientific research.[71] For example, under Article 9(4) of the GDPR, "Member States may maintain or introduce further conditions, including limitations, with regard to the processing of genetic data, biometric data or data concerning health."[72] Member State law may also specify conditions under which a researcher may use genetic data for research purposes without consent,[73] and Member states may adopt derogations that eliminate, in the context of research, rights generally afforded by the GDPR (e.g., access and correction rights, the right to object, and restrictions on processing), "in so far as such rights are likely to render impossible or

seriously impair the achievement of the specific purposes, and such derogations are necessary for the fulfilment of those purposes."[74]

Broad consent (i.e., a single consent for future, unspecific uses of data for scientific research)[75] is another important area where the GDPR defers heavily to EU or Member State law. Recital 33 allows Member Nations to permit broader, less specific consent than would generally be allowed by Article 9. Recognizing that "[i]t is often not possible to fully identify the purpose of personal data processing for scientific research purposes at the time of data collection," the recital states that "data subjects should be allowed to give their consent to certain areas of scientific research when in keeping with recognized ethical standards for scientific research."[76] It remains to be seen how Member States will interpret these provisions. For example, Germany's Conference of German Data Protection Authorities recently issued a resolution on its interpretation of Recital 33 in which it interpreted "certain areas of scientific research" relatively narrowly, requiring specific consent for the vast majority of research projects.[77] In situations where broad consent is indispensable to the research, German regulators specified several additional safeguards for researchers to consider, such as REC approval for additional research purposes and enhanced transparency and security measures, including restrictions on transfers of personal data to other countries with less stringent data protection laws.[78]

The result of the GDPR's deference to the law of Member States results in considerable uncertainty surrounding the cross-border use of personal data, including genetic information. Not all Member states have applicable laws governing research and/or genetic data, and those that do can vary considerably or even directly conflict with one another.[79] Despite the GDPR's deference to Member State laws in the several key areas discussed above, the GDPR lacks clarity surrounding the appropriate resolution of these potential intra-EU conflicts of law.[80] However, there are

indications that Member states are willing to work cooperatively to address such issues as they arise. For example, 13 European countries recently signed a declaration of cooperation[81] designed to facilitate the sharing of genetic information across borders for medical research.[82]

South Africa

South Africa is in the process of implementing data privacy regulations inspired by an early draft of the GDPR.[83] However, the Protection of Personal Information Act (POPIA),[84] passed in 2013 and slated to go into effect in 2020, lacks some of the research provisions added in subsequent drafts of the GDPR. As a result, many scholars and researchers fear the law has the potential to negatively affect scientific research in the country.[85] For example, there is considerable uncertainty surrounding the law's restrictions on broad consent,[86] which is currently permitted in South Africa under existing guidelines and endorsed by the Academy of Science of South Africa.[87] Although there is ongoing disagreement about the extent to which the POPIA will preclude broad consent, there are concerns that the law not only creates uncertainty for future research, but that the POPIA's restrictions could require the destruction of previously collected biospecimens unless individuals were re-consented, a development that would have dire consequences for biobanks and the researchers who rely on reanalysis of such biospecimens.[88] Others have expressed concerns that the law's restrictions on sharing certain types of sensitive information (e.g., HIV status) will hinder important infectious disease research.[89]

Developments in South Africa are being closely followed as the law has the potential to influence data protection legislation across the continent. Few African nations have adopted data privacy legislation (although several are considering it) and may look to South Africa as they contemplate data privacy legislation or research regulations of their own.[90]

India

Recent developments in India serve as a useful case study of how well-intentioned regulatory reform can create uncertainty that stifles scientific research. In the decades preceding 2013, India had become home to a robust clinical trials industry. However, widespread media reports began to emerge alleging that thousands of clinical trial participants within the country had died in just the last several years.[91] In response, India's Supreme Court issued a sweeping ruling in 2013 that placed restrictions on clinical trials conducted within the country.[92] The decision halted over 150 clinical trials, impacting local researchers, large multinational pharmaceutical companies, and dozens of NIH-funded clinical trials.[93]

The Indian government subsequently convened an "Expert Committee" tasked with issuing recommendations for improving regulation of clinical trials.[94] Among the Committee's numerous recommendations were accreditation requirements for institutions carrying out clinical trials,[95] mandatory audio-video recording of each trial participant providing informed consent,[96] requirements that researchers provide compensation for research-related injuries,[97] and the provision of ancillary medical care for study participants for medical issues that arose during the course of a trial, even those unrelated to the research.[98] In response to the recommendations, the government began to consider, and in some cases implement, a number of regulatory changes[99] that quickly resulted in considerable uncertainty amongst researchers, who worried about their potential liability for future compensation and medical care and expressed concerns about the unintended consequences of requirements such as mandatory video recording of study participants.[100] Indian investigators lamented that they were "suddenly looked upon as partners in the crime committed by a few of their kind" and that prior to the fallout created by the ruling,

"[their] poor patients who could not afford even the basic standard of care were getting the best care on these global trials."[101]

As the regulatory landscape in India continues to evolve, it remains to be seen whether the country will strike a balance that protects participants without unduly inhibiting scientific research. India has since issued clarifications regarding the scope of some of the regulations discussed above and has retreated entirely from certain requirements.[102] Despite some lingering uncertainty, there is evidence that clinical trials have begun to return to the country.[103] Regardless of the ultimate outcome, India's experience illustrates the dramatic effects that regulatory uncertainty can have on scientific research.

China

Other jurisdictions may adopt restrictions that specifically target international researchers, such as those that recently took effect in China.[104] In May 2019, the Chinese State Council released a new regulation governing scientific research within the country ("Regulation of Human Genetic Resources").[105] The regulation, which went into effect on July 1, 2019, broadly defines Human Genetic Resources (RGRs) to include biospecimens as well as the resulting data, and has the potential to dramatically affect international scientific research, including DTP research within the country.[106]

The regulations place a number of restrictions on international researchers, including a prohibition on accessing biospecimens or data from within the country without a Chinese collaborator.[107] These collaborations must be pre-approved by the Chinese Ministry of Science and Technology and are subject to, among other things, "a security review if it might affect public health, national security or public interest."[108] In addition, all scientific data resulting from such a collaboration must be made available to the Chinese government,[109] and any export of genetic

information also requires a permit that is subject to security review if it affects public health, national security, or the public interest.[110] Export of biospecimens is even more difficult, as it is permitted only if it is "truly necessary" to the collaboration.[111] The regulations impose steep penalties for engaging in research without approval or for obtaining biospecimens without informed consent; researchers who run afoul of the regulations could face steep monetary penalties of up to 10 million yuan (nearly $1.4 million U.S. dollars).[112]

Taken together, these restrictions are likely to serve as a barrier to foreign scientific research within the country, including DTP research. However, it is worth noting that China, unlike other countries that have implemented or may be contemplating research restrictions, has a relatively robust scientific infrastructure.[113] Chinese researchers may be able to fill the gap left by international researchers in a way that may not be possible in countries that lack such infrastructure (e.g., developing countries that are of intense interest to researchers, such as African nations).[114]

Regulatory Challenges

Effective regulation must balance the interests of various stakeholders, including research participants, researchers, and the public more broadly, and will require cross-border coordination and cooperation. Restrictive regulations may often be a legitimate response to ongoing or historical abuses, including concerns about exploitative research by international researchers. Yet, as the above examples indicate, well-intentioned regulations can have unintended consequences that can reduce participant autonomy, stifle scientific progress, and may ultimately be detrimental to public health.

V. International Research Ethics Equivalence

Some key findings of the 31 country analyses by our international legal experts are that a majority of the countries examined would require ethics review in both the home country of the researcher and of the participant, with some countries also requiring collaboration with a local researcher. These legal requirements seem based on the following assumptions: (1) having multiple ethics reviews is beneficial; (2) local ethics review is necessary to consider unique social and cultural conditions; and (3) local researcher involvement promotes important interests, such as scientific capacity building, economic development, and protection of the country's biological resources.

In considering these assumptions, it is important to remember that the various governments did not establish multi-site review with international DTP genomic research in mind. Rather, these legal enactments predate international DTP genomic research and therefore had "traditional" research in mind, meaning that each research undertaking involved, at most, a few countries; the research was more likely to be invasive or interventional and therefore of greater risk than DTP genomic research; and each research site had many more participants enrolled than typically enroll for DTP genomic research on rare diseases. Nevertheless, before advocating for a change from the legal status quo, we need to address the bases of the current rules.

It is clear from many studies that multiple ethics reviews often result in multiple ethics conclusions. This is not necessarily a function of different perspectives being considered internationally; multiple reviews in the same country often result in different conclusions. In short, RECs are inconsistent.[115] The different results are more likely a function of inadequate training of REC staff and committee members,[116] and frequently an overemphasis on idiosyncratic procedural requirements of each REC. Although it is important to consider social and cultural conditions,[117] there is no evidence of the relative effectiveness of domestic or local ethics review versus other forms of ethics review.

A recent study explored the opinions of 25 experts in research ethics review from a broad sampling of countries, specifically considering data-intensive research, the closest analogy to DTP genomic research yet reported.[118] Semi-structured interviews were used to probe the issue of multi-site ethics review. Among its conclusions: "The underlying thread in all the distinct problem areas identified is the notion of *systemic inefficiency* and *substantive weakness* reflected, for example, in apprehension to novel or emerging forms of science, a focus on tick-box procedures, and a lack of reasoned, principled decisions."[119]

Although different REC procedures and a lack of harmonization result in lamentable differences, the foundational values of independent ethics review are largely the same across many countries. The Global Alliance for Genomics and Health (GA4GH) published its Ethics Review Recognition Policy in 2017[120] to assess and regularize international genomic research review. The background research for this policy involved the assessment of research ethics review in 39 countries, including interviews with experts. The foundational principles of the Framework track those of individual countries: respect individuals, families, and communities; advance research and scientific knowledge; promote health, wellbeing, and the fair distribution of benefits; and foster trust, integrity, and reciprocity.[121]

The United Nations Educational, Scientific and Cultural Organization (UNESCO), in its Universal Declaration of Bioethics and Human Rights, specifies traditional ethics review criteria, including informed consent, privacy/confidentiality, benefit/risk ratio, return of results, protection of the interests of vulnerable persons/communities, and research integrity and safety.[122] We would note that for both the GA4GH and UNESCO declarations the key will be how these principles are applied in various settings.

It is also important to stress that having equivalent principles and processes does not mean homogenization. There may be different outcomes or rationales used by RECs in different locations, but this also characterizes the results of ethics review in different locations of the same country. Although better training and communication among ethics review organizations remains an overall goal, there is a fundamental research ethics equivalence of research ethics standards in much of the world. As applied to consensual, data intensive, low risk, international DTP genomic research, equivalency can be relied upon to achieve adequacy and justify reciprocity.[123]

VI. Cultural Considerations

Anthropologists and others have long challenged the notion of a universal bioethical paradigm, arguing that the principles of bioethics are steeped in tenets and assumptions of Western philosophical rationalist thought.[124] Scholars have argued that cultural interpretations of ethical concepts, such as autonomy and justice, "are not merely related to alternate understandings of knowledge, but often represent a fundamental difference in conceptions of the universe and ways of viewing the world."[125] Consequently, it has been asserted that researchers' reliance on the role of the individual, especially in the informed consent process, fails to account for the value that many groups place on shared governance and decision-making.[126]

In response to this criticism, community consultation has been used to obtain information about the interests, values, and traditions of groups, as well as earning the trust of participants and their community. Community or family consultation may be especially important in genomic research, in which data collection and dissemination may have potential risks and benefits to an entire group.[127] Further, in many parts of the world, and among diverse populations, consent is a

communal process of collective decision-making in which community leaders, councils of elders, religious authorities, extended families, or spouses may play important roles.[128]

The conclusions about the role of cultural considerations in research have been largely based on a research model where researchers directly recruit participants, often enroll several or numerous participants from the same community, interact directly with participants in the enrollment phase and throughout the study, and conduct research involving more than minimal risk, possibly including a risk of reputational harm for a community or population group.

International DTP genomic research on rare disorders shares few, if any, of these characteristics. Enrollment is online and may be initiated by the participant as well as the researcher, there is usually no personal interaction between the researcher and participant, there may be only a single individual from a geographical area or community enrolled, and the research is data based (i.e., non-interventional) and generally considered to be "low risk."

An important area in which socio-cultural considerations should be explored is in the concept of "minimal risk" or "low risk," a crucial element of our proposal for single-site ethics review for international DTP genomic research. Some threshold questions are: How is the concept of minimal risk research viewed in diverse countries and communities? Who determines it? What criteria are used to assess the level of risk of a particular protocol? How does risk vary in discrete populations, including minority and indigenous groups? While recognizing the importance of thoroughly and sensitively exploring these questions, we argue below that, in the context of genomic research on rare disorders, these questions can be addressed in single-site review.

To the extent that community consultation is valuable for international DTP genomic research, the relevant "community" may be families with a rare genetic disease, and the researchers may be able to interact with community members all over the world through their online

community before, during, and after the study. In communities requiring that participation decisions involve individuals other than the prospective participant, the prospective participants *themselves* (to the extent they can do so without personal risk) may want to seek consultation with individuals or groups they deem to be most appropriate.

Local cultural considerations are important to ethics review, especially as applied to minority or indigenous populations.[129] Nevertheless, it is not clear that local ethics review is necessary to ensure that socio-cultural conditions are considered so long as external ethics review incorporates knowledgeable input on local considerations.[130] In additon to the balancing of risks and benefits and informed consent, other cross-cultural issues for researchers and RECs to consider include storage and future re-use of samples, secondary data and sample sharing, and return of results.[131] Further research is critical to determining the ways in which cultural considerations should be included in international DTP genomic research.

VII. Ethical and Policy Analysis

Our analysis in the preceding sections makes it clear that there are significant legal barriers to expanding DTP genomic research across international boundaries. Far from uncovering a simple solution, our examination of the legal frameworks of 31 countries helps bring into focus the complexity of these issues. Although ethics review is required by virtually every country, the specifics of this review vary from country to country. For example, the specific process for investigators to seek approval for their protocols, and the process used by ethics review members to evaluate these protocols, is not consistent.

These discrepancies represent a core challenge for international DTP genomic research. Because of these procedural differences, international research has typically been conducted using

a multi-site, networked approach. In this model, there is at least one collaborator in each country where participants will be recruited, with ethics approval sought independently according to the requirements of each country. As we have discussed, however, this is simply not a scalable model for international DTP genomic research. Because much of this research and the use case for this article focus on rare diseases, there may be as few as only one or two persons in each country with a condition of interest. As a result, obtaining separate ethics review in each country quickly reaches a point of diminishing returns and infeasibility.

Our examination of the legal frameworks in each country brings the challenge of international DTP genomic research into stark relief, but it also hints at a possible solution. As noted previously, the underlying frameworks of research ethics in much of the world are remarkably consistent. For example, the requirement for prospective ethics review of research protocols is nearly universal, and the principles of research ethics that RECs are expected to apply in their review are nearly always compatible with one another. This consistency in the ethical frameworks underlying research policies around the world is likely attributable to the common conceptual and historical roots of these policies. Many of these principles were first articulated in the Nuremberg Code in 1947.[132] Subsequently, the Declaration of Helsinki[133] of 1964 was developed and revised by the World Medical Association through decades of international collaboration. As a result, the Declaration of Helsinki has become a *de facto* standard for both its explication of the principles of ethical research and its description, in general terms, of the mechanisms that should be used to ensure that research with humans is conducted in an ethical manner. This standard has proven influential throughout the world as countries have sought to codify these principles into policy.

The fundamental agreement of research policies around the world indicate that single-site review for international DTP genomic research (in the U.S., often referred to as "central IRB review") may be a viable solution to the lack of scalability created by country-by-country review. In the international single-site review model, investigators in one country would receive prospective ethics review in their own country for their international DTP genomic research protocol. The approval would then be deemed adequate by all countries that recognize approval in the investigator's country as a legally effective approval for research with residents in the participants' country. This approach is analogous to in-country central review, an option already available in many countries, but it would extend the authority of central review across international borders.

In this section, we consider the ethical considerations and historical contingencies that led to the use of local, site-by-site ethics review throughout most of the world. We then review the factors that have led over time to the development of frameworks for in-country, single-site review, and why the extension of single-site review across international borders is acceptable from a policy and ethics perspective. We then lay the groundwork for our recommendations by examining why this approach is well-suited for international DTP genomic research.

A. *History of Local Ethics Review*

Extending back to its earliest applications in the 1950s,[134] ethics review of human research protocols has been primarily a local activity. Throughout the world, ethics reviewers typically live in the same community or even work in the same institution as the researcher proposing the research. When the NIH introduced peer review for intramural research conducted with healthy volunteers in 1953, the review panel was composed of peer researchers also working in the NIH Clinical Center.[135] Over twenty years later, when the first regulations applicable to extramural

researchers were promulgated in the U.S., they called for institutions to develop their own review boards composed of both local experts and community members.[136] This is precisely the reason why ethics review committees in the U.S. are referred to as *Institutional* Review Boards; they largely operate within a single institution. Despite the difference in terminology, RECs throughout the world still operate primarily on a local scale.

Several interrelated factors have contributed to the adoption of local review, as opposed to regional or national review. Most research with human participants conducted in the twentieth century was conducted at a single site, typically under the direction of a single lead investigator. Because most research was designed and carried out locally, local review allowed review committees to discuss research protocols with the lead investigator, to maintain oversight and accountability to ensure that research is conducted according to the protocol, and perhaps even to learn which investigators can be trusted to conduct research responsibly.[137]

Critically, however, the tradition of local ethics review has not been driven exclusively by practical considerations. At least two related normative concerns have also driven this practice. The first normative concern is that members of local communities might have values or needs that are not identical with those of other communities, and that needed to be addressed during the ethics review process. To take a recent example, members of African-American communities in Baltimore might have grown more skeptical of biomedical research as a result of the disclosure that Johns Hopkins Hospital collected cervical cancer cells from Henrietta Lacks and developed a cell line without her or her family's permission.[138] For this reason, it might be important for a local IRB at this institution to consider the implications of this story in the approval of new research protocols that would include members of local African-American communities.[139]

The second normative concern that has been offered to support local research ethics review is that it is important for local institutions and communities that research ethics committees retain some degree of autonomy and independence. As discussed above, local committees might require autonomy so that they can represent the values and needs of local communities in their review of research protocols. Potential research participants may also be reassured that the local institution, which they know and trust, has reviewed and approved a study. The independence of local RECs has also been emphasized as an approach that can reduce conflicts of interest. For example, in countries with national healthcare systems, such as the United Kingdom (U.K.), a local REC that operates independently from the national healthcare system is seen as a way to ensure that research studies are approved on the basis of their ethical and scientific merits, and not on financial or political considerations.[140]

B. *Single-Site Domestic Review*

Even though most research ethics review has remained local, researchers, patient advocates, and other stakeholders have long expressed interest in more centralized approaches. A great deal of this interest has been driven by concerns that local ethics review can significantly increase the effort required to carry out multi-site research. Although research conducted in large networks has grown increasingly popular in the past decade,[141] multi-site designs for clinical trials have been used for decades. Beginning in the early 1990s, for example, investigators in the U.K. began to explore regional or national review for multi-site clinical trials on the grounds that applying for ethics approval at each individual site took significant effort and tended to delay the start of trials.[142] This critique has been supported by reports demonstrating significant variability in the amount of time required by local RECs to review protocols for multi-site studies, with some sites requiring weeks to months to complete this review.[143]

In addition to these practical concerns, support for centralized approaches to ethics review has been bolstered by growing evidence that local variability in research ethics review often does not seem attributable to local differences in values or the specific needs of communities. In a 2003 report, for example, investigators categorized proposed revisions to the language of consent forms from two trials that were reviewed locally at 25 sites.[144] They found that revisions proposed by local IRBs tended to make consent forms longer and score lower on readability scales. IRBs sometimes proposed wording changes that did not alter meaning, and even introduced errors. These changes were made at the cost of a median review time of over 100 days, with some sites requiring nearly a year to complete their review. Reports demonstrating similar issues with variation in local research ethics review come from the U.K.,[145] the U.S.,[146] and Canada.[147]

Taken as a whole, the experience with local ethics review over the past decades shows that this approach creates significant practical challenges for multi-site research, and often does not address the normative concerns that originally motivated the adoption of this approach around the world. As a result, many countries have adopted alternative approaches that can be utilized in some circumstances. In 1997, the U.K. created 13 multicenter research ethics committees to review research studies that would take place at five or more sites.[148] In 1981, the Food and Drug Administration in the U.S. issued regulations that allowed study sponsors to create their own IRBs for multi-site studies, and in 1998 for sites to delegate research ethics review to another site.[149] However, many IRBs remained reticent to delegate their authority to central IRBs. As a result, a regulatory change was introduced in January 2019 that made central IRB review obligatory for multi-site studies.[150]

C. *Single-Site International Review*

Given that individual countries have successfully adopted single-site review within their borders, it is perhaps inevitable that researchers and other stakeholders would begin to consider whether such an approach could be adopted across international borders. As we have noted, this approach is particularly attractive in contexts like international DTP genomic research where the incremental burden of seeking review in additional countries is large while the benefit in recruiting additional participants is likely to be small. Although we believe that international single-site review could prove successful from both a practical and an ethical perspective, we recognize that international single-site review raises issues that are not necessarily identical with those raised by in-country central review. Before recommending a strategy to adopt international single-site review, then, it is important to first consider the unique issues raised in the international context.

Perhaps the most obvious challenge raised by single-site review for international research is that the policies adopted in each country differ, and sometimes in significant ways. When multi-site studies undergo central review *within* a country, that central review typically utilizes the same process and applies the same criteria that would have been used had the study been reviewed locally. The same consistency would not be expected in an international context. Even countries with deep historical and cultural ties like Canada and the U.K. utilize review criteria and processes that are different from one another. For example, research policies in many countries allow for an expedited review process when a study poses only minimal risk to participants. However, as shown in one study that underwent ethics review in five countries (Canada, Israel, New Zealand, U.K., and the U.S.), both the criteria for determining when a study poses minimal risk and the interpretation of those criteria in practice can vary significantly.[151] Our examination of the legal frameworks of 31 countries presented above also clearly demonstrates this type of variation.

Although this type of variation in process and review criteria clearly takes place, it remains unclear whether that variation should be considered a "feature" or a "bug" of country-by-country review of international research. On the one hand, some of that variation seems irrelevant to the goal of ensuring that research is conducted in an ethically appropriate way. The fact that one country requires one set of forms and another country requires a different set of forms has little impact on the goal of ensuring that research participation is voluntary and its risks are minimized. However, it is dangerous to disregard all variation as undesirable. For example, in the minimal risk study conducted in five countries, the differences in the classification of risk might legitimately reflect differing perspectives on the risk of research participation that correspond with cultural values that differ across the five countries. This example is important because in contrast to the examples of in-country variation cited earlier, the differences in review observed in this study did seem to reflect differences in perspective on an ethically important issue: the interpretation of risks posed by research.

In our proposal for adopting international single-site review for DTP genomic research, therefore, we do not intend to disregard the variation in perspectives on the conduct of research around the world. Instead, we argue that important differences in culture and values among countries can be addressed – and perhaps are even better addressed – through strategies other than additional REC review. As discussed above, researchers working to develop an international DTP genomic research protocol can engage with appropriate stakeholders through a variety of methods. The community of patients and family members most interested in a particular rare disease typically engage through online platforms like Facebook, although this is not an option in some countries. This is by necessity, since they are usually scattered around the world. These types of

communities are key stakeholders in DTP genomic research and are generally enthusiastic about the opportunity to engage with researchers through online platforms.

Depending on the focus of a study, the relevant stakeholders may not be accessible through a single online community, but researchers can seek the input of stakeholders in other ways. Expatriates in the researcher's own country may be able to serve as cultural liaisons to the populations that live in their country of origin. Leaders from government, medicine, and public health in target countries, reached by phone or videoconference, may also be able to help researchers and RECs address local cultural needs and design research to respect these differences. This type of engagement can be carried out, and used to inform study design, without the need for country-by-country ethics review.

REC review is designed to ensure that proposed research is designed in ways that respects the autonomy of participants, maximizes benefits and minimizes risks, and approaches recruitment and other procedures in a just way, among other ethical concerns. The priorities reflected in this ethical framework – the same framework explicated in the Declaration of Helsinki and applied across the globe – are consistent enough to provide a basis for mutual recognition of ethics approval among most countries. To the extent that variation in cultural values need to be considered in the design and operation of a study, a single REC should evaluate whether the investigators have undertaken appropriate consultation and are proposing sufficient strategies to continue that engagement throughout the course of a study. For example, the REC itself could retain consultants to assist it in considering the implications of a research study in different cultural contexts. All of these measures could be utilized without REC review in each country, and does not prevent studies from adopting slightly different procedures in different countries in order to

accommodate values or legal requirements that are relevant in certain communities or jurisdictions.[152]

D. *Low Risk International DTP Genomic Research*

Although it is perhaps possible to make a strong ethical case for international single-site ethics review for *all* research with humans, we are focused in this work on a single type of research: international DTP genomic research on rare disorders. Our conclusion is that single-site ethics review would work well with international DTP genomic research because participants are literally few and far between and genetic diversity carries special scientific value. Moreover, DTP genomic research does not raise many of the issues that benefit most from close REC oversight.

First, DTP genomic research is typically minimal risk[153] and non-interventional. The collection of DNA in this type of research requires participants to spit into a vial or swab the inside of their cheeks. This does not carry the types of risks conferred by research involving the invasive collection of a biospecimen or the administration of an investigational drug. Researchers conducting DTP genomic research eventually may use their findings to develop new pharmaceuticals, but studies testing those pharmaceuticals would require their own approvals in the future, often including regulatory considerations that fall outside the scope of this analysis, such as Investigational New Drug approvals by the Food and Drug Administration. The fact that future research might carry higher risks (and require its own approvals) should not affect the approval of DTP genomic research.

One dimension of DTP genomic research that carries an element of intervention is the return of genomic results to participants. As discussed above, this is often viewed by participants as a positive because many are interested in learning more about their genetic makeup. It could carry risks, however, such as if a participant receives information about their risk for developing a

condition and then responds to the information by pursuing invasive medical tests. These possibilities need to be considered when a REC is reviewing a DTP genomic research protocol involving the return of genomic results, especially when those results are so-called secondary findings because they do not relate to the original study. Nevertheless, there is no reason to believe that country-by-country review would be superior to single-site review in this context, and appropriate guidelines are available for minimizing the risks of returning results. [154]

The second feature of international DTP genomic research that makes it amenable to single-site review is the low risk it is likely to carry for creating a therapeutic misconception. In many forms of conventional health research, participants may misunderstand their research participation as a form of medical care. This misconception is reinforced by the fact that much of this research takes place in academic medical centers, sometimes with a patient's own healthcare provider as an investigator in the study. This misconception is ethically problematic because it increases the chances that individuals will overlook the potential risks of research or even fail to recognize that they are participating in research. In our view, individuals choosing to submit their biospecimens for DTP genomic research are unlikely to make such a mistake.

A far greater risk is that they will participate due to a *diagnostic* misconception; in other words that they are participating in research in order to obtain a diagnosis for themselves or their child with an undiagnosed rare disease. It is not clear, however, that this would be a misconception of the goals of this type of research.[155] Genomic research on rare diseases is often designed with a dual research and clinical purpose. This research typically involves individuals who are known to have a clinical condition (such as a neurodevelopmental disorder or an immune deficiency), but for whom the genetic cause of this condition is not known. Researchers analyze participants' genomic data to identify genetic variants that may be causing this condition. The research finding,

if it meets appropriate standards for validity, will then often be disclosed to parents as the genetic cause of their child's condition.

Although the ethical implications of this dual-purpose research needs to be explored further,[156] it is sufficient in this context to observe that there are two potential risks created by this "diagnostic misconception": (1) the risk that parents would allow their child to participate in research that creates undue risks in order to obtain a diagnosis for the child; and (2) the risk that parents will pursue ill-advised medical interventions on the basis of unverified research results. The former risk is significantly mitigated in the context of DTP research, since this research is typically minimal risk and non-interventional. The latter risk can be mitigated in part through clear communication that any diagnostic information generated in the research context would need to be confirmed in a clinical context. The protocol for this communication can be appropriately reviewed by a single-site review, especially if high standards are followed for translation of information into other languages, such as the confirmation of translation through back-translation.

E. *Participant Autonomy*

We have previously discussed the importance of autonomy to potential research participants. In this section we consider autonomy in the enrollment process as a practical limitation on regulation.

DTP genomic research does not only involve researchers soliciting potential participants, but in an indeterminate number of cases an individual will learn of the research, contact the researchers, and ask to enroll. The individual may be informed of the research by an already-enrolled participant, read about the research on a disease-specific website, or learn about the research through some other means. The 31 country reports appearing in this symposium clearly indicate that, regardless of the laws in their country, no individual would be legally sanctioned for

participating in a DTP genomic research project conducted abroad where the research was not approved in the individual's country.[157]

If no attempt is made to bring civil or criminal legal proceedings against a participant, then any legal action would have to be brought against a DTP researcher.[158] We think it is also highly impractical and therefore unlikely that a legal action would be brought against a foreign researcher who does not have domestic ethics approval, except in the case of a researcher with ongoing operations in the participant's country, such as a pharmaceutical company or a university with multiple research protocols.[159] Based on the reluctance to proceed against individuals, it is reasonable to assume that enrollment initiated by the participant will not result in a legal action. Indeed, it is likely that virtually all international DTP genomic research will be free from legal actions. As the author of the country report on Germany has observed: "It is difficult to envisage a regulatory regime capable of effectively governing cross-border activity that involves private individuals, exempt specimens that can be sent by ordinary post, and the processing of data in the context of globalized networks."[160]

Furthermore, it will be extremely difficult to neatly divide the wide range of enrollment circumstances into researcher-solicited (assumedly unlawful) versus participant-initiated (assumedly lawful) enrollment. To illustrate this point, we describe two of the many possible scenarios.

Example 1: A researcher mentions at an international medical conference that he or she is conducting genomic research on a certain rare disorder and asks international colleagues to help identify affected individuals. If a conference attendee mentions the study to a patient and the patient contacts the researcher, is this researcher-solicited or participant-initiated enrollment?

Would this be different from having the physician mention the study to the patient and, with the patient's consent, sending the patient's contact information to the researcher?

Example 2: An individual reads about an international DTP genomic study online and contacts the researcher. After discussing enrollment criteria, the researcher says that the individual does not qualify for the current phase of the study, but the individual would qualify for a new phase beginning the following year. At the individual's request, the researcher contacts the individual when the new phase of the study is beginning. Is this researcher-solicited or participant-initiated enrollment? If the patient, with or without authorization, supplies the researcher with contact information of other patients, would subsequent contact by the researcher be researcher-solicited or patient-initiated?

The difficulty and undesirability of drawing distinctions among various types of recruitment and enrollment to enforce research laws that were not enacted to regulate DTP research supports our recommendation that ethics approval by an adequate ethics review body in the researcher's country should permit international DTP genomic research in the participant's country of residence.

F. *Data Protection Precedent*

The concept of deferring to another country's legal protections following a determination of adequacy is becoming an accepted principle in international law. Perhaps the best example is in the area of data protection. Although European concerns about the transfer of data to other countries dates to the 1970s,[161] the first major development was the enactment of the European Data Protection Directive of 1995.[162] Its aim was to harmonize rules on data processing by members of the European Union (E.U.) and to restrict the transfer of personal data to non-member countries that did not ensure "an adequate level of protection." Without obtaining a formal

determination of adequacy, the E.U. and the U.S. entered into the Safe Harbor Framework Agreement in 2000, which provided that certain U.S. entities may be considered as offering essentially equivalent data protection as in the E.U. Directive. To merit such a status, U.S. companies had to file an annual self-certification, pledging that they were in compliance with the principles of the Directive as set forth on the website of the U.S. Department of Commerce. The companies also were required to publicize that they were following these principles and, if they failed to do so, it would constitute a deceptive trade practice in violation of section 5 of the Federal Trade Commission Act.[163]

The Safe Harbor Framework Agreement was in effect until 2015, when it was struck down by the European Court of Justice. The case of *Schrems v. Data Protection Commissioner*[164] was brought after Edward Snowden revealed that Facebook and other technology companies disclosed personal data of E.U. citizens to the U.S. National Security Agency. Because such disclosures were not prevented by the Safe Harbor Agreement, the court invalidated the entire agreement. In 2016, the Privacy Shield was established to replace the Safe Harbor Agreement.[165] Its structure, self-certification and publication of an assurance of compliance, were the same as before, but there were two key differences. First, Privacy Shield strengthened the enforcement provisions to require that organizations respond expeditiously to complaints by E.U. state authorities through an independent mechanism, establish damages for harms flowing from improper disclosures, and increase the ability of individuals to access their personal data.[166] Second, the U.S. government provided assurances that its national security agencies would not engage in mass surveillance of data transferred pursuant to the Privacy Shield.

In 2018, the E.U.'s General Data Protection Regulation (GDPR)[167] replaced the 1995 Directive, but the same approach to transfer of personal data to third countries applies. Under

Article 45 of the GDPR, personal data may be exported to a country outside of the E.U. only if the European Commission has acknowledged the adequacy of data protection in the recipient country.

So far, the European Commission has recognized Andorra, Argentina, Canada (application limited to private entities falling under the scope of Canadian Personal Information Protection and Electronic Documents Act), Faroe Islands, Guernsey, Israel, Isle of Man, Japan, Jersey, New Zealand, Switzerland, Uruguay and the United States (limited to the Privacy Shield framework) as providing adequate protection.[168] With the exception of Japan, the other governmental policies were assessed under the previous Data Protection Directive framework. Article 45(9) of the GDPR provides that these earlier decisions will be amended, replaced or repealed by a Commission decision during a periodic review, which must take place at least every four years. Changes in the legal framework of a third country or international organization may warrant sooner review.[169]

Substantively, adequacy requires compliance with 10 principles, the first six of which were previously part of the Data Protection Directive:

1. purpose limitation principle;

2. data quality and proportionality principle;

3. transparency principle;

4. security principle;

5. right of access, rectification and opposition;

6. restrictions on onward transfers;

7. the foreign country's legislation should include basic data protection concepts and remain consistent with the principles enshrined in the GDPR;

8. data must be processed in a lawful, fair, and legitimate manner while being set out in a sufficiently clear manner;

9. the data retention principle ensures that data is kept no longer than necessary for the purposes for which personal data is processed;

10. the confidentiality principle complements the security principle by stipulating that data must be protected against unauthorized or unlawful processing as well as accidental loss, destruction or damage.[170]

The E.U.-U.S. data protection agreement, as well as a similar Switzerland-U.S. agreement,[171] clearly suggests that without adopting identical laws and procedures it is still possible for countries to use adequacy determinations as a way of deferring to the laws of other nations. Comparable measures could enable the use of adequacy determinations to permit single-site ethics review for international DTP genomic research.

Because of the centrality of equivalence and adequacy to the recommendations in this article, it is important to distinguish these two concepts. "Equivalence" is based on a comparison of research ethics provisions in more than one country. By contrast, "adequacy" is based on a comparison of the research ethics review process and outcomes in more than one country. Therefore, a country with equivalent research ethics provisions that failed to apply or enforce them would not be adequate, and a country without equivalent provisions could achieve adequacy through other means, such as ad hoc administrative determinations or explicit international agreements. In our analytical framework, both concepts are important, and equivalence supports the finding of adequacy.

G. *Equivalency Provision in the Common Rule*

Single-site ethics review with deferral to the ethics determination in the researcher's country is consistent with the following provision that has been a part of the Common Rule since 1991:

> (h) When research covered by this policy takes place in foreign countries, procedures normally followed in the foreign countries to protect human subjects may differ from those set forth in this policy. In these circumstances, if a department or agency head determines that procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the department or agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy. Except when otherwise required by the statute, Executive Order, or the department or agency head, notices of these actions as they occur will be published in the Federal Register or will be otherwise published as provided in department or agency procedures.[172]

Strictly construed, this provision permits U.S.-supported researchers to comply with foreign ethics procedures if there is a determination by the U.S. agency or department sponsoring the research that the foreign procedures are equivalent to the Common Rule.[173] Without an equivalency determination, foreign researchers participating in a multinational study funded by an American agency would have to comply with the Common Rule, despite a greater familiarity with their own comparable research provisions.[174]

This provision has not been used, however, and the Office for Human Research Protections (OHRP) of the Department of Health and Human Services (HHS) has never deemed any country to have equivalent protections. Not only should this provision be used to permit researchers to comply with comparable ethics review requirements in the countries of participants, but the spirit

of this provision supports a wider application of equivalency. We believe that reports in this symposium from 31 diverse countries, our review showing adequacy and equivalency of laws regulating research with human subjects around the world, and the low risk and high potential benefit of international DTP genomic research present a compelling case for recognizing the determinations of single-site ethics review conducted in the researcher's home country.[175]

VIII. Recommendations

1. International DTP genomic research approved by an ethics review body in the researcher's country should be deemed approved in the participant's country if ethics review in the researcher's country has been determined to be adequate by the participant's country.

2. To facilitate international DTP research and to inform potential researchers and participants, a list of countries whose ethics review is deemed adequate should be posted on the website of the regulatory authority responsible for the ethical conduct of research with human participants, such as the OHRP in the United States.[176] Compilations of these country-developed adequacy determinations by international organizations would facilitate international reviews.

3. Ethics review bodies evaluating proposals for international DTP genomic research submitted by researchers in their home country should consider whether the countries from which participants will be enrolled accept single-site ethics review in the researcher's home country.

4. Ethics review bodies reviewing proposals for international DTP genomic research submitted by researchers in their home country should evaluate whether the researchers have given due regard to cultural considerations in the countries from which participants will be enrolled.

5. Regulatory authorities responsible for the ethical conduct of research with human participants should inform ethics review bodies under their jurisdiction of the approval criteria for international DTP genomic research.

6. Additional research is needed to assess the socio-cultural implications of international DTP genomic research in various population subgroups, including minority and indigenous populations.

These recommendations provide a broad framework for ethics review of international DTP genomic research. They are not intended to be the final word, as many questions remain, including the following. How are substantial equivalence and adequacy determined? What is the process for identifying and disclosing the countries determined to have adequate research ethics review? How should socio-cultural conditions in the country or locale of research participants be considered? What rules should apply on an interim basis while equivalence and adequacy are determined? Consequently, additional work remains in implementing these recommendations.

IX. Implementation

A. *Legal Requirements*

Our primary recommendation is to have single-site ethics review in the researcher's country. The most direct way to accomplish this would be to have a multinational treaty or a series of bilateral agreements establishing reciprocal recognition of research ethics determinations. Although this may be simple in theory, it would be exceedingly difficult to achieve because international agreements often require time-consuming, contentious negotiations and significant political support.[177]

Another way in which our primary recommendation could become legally binding is through unilateral action. A country could declare that the research ethics review procedures of certain named countries are equivalent to their own and therefore adequate to satisfy the laws of the research participant's country. For example, the U.S. OHRP could make a determination that ethics review in Canada is equivalent to review in the U.S. and therefore it is adequate to satisfy the Common Rule.[178] The effect would be to permit Canadian researchers to conduct DTP genomic research in the U.S. without local IRB approval.[179]

For this approach of unilateral recognition of adequacy to be effective a substantial number of countries would need to declare the research ethics review of a considerable number of other countries as equivalent. There could be reciprocal, unilateral agreements or multinational agreements. For example, the E.U. could determine that the H3Africa countries have equivalent ethics review and vice versa.

As noted earlier, focusing on the participant's country seems to burden the participant's country rather than the researcher's country and, consequently, raises the question of why the participant's country would agree to accept the determinations of the researcher's ethics review body. The answer, to reiterate, is that DTP genomic research is consensual, non-interventional, data based, and low risk. Potential participants excluded from genomic studies would be adversely affected if the individuals enrolled do not sufficiently represent the global population. We believe that any minor variation or deviation in established research review procedures for this type of research is more than offset by the public policy supporting potentially valuable genomic studies.

As a matter of strategy, it might be better for the countries performing significant amounts of genomic research, such as the U.S., to take the lead in recognizing the equivalence of other countries. Then, other countries may be more likely to reciprocate.

B. *Ethical Guidelines and Best Practices*

Besides legally binding provisions there are other international documents and principles that currently do or could be revised to expressly support single-site review in the researcher's country for international DTP genomic research. These include the Council for International Organizations of Medical Sciences (CIOMS) and World Health Organization (WHO) International Ethical Guidelines for Biomedical Research Involving Human Subjects (2016);[180] United Nations Educational, Scientific and Cultural Organization (UNESCO) Universal Declaration of Bioethics and Human Rights (2005)[181] and Task Force on Privacy and Protection of Health-Related Data (2019);[182] Council of Europe, Recommendation on the Protection of Health-Related Data (2019);[183] Human Heredity and Health in Africa (H3Africa) Guidelines on Informed Consent;[184] and the World Medical Association's Declaration of Helsinki (2013).[185]

Indeed, a review of international ethics norms from these recognized bodies over the last 25 years reveals remarkable symmetry and complementarity as concerns both the principles for genomic research and for ethics review. Even "classical" biomedical principles of respect for persons, beneficence, and justice have been translated into more genetic-specific guidance. They now also include familial or community interests in genetic information, the need to examine possible group stigmatization or discrimination (insurance/employment) concerns, and more recently, consideration of the impact on future generations and ensuring equitable access. This move from strictly individualistic ethics protection to including the welfare of others affected by genetic conditions or the need for health care to include the sharing of genetic data are common to the guidance provided in the norms of these international bodies. These shared principles and guidance for ethics review in genomic research bode well for the recognition of single site ethics review.

In addition to international declarations and ethical guidelines, funders of international research, such as the Wellcome Trust[186] and the Gates Foundation,[187] could condition funding on single-site ethics review in the researcher's country for international DTP genomic research. Organizations of genomic researchers, such as the Global Alliance for Genomics and Health (GA4GH)[188] could also adopt best practices calling for this procedure for ethics review. This "soft" regulation could generate momentum for acceptance of this review process. The most persuasive evidence of the appropriateness of this approach, however, would be the successful use of these procedures in international DTP genomic research without significant difficulty or complaints from participants, researchers, or governments.

X. Conclusion

The primary recommendation of this article, single-site ethics review in the researcher's country, is quite limited. It applies only to international direct-to-participant (DTP) genomic research, and specifically to the use case of rare disorders. This research is low risk, non-interventional, and consensual. The participants in the research are often highly motivated families with a history of the disorder being studied who are seeking to obtain information and advance scientific discovery. Without a method for avoiding redundant ethics review in multiple countries, much promising genomic research on rare diseases and cancers is likely to be curtailed or precluded. Special cultural conditions in communities or countries ought to be addressed, but we believe it can be done as part of the single-site review and does not need additional domestic or local review.

At a time when international cooperation is increasingly under strain, the primary recommendation does not require international collaboration or agreements. Our proposal merely recognizes the status quo of broad equivalence of research ethics criteria that have been a part of

international documents, such as the Declaration of Helsinki, for many years. In analogous areas, such as international data protection, the finding of equivalent standards leads to a determination of adequacy, which supports unilateral action by one country or reciprocal actions by multiple countries. International DTP genomic research can flourish under a similar arrangement.

1242 Appendix 1: Country Reports and Authors

Country Reports	Authors
Australia	Don Chalmers
Brazil	Suelie G. Dallari, Marina de Neiva Borba
Canada	Miriam Pinkesz, Yann Joly
China	Haidan Chen
Denmark	Mette Hartlev
Estonia	Liis Leitsalu
Finland	Sirpa Soini
France	Emmanuelle Rial-Sebbag
Germany	Nils Hoppe
Greece	Tina Garani-Papadatos, Panagiotis Vidalis
India	Krishna Ravi Srinivas
Israel	Gil Siegal
Italy	Stefania Negri
Japan	Ryoko Hatanaka
Jordan	Maysa Al-Hussaini, Amal Al-Tabba’
Mexico	Lourdes Motta, Laura Estela Torres Moran
Netherlands	Aart Hendriks
Nigeria	Obi Nnamuchi
Peru	Rosario Isasi
Poland	Dorota Krekora-Zajac
Qatar	Eman Sadoun
Singapore	Calvin Ho
South Africa	Pamela Andanda
South Korea	Won Bok Lee
Spain	Pilar Nicolás
Sweden	Titti Mattsson
Switzerland	Vladislava Talanova, Alexandre Dosch, Dominique Sprumont
Taiwan	Chien-Te Fan, Tzu-Hsun Hung
Uganda	Obi Nnamuchi
United Kingdom	Jane Kaye, Andelka Phillips, Heather Gowans, Nisha Shah
United States	James W. Hazel

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Appendix 2: Survey Questions

1. As far as you know, is DTP genomic research a topic of interest to researchers or other stakeholders in your country?

2. Assume that a researcher in your country wants to conduct DTP genomic research with participants in your country and that such research is subject to IRB/REC review. Please describe the conditions for IRB/REC approval, if it could be approved at all.

3. Assume that a researcher in your country wants to conduct DTP genomic research in another country. Please describe the conditions that must be satisfied for IRB/REC approval in your country, if it could be approved at all. Would your IRB/REC also require approval from a research ethics review body in the other country?

4. Assume that a researcher from outside your country wants to conduct DTP genomic research in your country:

A. Would it be lawful for the researcher to do so without IRB/REC approval in either the researcher's country or your country?

B. Would it be lawful for the researcher to do so if the research were approved by an IRB/REC in the researcher's own country, but was not submitted for approval in your country?

C. Would the external researcher be required to have a collaborator in your country?

D. Would it matter whether the external researcher is based at a commercial, governmental, or academic entity?

5. As far as you know, what are the perceived benefits and risks that could occur if a researcher from another country conducted IRB/REC-approved genomic research on samples or data obtained from your country? Please consider the perspectives of the public, research participants, socially-defined groups (e.g., indigenous or minority populations), researchers, and other professional or government entities.

6. Does your country have biohazard committees, data protection boards, export permit authorities, or other entities that regulate the transferring of data across borders for research? If so, do these requirements apply to individual citizens as well as research and medical institutions?

7. Does your country have laws, policies, or guidelines dealing with genetic or genomic research or genetic or genomic privacy that would apply to international DTP research? Do your national laws on these issues apply outside of your country when residents or citizens of your country enroll in a DTP study conducted abroad?

8. Does your country have laws, policies, guidelines, or cultural expectations regarding the return of individual or aggregate research results?

9. Does your country have laws, policies, or guidelines regarding "direct-to-consumer" genetic testing (e.g., 23andMe) and, if so, what do they provide?

10. How, if at all, do you anticipate that your country's laws, policies, or guidelines will change in the next 5-10 years in response to international DTP genomic research?

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References:

[1] Institutional Review Board is used to refer to ethics review bodies in the United States; Research Ethics Committee is used to refer to ethics review bodies in all other countries.

[2] Our research methodology is summarized in M.A. Rothstein and B.M. Knoppers, "Regulation of International Direct-to-Participant Genomic Research: Symposium Introduction," *Journal of Law, Medicine & Ethics* 47, no. 4 (2019): ___ and M.A. Rothstein, M.H. Zawati, and B.M. Knoppers, "Introduction to the Country Reports," *Journal of Law, Medicine & Ethics* 47, no. 4 (2019): ___.

[3] M.T. Nguyen et al., "Model Consent Clauses for Rare Disease Research," *BMC Medical Ethics* 20, no. 55 (2019): 1-7, 2, https://doi.org/10.1186/s12910-019-0390-x.

[4] P. Jongen et al., "Adherence to Web-Based Self-Assessments in Long-Term Direct-to-Patient Research: Two-Year Study of Multiple Sclerosis Patients." *Journal of Medical Internet Research* (2017): 19,7 e249; J. Krischer et al., "Experience with Direct-to-Patient Recruitment for Enrollment Into a Clinical Trial in a Rare Disease: A Web-Based Study," *Journal of Medical Internet Research* (2017): 19,2 e50; All of Us Research Program Investigators, "The 'All of Us' Research Program," *New England Journal of Medicine* 381, no. 7 (2019): 668-676; N. Boutin et al., "Implementation of Electronic Consent at a Biobank: An Opportunity for Precision Medicine Research." *Journal of Personalized Medicine* (2016): 6, no. 2, 17, https://doi.org/10.3390/jpm6020017.

[5] Comprehension is a special concern in countries where consent documents must be translated. Other concerns include different cultural meanings attached to risk or the value of scientific research. For a further discussion, see Part VI *infra*.

[6] C. Grady et al., "The Changing Face of Informed Consent," *New England Journal of Medicine* 376, no. 9 (2017): 856-867; M Doerr et al, "Developing a Transparent, Participant-Navigated Electronic Informed Consent for Mobile-Mediated Research" (2016), *available at* http://dx.doi.org/10.2139/ssrn.2769129 (last visited September 6, 2019).

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[7] Count Me In, About Us, *available at* https://joincountmein.org/About (last visited September 4, 2019).

[8] C. Painter et al, "The Angiosarcoma Project: Enabling Genomic and Clinical Discoveries in a Rare Cancer through Patient-Partnered Research," bioRxiv preprint first posted online August 26, 2019; doi: http://dx.doi.org/10.1101/741744 (used with permission of the authors).

[9] All of Us, About the All of Us Research Program, *available at* https://allofus.nih.gov/about/about-all-us-research-program (last visited September 4, 2019).

[10] See All of Us, *supra* note 4.

[11] See section VII-E, *infra*.

[12] Nat'l Comm'n for the Protection of Human Subjects of Biomedical and Behavioral Research, Ethical Principles for the Protection of Human Subjects of Research – The Belmont Report (1979), 4, *available at* https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html (last visited August 22, 2019).

[13] The societal benefits of any health research depend on socio-economic and socio-cultural considerations related to the individual country. Individuals in low- and middle-income countries may not realize the same health benefits, and may have greater social risks, as individuals in high income countries.

[14] M. Lek et al., "Analysis of Protein-Coding Genetic Variation in 60,706 Humans, *Nature* 536, no. 7616 (2016): 285-291; A.K. Manrai et al., "Genetic Misdiagnoses and the Potential for Health Disparities," *New England Journal of Medicine* 375, no. 7 (2016): 655-665.

[15] NIH, Genetic and Rare Diseases Information Center, FAQs about Rare Diseases, *available at* https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases (last visited August 27, 2019).

[16] WHO, Priority Medicines for Europe and the World 2013 (2013), *available at* https://www.who.int/medicines/areas/priority_medicines/Ch6_19Rare.pdf (last visited August 27, 2019).

[17] *Id.*

[18] *See* Rothstein, Zawati, and Knoppers, *supra* note 3.

[19] France, Greece, India, Israel, Italy, Japan, Nigeria, Poland, and Spain.

[20] Australia, Brazil, Canada, China, Denmark, Greece, India, Israel, Italy, Japan, Mexico, Netherlands, Nigeria, Peru, Qatar, South Africa, Spain, Sweden, Switzerland, Taiwan, Uganda, and the United Kingdom. Note: We include Peru within these 22 countries despite an "unsure" response in its report as it was stated, based on existing legislation, that HREC approval was a prerequisite for all forms of scientific research in the country. Finland answered both "yes" and "no," therefore we categorized the response as "unsure/other." Similarly, we categorized South Korea's response as "unsure/other" as the explanation did not state that DTP genomic research would be unlawful without external or local REB approval.

[21] Brazil, China, Denmark, Italy, Israel, Mexico, the Netherlands, Peru, Spain, Sweden, Switzerland, and Taiwan.

[22] Australia, Canada, Greece, India, Japan, Qatar, South Africa, Uganda, and the United Kingdom.

[23] Estonia, France, Jordan, Poland, and South Korea.

[24] Finland, Singapore, and the United States.

[25] Brazil, China, Denmark, India, Israel, Italy, Mexico, the Netherlands, Nigeria, Peru, Qatar, South Africa, Sweden, Switzerland, Taiwan, Uganda, and the United Kingdom.

[26] Brazil, China, Denmark, Israel, Italy, Mexico, the Netherlands, Nigeria, Peru, Sweden, Switzerland, and Taiwan.

[27] India, Qatar, South Africa, Uganda, and the United Kingdom.

[28] Australia, Canada, and Japan.

[29] Estonia, France, Greece, Finland, Jordan, Poland, Singapore, South Korea, and the United States.

[30] Germany, the Netherlands, Peru, and Taiwan.

[31] Australia, Canada, Greece, and Japan.

[32] Brazil, China, Israel, Italy, and Mexico.

[33] India, Qatar, South Africa, and Uganda.

[34] Denmark, Singapore, South Korea, and the United Kingdom.

[35] Finland and the United States.

[36] Nine responded "Yes," 4 stated it would be practical, and 2 stated it would depend on the context of the research.

[37] We included Germany and South Korea in this grouping, despite their uncertainty as to their responses because their legislation does not explicitly preclude commercial entities from conducting research. Rather, in certain circumstances, commercial entities may be subject to additional scrutiny during HREC approval (South Korea) or stricter regulation in the conduct of their research (Germany).

[38] Brazil, Denmark, Finland, Israel, Italy, Mexico, the Netherlands, Nigeria, Peru, Singapore, Sweden, Switzerland, and Taiwan.

[39] Australia, Canada, Japan, Greece, South Africa, Uganda, the United Kingdom, and the United States.

[40] We were not able to categorize Estonia, Nigeria, and Spain as there were insufficient indications as to the types of normative documents relied on to provide their responses.

[41] China, India, Poland, and Qatar.

[42] France and Jordan.

[43] Australia, Brazil, China, Denmark, Estonia, Finland, France, Germany, Greece, Israel, Italy, Japan, Spain, Sweden, the United Kingdom. Note: we include countries which listed the GDPR within this list as it contains provisions regarding the protection of genetic data.

[44] Canada, Mexico, the Netherlands, Nigeria, Peru, Poland, Singapore, Switzerland, Taiwan, Uganda, and the United States.

[45] India, Jordan, Qatar, South Africa, and South Korea.

[46] Canada, China, Nigeria, South Korea, Spain, Switzerland, Taiwan, Uganda, the United Kingdom, and the United States.

[47] See, for example, Canada, Spain, Switzerland, and Taiwan.

[48] Australia, Estonia, Finland, France, Germany, Greece, Israel, Italy, the Netherlands, and Sweden.

[49] Estonia, Finland, France, Germany, Greece, Italy, the Netherlands, and Sweden.

[50] See Finland, France, the Netherlands, and Sweden.

[51] Denmark, Mexico, Peru, and Singapore.

[52] Brazil, Japan, and Poland.

[53] India, Jordan, Qatar, and South Africa.

[54] See Question 10 of Country Reports: Brazil, Denmark, Finland, France, Greece, Israel, Italy, Jordan, Mexico, the Netherlands, Nigeria, South Africa, South Korea, Spain, Sweden, Switzerland, Taiwan, Uganda, and the United Kingdom

[55] E.W. Clayton et al., "The Law of Genetic Privacy: Applications, Implications, and Limitations," *Journal of Law and the Biosciences* (2019): 1-36, doi:10.1093/jlb/lsz007.

[56] National Human Genome Research Institute, *Genome Statute and Legislation Database*, NHGRI website, *available at* <https://www.genome.gov/about-genomics/policy-issues/Genome-Statute-Legislation-Database> (last visited August 31, 2019).

[57] *See, e.g.*, Alaska Stat. § 18.13.010(a)(2); Colo. Rev. Stat. § 10-3-1104.7(1)(a); Fla. Stat. § 760.40(2)(a); Ga. Code Ann. § 33-54-1(1); La. Rev. Stat. Ann. § 22:213.7(E).

[58] *See, e.g.*, Alaska Stat. Ann. § 18.13.010(a)(2); Ariz. Rev. Stat. **§** 20-448.02; Del. Code tit. 16, §1201 et seq.; Fla. Stat. Ann. § 760.40(2)(a).

[59] *See, e.g.*, Del. Code tit. 16, §1201 et seq.; Nev. Rev. Stat. §629.101 et seq.; N.J. Rev. Stat. §10:5-43 et seq.; Tex. Bus. & Com. Code § 546.001 et seq.; Wyo. Stat. § 35-31-101 et seq.

[60] *See, e.g.*, Fla Stat. §7 60.40); Ky. Rev. Stat. §61.931 et seq.; Me. Stat. tit. 22, § 1711C.

[61] *See, e.g.*, Cal. Health and Safety Code § 24170 et seq.; Md. Health Code §13-2001 et seq.; N.Y. Public Health Code §2440 et seq.; Code of Va. § 32.1-162.16.

[62] *See* E.W. Clayton et al., *supra* note 55 (discussing the various federal statutes governing genetic information and research, including issues of preemption).

[63] California Consumer Privacy Act of 2018, *available at* <https://leginfo.legislature.ca.gov/faces/billTextClient.xhtml?bill_id=201720180SB1121> (last visited August. 31, 2019).

[64] *See* M.A. Rothstein and S.A. Tovino, "California Takes the Lead on Data Privacy Law," *Hastings Center Report* 49, no. 5 (2019): 4-5.

[65] General Data Protection Regulation, Regulation (EU) 2016/679.

[66] *See, e.g.*, Protection of Personal Information Act, 2013 (South Africa), *available at* http://www.justice.gov.za/inforeg/docs/InfoRegSA-POPIA-act2013-004.pdf (last visited August 31, 2019); California Consumer Privacy Act of 2018, *supra* note 63.

[67] Regulation (EU) 2016/679, Article 9(2).

[68] Regulation (EU) 2016/679, Article 9(2)(a).

[69] Regulation (EU) 2016/679, Article 9(2)(j).

[70] Regulation (EU) 2016/679, Article 5(1)(e).

[71] K. Pormeister, "Genetic Research and Applicable Law: The Intra-EU Conflict of Laws as a Regulatory Challenge to Cross-Border Genetic Research," *Journal of Law and the Biosciences* 5, no. 3 (2018): 1-18.

[72] Regulation (EU) 2016/679, Article 9(4).

[73] Regulation (EU) 2016/679, Article 9(2)(g) and (j); Article 6(e).

[74] Regulation (EU) 2016/679, Article 89(2).

[75] *See* M.A. Rothstein et al., "Broad Consent for Future Research: International Perspectives," *Hastings Center Report* 40, no. 6 (2018): 7-12.

[76] Regulation (EU) 2016/679, Recital 33.

[77] A. Senger and S. Schonhofen, "German DPAs Publish Resolution on Concept of 'Broad Consent' and the Interpretation of 'Certain Areas of Scientific Research,'" *Technology Law Dispatch* (April 25, 2019), *available at* https://www.technologylawdispatch.com/2019/04/privacy-data-protection/german-dpas-publish-resolution-on-concept-of-broad-consent-and-the-interpretation-of-certain-areas-of-scientific-research/ (last visited August 31, 2019); the full text of the resolution (in German) is available at https://www.datenschutzkonferenz-online.de/media/dskb/20190405_auslegung_bestimmte_bereiche_wiss_forschung.pdf (last visited August 31, 2019).

[78] *Id.*

[79] K. Pormeister, *supra* note 71.

[80] *Id.*

[81] European Commission, "Declaration of Cooperation: Towards Access to at least 1 Million Sequenced Genomes in the European Union by 2022," *available at* https://ec.europa.eu/newsroom/dae/document.cfm?doc_id=50964 (last visited August 31, 2019).

[82] European Commission, "13 European Countries Have Signed a Declaration for Delivering Cross-border Access to Their Genomic Information," *available at* https://ec.europa.eu/digital-single-market/en/news/eu-countries-will-cooperate-linking-genomic-databases-across-borders (last visited August 31, 2019);

[83] L. Nordling, "A New Law was Supposed to Protect South Africans' Privacy. It May Block Important Research Instead," *Science News* (February 20, 2019), *available at* https://www.sciencemag.org/news/2019/02/new-law-was-supposed-protect-south-africans-privacy-it-may-block-important-research (last visited August 31, 2019).

[84] Protection of Personal Information Act, *supra* note 66.

[85] C. Staunton et al., "Ethical and Practical Issues to Consider in the Governance of Genomic and Human Research Data and Data Sharing in South Africa: a Meeting Report," *AAS Open Research* 2, no. 15 (2019): 1-11.

[86] M.S. Pepper et al., "ASSAf Consensus Study on the Ethical, Legal and Social Implications of Genetics and Genomics in South Africa," *South African Journal of Science* 114 no. 11/12 (2018): 1-3 at 2; C. Staunton et al., *supra* note 85, at 3-4.

[87] M.S. Pepper et al., *supra* note 86.

[88] L. Nordling, *supra* note 83.

[89] *Id.*

[90] J. de Vries et al., "Regulation of Genomic and Biobanking Research in Africa: A Content Analysis of Ethics Guidelines, Policies and Procedures from 22 African Countries," *BMC Medical Ethics* 18, no. 8 (2017): 1-9; C.

Rich, "Privacy Laws around the World," *Bloomberg Law* (2016), *available at* http://garnerhealth.com/wp-content/uploads/2014/02/privacy-laws-around-the-world-report.pdf (last visited August 31, 2019).

[91] D. Mahapatra, "2,644 Died During Clinical Trial of Drugs in 7 Years: Gov't to SC," *Times of India* (April 25, 2013), *available at* https://timesofindia.indiatimes.com/india/2644-died-during-clinical-trial-of-drugs-in-7-years-Govt-to-SC/articleshow/19719175.cms (last visited August 31, 2019).

[92] M. Kay, "Indian Supreme Court Tells Government to Act on Illegal Clinical Trials," *British Medical Journal* 346, no. f51 (2013): doi: https://doi.org/10.1136/bmj.f51. *See* Swasthya Adhikar Manch v. Union of India, Writ Petition (Civil) No. 33 of 2012.

[93] S. Reardon, "NIH Makes Wary Return to India, "*Nature News* 506, no. 7487 (2014): 143-144.

[94] Report of the Prof. Ranjit Roy Chaudhury Expert Committee to Formulate Policy and Guidelines for Approval of New drugs, Clinical Trials and Banning of Drugs (July 2013), *available at* http://www.indiaenvironmentportal.org.in/files/file/clinical%20trials1.pdf (last visited August 31, 2019).

[95] *Id*. at 2, 40-49; *see* M. Barnes et al., "The Evolving Regulatory Landscape for Clinical Trials in India," *Food and Drug Law Journal* 73, no. 601 (2018): 601-623, 611.

[96] Expert Committee Report, *supra* note 94, at 2-3, 76-77*; see* Barnes et al., *supra* note 95, at 611-614.

[97] Expert Committee Report, *supra* note 94, at 3, 78-89; *see* Barnes et al., *supra* note 95, at 606-610.

[98] Expert Committee Report, *supra* note 94, at 3, 78-89; *see* Barnes et al., *supra* note 95, at 611-614.

[99] R.R. Chaudhury and D. Mehta, "Regulatory Developments in the Conduct of Clinical Trials in India," *Global Health, Epidemiology and Genomics* 1, no. e4 (2016): 1-6.

[100] K. Mallath and T. Chawla, "Investigators' Viewpoint of Clinical Trials in India: Past, Present and Future," *Perspectives in Clinical Research* 8, no. 1 (2017): 31-36.

[101] *Id*.

[102] Barnes et al., *supra* note 95, at 618-622.

[103] J. Shelar, "After a Lull of Five Years, Clinical Trials on the Rise in India," *The Hindu* (June 2, 2018), *available at* https://www.thehindu.com/news/national/after-a-lull-of-five-years-clinical-trials-on-the-rise-in-india/article24069487.ece (last visited August 31, 2019); M. Ilancheran, "Measuring the Impact of Reforms on India's Clinical Trial Environment," *Clinical Leader* (October 12, 2017), *available at* https://www.clinicalleader.com/doc/measuring-the-impact-of-reforms-on-india-s-clinical-trial-environment-0001 (last visited August 31, 2019).

[104] D. Normile, "China Asserts Firm Grip on Research Data," (April 9, 2018), *available at* https://www.sciencemag.org/news/2018/04/china-asserts-firm-grip-research-data (last visited August 31, 2019).

[105] H. Lovells, "New Human Genetic Resources Regulations in China (July 2019)," *available at* https://f.datasrvr.com/fr1/319/56529/New_human_genetic_resources_regulations_in_China_-_July_8_2019.pdf (last visited August 31, 2019); the full text of the resolution (in Chinese) is available at http://www.gov.cn/zhengce/content/2018-04/02/content_5279272.htm (last visited August 31, 2019).

[106] *Id.* at 1.

[107] *Id.* at 1-2.

[108] *Id.*

[109] *Id.* at 2-3.

[110] *Id.* at 3.

[111] *Id.*

[112] *Id.* at 3-4.

[113] B. Guarino, E. Rauhala, and W. Wan, "China Increasingly Challenges American Dominance of Science," *Washington Post* (June 3, 2019), *available at* https://www.washingtonpost.com/national/health-science/china-challenges-american-dominance-of-science/2018/06/03/c1e0cfe4-48d5-11e8-827e-190efaf1f1ee_story.html (last visited August 31, 2019).

[114] *See, e.g.*, J. de Vries et al., *supra* note 90.

[115] D. Resnik, "Consistency in IRB Review," *Journal of Clinical Research Best Practices* 10, no. 12 (2014): 1-8.

[116] A.A. Lemke et al., "Broad Data Sharing in Genetic Research: View of Institutional Review Board Professionals," *IRB* 33, no. 3 (2011): 1-5.

[117] *See* section VI *infra.*

[118] E.S. Dove and C. Garattini, "Expert Perspectives on Ethics Review of International Data-Intensive Research: Working Towards Mutual Recognition," *Research Ethics* 14, no. 1 (2018): 1-25.

[119] *Id.* at 8.

[120] Global Alliance for Genomics and Health, Ethics Review Recognition Policy (2017), *available at* https://www.ga4gh.org/wp-content/uploads/GA4GH-Ethics-Review-Recognition-Policy.pdf (last visited September 9, 2019).

[121] *Id.* at 2.

[122] UNESCO, Universal Declaration of Bioethics and Human Rights (2005), *available at* http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/bioethics-and-human-rights/ (last visited September 9, 2019).

[123] *See* E.S. Dove et al., "Ethics Review for International Data-Intensive Research," *Science* 351, no. 6280 (2016): 1398-1399.

[124] A. Kleinman, "Culture, Health Care, and Clinical Reality," in: A. Kleinman, ed., *Patients and Healers in the Context of Culture: An Exploration of the Borderland Between Anthropology, Medicine, and Psychiatry* (Berkeley: University of California Press, 1980): 24-70; P.A. Marshall, "Informed Consent in International Health Research," *Journal of Empirical Research on Human Research Ethics* 1, no. 1 (2006): 25-42; C. Smith-Morris, "Autonomous Individuals or Self-Determined Communities? The Changing Ethics of Research among Native Americans," *Human Organization* 66, no. 3 (2007): 327-336.

[125] M. Hudson, "Think Globally, Act Locally: Collective Consent and the Ethics of Knowledge Production," *International Social Science Journal* 60, no. 195 (2009): 125-133, 128.

[126] Marshall, "Informed Consent in International Health Research," *supra* note 124; Smith-Morris, *supra* note 124; W. De Craemer, "A Cross-Cultural Perspective on Personhood,"*Milbank Memorial Fund Quarterly Health and Society* 61, no. 1 (1983): 19-34; P. Marshall and B. Koenig, "Accounting for Culture in a Globalized Bioethics," *Journal of Law, Medicine and Ethics* 32, no. 2 (2004): 252-266; R.J. Levine, "Informed Consent: Some Challenges to the Universal Validity of the Western Model," *Law, Medicine and Health Care* 19, no. 3-4 (1991): 207-213; P.A. Marshall, "'Cultural Competence' and Informed Consent in International Health Research," *Cambridge Quarterly of Healthcare Ethics* 17, no. 2 (2008): 206-215; R. Gilbar and J. Miola, "One Size Fits All? On Patient Autonomy, Medical Decision-Making, and the Impact of Culture," *Medical Law Review* 23, no. 3 (2014): 375-399.

[127] M.W. Foster and R.R. Sharp, "Genetic Research and Culturally Specific Risks: One Size Does Not Fit All," *Trends in Genetics* 16, no. 2 (2000): 93-95; J. de Vries et al., "Ethical Issues in Human Genomics Research in Developing Countries," *BMC Medical Ethics* 12 (2011); N.A. Garrison et al., "Genomic Research Through an Indigenous Lens: Understanding the Expectations," *Annual Review of Genomics and Human Genetics* 20, no. 1 (2019).

[128] Hudson, *supra* note 125; M.J. Clark, "Cross-Cultural Research: Challenge and Competence," *International Journal of Nursing Practice* 18, no. s2 (2012): 28-37; Foster and Sharp, *supra* note 127; A.A. Hyder and S.A. Wali, "Informed Consent and Collaborative Research: Perspectives from the Developing World," *Developing World Bioethics* 6, no. 1 (2006): 33-40; D.J. Krogstad et al., "Informed Consent in International Research: The Rationale for Different Approaches," *American Journal of Tropical Medicine and Hygiene* 83, no. 4 (2010): 743-747; P.A. Marshall, "Human Subjects Protections, Institutional Review Boards, and Cultural Anthropological Research," *Anthropological Quarterly* 76, no.2 (2003): 269-285; P.A. Marshall, "The Individual and the Community in International Genetic Research," *Journal of Clinical Ethics* 15, no. 1 (2004): 76-86; L. Dawson and N.E. Kass, "Views of US Researchers About Informed Consent in International Collaborative Research," *Social Science and Medicine* 61, no.6 (1982): 1211-1222.

[129] K.G. Claw et al., "A Framework for Enhancing Ethical Genomic Research with Indigenous Communities," *Nature Communications* 9 (2018): 2957; K.S. Tsosie, J.M. Yracheta, and D. Dickenson, "Overvaluing Individual Consent Ignores Risks to Tribal Participants," *Nature Reviews Genetics* 20, no. 9 (2019): 747-798; Hudson, *supra* note 125; Garrison, *supra* note 127; K.L. Henare et al., "Mapping a Route to Indigenous Engagement in Cancer Genomic Research," *The Lancet Oncology* 20, no. 6 (2019): e327-e335; Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, "Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans" (2010); Indigenous People Council of Biocolonialism, "Indigenous Research Protection Act," A Model Tribal Ordinance for the Protection of Indigenous Knowledge and Biological Resources (2000); R.R. Sharp and M.W. Foster, "Community Involvement in the Ethical Review of Genetic Research: Lessons from American Indian and Alaska Native Populations," *Environmental Health Perspectives* 110 (Supp. 2) (2002): 145-148; Z.A. Bhutta, "Ethics in International Health Research: A Perspective from the Developing World," *Bulletin of the World Health Organization* 80, no. 2 (2002): 114-120; R.E. McWhirter et al., "Ethical Genetic Research in Indigenous Communities: Challenges and Successful Approaches," *Trends in Molecular Medicine* 18, no. 12 (2012): 702-708.

[130] *See* E.S. Dove, "Requiring a Single IRB for Cooperative Research in the Revised Common Rule: What Lessons Can Be Learned from the UK and Elsewhere?" *Journal of Law, Medicine & Ethics* 47, no. 1 (2019): 264-282, 271 (stating that "the case for local IRB review rests more on the force of its rhetoric than the force of its logic").

[131] J. de Vries et al., *supra* note 90; K. Moodley et al., "'It's My Blood': Ethical Complexities in the Use, Storage and Export of Biological Samples: Perspectives from South African Research Participants," *BMC Medical Ethics* 15 (2014); D.A. Chokshi et al., "Valid Consent for Genomic Epidemiology in Developing Countries," *PLoS Medicine* 4 (2007): e95-e95; N.A. Garrison, "Considerations for Returning Research Results to Culturally Diverse Participants and Families of Decedents," *Journal of Law, Medicine and Ethics* 43, no. 3 (2015): 569-575; E. Brief, J. Mackie, and J. Illes, "Incidental Findings in Genetic Research: A Vexing Challenge for Community Consent," *Minnesota Journal of Law, Science & Technology* 13, no. 2 (2012): 541-558; L. Arbour and D. Cook, "DNA on Loan: Issues to Consider when Carrying Out Genetic Research with Aboriginal Families and Communities," *Public Health Genomics* 9, no. 3 (2006): 153-160.

[132] The Nuremberg Code, *available at* https://history.nih.gov/research/downloads/nuremberg.pdf (last visited August 25, 2019).

[133] World Medical Association, Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (2013), *available at* https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (last visited August 25, 2019).

[134] C.R. McCarthy, "The Origins and Policies that Govern Institutional Review Boards," in E. Emanuel et al., eds., *Oxford Textbook of Clinical Research Ethics* (New York, NY: Oxford University Press, 2008): 541-551, 545.

[135] *Id.*

[136] *Id.* at 549.

[137] R. Klitzman, "How Local IRBs View Central IRBs in the U.S.," *BMC Medical Ethics* 12, no. 13 (2011): 13-26.

[138] R. Skloot, *The Immortal Life of Henrietta Lacks* (New York: Crown Publishing Group, 2010).

[139] The possibility that ethics review of research protocols might need to account for local concerns has been offered as a justification for local review since at least 1978. In that year, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in the U.S. published recommendations for regulations on Institutional Review Boards. The Commission stated that local ethics review might be desirable because it provides an opportunity to consider values or needs that are specific to a particular community: "In its deliberations, it is desirable that the IRB show awareness and appreciation of the various qualities, values and needs of the diverse elements of the community served by the institution or in which it is located." National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1978).

[140] M.E. Redshaw, A. Harris, and J.D. Baum, "Research Ethics Committee Audit: Differences between Committees," *Journal of Medical Ethics* 22, no. 2 (1996): 78-82, 79.

[141] K.B. Brothers et al., "A Belmont Reboot: Building a Normative Foundation for Human Research in the 21st Century," *Journal of Law, Medicine & Ethics* 47, no. 1 (2019): 165-172.

[142] Royal College of Physicians, *Guidelines on the Practice of Ethics Committees in Medical Research with Human Participants* (4th ed. 2007).

[143] A.H. Ahmed and K.G. Nicholson, "Delays in the Practice of Local Research Ethics Committees," *Journal of Medical Ethics* 22, no. 5 (1996): 263-266.

[144] W. Burman et al., "The Effects of Local Review on Informed Consent Documents from a Multicenter Clinical Trials Consortium," *Controlled Clinical Trials* 24, no. 3 (2003): 245-255.

[145] Ahmed and Nicholson, *supra* note 143; T.J. Berry, T.E. Ades, and C.S. Peckham, "Too Many Ethical Committees," *British Medical Journal* 301, no. 6763 (1990): 1274; P. Garfield, "Cross District Comparison of Applications to Research Ethics Committees," *British Medical Journal* 311 (1995): *available at* https://doi.org/10.1136/bmj.311.7006.660 (last visited September 5, 2019); C. Gilbert, K.W. Fulford, and C. Parker, "Diversity in the Practice of District Ethics Committees," *British Medical Journal* 299, no. 6713 (1989): 1437-1439; M. Hotopf, S. Wessely, and N. Noah, "Are Ethical Committees Reliable?" *Journal of the Royal Society of Medicine* 88, no. 1 (1995): 31-33.

[146] K. Dziak et al., "Variations among Institutional Review Board Reviews in a Multisite Health Services Research Study," *Health Services Research* 40, no. 1 (2005): 279-290; J. Mansbach et al., "Variation in Institutional Review Board Responses to a Standard, Observational, Pediatric Research Protocol," *Academic Emergency Medicine* 14, no. 4 (2007): 377-380; R. McWilliams, J. Hoover-Fong, and A. Hamosh, "Problematic Variation

in Local Institutional Review of a Multicenter Genetic Epidemiology Study," *Journal of the American Medical Association* 290, no. 3 (2003): 360-366; B. Ravina et al., "Local Institutional Review Board Review of a Multicenter Trial: Local Costs without Local Context," *Annals of Neurology* 67, no. 2 (2010): 258-260; H. Silverman, S.C. Hull, and J. Sugarman, "Variability among Institutional Review Boards' Decisions within the Context of a Multicenter Trial," *Critical Care Medicine* 292, no. 2 (2001): 235-241; T.O. Stair et al., "Variation in Institutional Review Board Responses to a Standard Protocol for a Multicenter Clinical Trial," *Academic Emergency Medicine* 8, no. 6 (2001): 636-641; A.R. Stark, J.E. Tyson, and P.L. Hibberd, "Variation among Institutional Review Boards in Evaluating the Design of a Multicenter Randomized Trial," *Journal of Perinatology* 30, no. 3 (2010): 163-169; C.C. Vick et al., "Variation in Institutional Review Processes for a Multisite Observational Study," *American Journal of Surgery* 190, no. 5 (2005): 805-809.

147 Stair et al., *supra* note 146.

148 R. Al-Shahi, "Research Ethics Committees in the UK – The Pressure Is Now on Research and Development Departments," *Journal of the Royal Society of Medicine* 98, no. 10 (2000): 444-447.

149 R.J. Levine and L. Lasagna, "Demystifying Central Review Boards: Current Options and Future Directions," *IRB* 22, no. 6 (2000): 1-6.

150 45 C.F.R. § 46.114(b)(1).

151 F. Goodyear-Smith, "International Variation in Ethics Committee Requirements: Comparisons across Five Westernised Nations," *BMC Medical Ethics* 19, no. 3 (E2) (2002).

152 E.S. Dove et al., "Ethics Review for International Data-Intensive Research," *Science* 351, no. 6280 (2016) 1399-4001.

153 In some cultures, any analysis of human biospecimens may be viewed with great skepticisim or at least as raising very important issues. The possible use of information derived from specimens may raise other important issues. On a global basis, these issues arising from international DTP genomic research deserve further study, as we recommend. On a study-by-study basis, the investigators and their ethics review bodies ought to consider the issues in the context of the range of countries from which participants will be recruited or accepted.

154 A. Thorogood, G. Dalpe, and B.M. Knoppers, "Return of Individual Genomic Research Results: Are Laws and Policies Keeping Step?" *European Journal of Human Genetics* (2019): https://doi.org/10.1038/s41431-018-0311-3 (review of laws and policies in 20 countries found discrepancies on return of results). The questionnaire results from this study had a similar finding. *See* M.H. Zawati, ed., "31 Country Reports on International Direct-to-Participant Genomic Research," *Journal of Law, Medicine & Ethics* 47, no. 4 (2019): _____.

155 *See* J.E. Childerhose et al., "Participant Engagement in Translational Genomics Research: Respect for Persons – and Then Some," *Ethics and Human Research* 41, no. 1 (2019): 2-15.

156 *Id.*

[157] Even in countries where direct-to-consumer genetic testing is illegal, there have been no reported cases of legal actions being brought against consumers who obtain these services.

[158] We do not reach the complicated legal issue of how a country would obtain jurisdiction over researchers who never entered the country.

[159] Researchers who perform research in other countries without approval by their own IRB, however, will likely be subject to sanctions.

[160] N. Hoppe, "Germany Country Report," *Journal of Law, Medicine & Ethics* 47, no. 4 (2019): ___-___ (answer to question 10).

[161] *See* J. Wagner, "The Transfer of Personal Data to Third Countries under the GDPR: When Does a Recipient Country Provide an Adequate Level of Protection?" *International Data Privacy Law* 8, no. 4 (2018): 318-337, 319.

[162] Dir. 95/46/EC (1995).

[163] 15 U.S.C. § 45.

[164] C-362/14, EU:2015:650 (Eur. Ct. Just. 2015). *See* M.A. Rothstein, "International Health Research after *Schrems v. Data Protection Commissioner*," *Hastings Center Report* 46, no. 2 (2016): 5-6.

[165] Int'l Trade Admin., Dep't of Commerce, Privacy Shield Overview, *available at* https://www.privacyshield.gov/Program-Overview (last visited August 20, 2019).

[166] *See* P.M. Schwartz, "Global Data Privacy: The EU Way," *New York University Law Review* 94, no. __ (2019): ___-___, ___.

[167] Regulation (EU) 2016/679 of the European Parliament.

[168] "Adequacy Decisions." European Commission - European Commission. Accessed September 4, 2019. https://ec.europa.eu/info/law/law-topic/data-protection/international-dimension-data-protection/adequacy-decisions_en.

[169] "ARTICLE29 Newsroom - Working Document on Adequacy Referential (Wp254rev.01) - European Commission." https://ec.europa.eu/newsroom/article29/item-detail.cfm?item_id=614108 (last visited September 4, 2019).

[170] *Id.*

[171] *See* Privacy Shield Framework, *available at* https://www.privacyshield.gov/Individuals-in-Europe (last visited August 21, 2019). Another example is the Asia-Pacific Economic Cooperation agreement involving 21 countries. *See* Asia-Pacific Economic Cooperation, What Is the Cross-Border Privacy Rules System? *Available at* https://www.apec.org/About-Us/About-APEC/Fact-Sheets/What-is-the-Cross-Border-Privacy-Rules-System (last visited August 21, 2019).

[172] 45 C.F.R. § 46.101(h).

[173] Another provision of the Common Rule, setting forth the applicability of the Common Rule, provides in pertinent part: "It also includes research conducted, supported, or otherwise subject to regulation by the Federal Government outside the United States." 45 C.F.R. § 46.101(a).

[174] *See* Sec'y Advisory Comm. on Human Research Protections, SACHRP Minutes (July 19-20, 2011), *available at* http://www.hhs.gov/ohrp/sachrp/mtgings/mtg07-11/july2011minutes.pdf.pdf (last visited July 24, 2019).

[175] See E.S. Dove, B.M. Knoppers, and M.H. Zawati, "Towards an Ethics Safe Harbor for Global Biomedical Research," *Journal of Law and the Biosciences* 3-51 (2014), doi:10.1093/jlb/lst002; J.V. Lavery, M. McDonald, and E.M. Meslin, "Research Ethics Across the 49th Parallel: The Potential Value of Pilot Testing 'Equivalent Protections' in Canadian Research Institutions," *Health Law Review* 13, no. 2-3 (2005): 86-96; J. Sugarman, "Should the Gold Rule? Assessing 'Equivalent Protections' for Research Participants across International Borders," *Hastings Center Report* 35, no. 5 (2005): 12-13.

[176] The OHRP International Program "works to ensure that human subjects outside of the United States who participate in research projects conducted or funded by HHS receive an equal level of protection as research participants inside the United States." HHS Office for Human Research Protections, *International*, *available at* https://www.hhs.gov/ohrp/international/index.html (last visited September 2, 2019). It also publishes a list of international laws, regulations, and guidelines relevant to research with human subjects. HHS Office for Human Research Protections, *International Compilation of Human Research Standards*, *available at* https://www.hhs.gov/ohrp/international/compilation-human-research-standards/index.html (last visited September 2, 2019).

[177] Another possibility is to establish international ethics review entities to approve international studies, but the proposal has not received any favorable response. *See* E.S. Dove, B.M. Knoppers, and M.H. Zawati, *supra* note 175.

[178] Arguably, such a determination is not necessary under current U.S. law, but it would be necessary for a country that currently requires local ethics review for a researcher outside of the country.

[179] As discussed in section V, there is considerable alignment of the criteria and procedures for research ethics review around the world, but we do not reach the issue of what specific standards ought to be developed or applied to satisfy equivalency and adequacy. An example of proposed guidelines is Global Alliance for Genomics and Health, Ethics Review Recognition Policy, *available at* https://www.ga4gh.org/wp-content/uploads/GA4GH-Ethics-Review-Recognition-Policy.pdf (last visited August 26, 2019).

[180] CIOMS/WHO, International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002), *available at* https://cioms.ch/wp-content/uploads/2016/08/International_Ethical_Guidelines_for_Biomedical_Research_Involving_Human_Subjects.pdf (last visited September 30, 2019).

[181] UNESCO, Universal Declaration of Bioethics and Human Rights (2005), *available at* http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/bioethics-and-human-rights/ (last visited August 23, 2019).

[182] UNESCO, Draft Recommendation on Privacy and Protection of Health-Related Data (2019)), *available at* https://www.ohchr.org/EN/Issues/Privacy/SR/Pages/HealthRelatedData.aspx (last visited August 23, 2019).

[183] Council of Europe, Recommendation of the Committee of Ministers to Member States on the Protection of Health-Related Data (2019), *available at* https://search.coe.int/cm/pages/result_details.aspx?objectid=090000168093b26e (last visited August 23, 2019).

[184] H3Africa Guidelines for Informed Consent, *available at* http:/h3africa.org/ethics/17-ethics/71-informedconsent (last visited August 23, 2019).

[185] World Medical Association, *supra* note 133.

[186] Wellcome Trust, https://wellcome.ac.uk/ (last visited August 23, 2019).

[187] Bill and Melinda Gates Foundation, https://www.gatesfoundation.org/ (last visited August 23, 2019).

[188] Global Alliance for Genomics and Health, https://www.ga4gh.org/ (last visited August 23, 2019).