Overcoming legal obstacles to international direct-to-participant genomic research*

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The relationship between genetics/genomics and the law has been varied, complicated, and continually evolving. In some areas, such as eugenics-inspired sterilization laws, it has been disastrous. In other areas, such as newborn screening and DNA forensics, legislation has been generally beneficial. In research and clinical applications, the record has been mixed, containing legislative successes tempered by occasional failures that serve as cautionary tales. Such is the case with laws applicable to international genomic research. This article reviews legal regulation of international direct-to-participant (DTP) genomic research as a case study of the challenges of combining science, law, ethics, and other issues.

Among the most important recent trends in genomic research are international collaborations and DTP recruitment of research participants. The combination of these two elements is essential for research on rare disorders because there may not be enough affected individuals in any country to study and genomic heterogeneity is often a key element of the research strategy. The use of DTP recruitment using the internet, especially when endorsed and supported by patient advocacy groups, has received approval from institutional review boards (IRBs) and research ethics committees (RECs) for national studies, and it has proven to be effective in genomic research compiling and analyzing biospecimens. It is usually far more challenging, however, to obtain a positive research ethics review for international studies because the scope is greater and the legal systems in numerous countries vary considerably and may be difficult to discern. Consequently, the prospect of needing separate approval of a research protocol in every country where only a few individuals may participate will make international recruitment impractical and thwart genomic research on rare disorders.

This article draws lessons from a 31-country study of international DTP genomic research funded by the National Institutes of Health of the United States and published in 2019.[1] The study deals with the conceptual and practical challenges of promoting international genomic research while ensuring compliance with the letter and spirit of international laws and local norms governing research ethics. It also serves as a case study for the larger issues of reconciling legal principles around the world to enable genomic research.

Assessing the Laws in Numerous Countries

Researchers undertaking genomic research on rare disorders face many legal challenges in expanding their efforts to multiple countries. To begin with, there is no easy way to learn what, if any, laws around the world apply to foreign researchers soliciting individuals to participate in

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[1] M.H. ZAWATI, ED., *Country Reports*, in *Journal of Law, Medicine & Ethics* 47, 4, 2019, 582-704.

genomic research or facilitating the submission of biological specimens and health information. Some compilations of international research laws and regulations are published periodically,[2] but most of the information sources rarely cover emerging issues, such as DTP recruitment, and published information is soon out of date.

Next, there are language and translation issues. For example, a law might provide that "consent" is required, but consent has numerous meanings, such as informed consent, written consent, broad consent, and presumed consent. Therefore, it is still necessary to identify and retain legal experts from every country in which research is proposed to explain the precise meaning of a law or regulation. The difficulty, time, and expense of such inquiries in numerous countries imperils international research.

In our study of DTP genomic research, we learned that very few countries have enacted laws directly on point, which was not surprising because of the recency of DTP online recruitment. Therefore, we had to extrapolate from existing laws (e.g., direct-to-consumer genetic testing laws, human subjects research laws, and genetic privacy laws), to infer the likely legal position of each country on DTP genomic research. Furthermore, we needed to identify "soft" law in the form of regulations, norms, and cultural considerations so that proposed research would align with a broad array of values in each country. Fortunately for our study, we were able to assemble an incomparable group of 45 experts to prepare the country reports that led to the study's conclusions and recommendations.

Equivalency of Common Principles

Early on, it became clear that an international treaty or a series of bilateral agreements would be infeasible. Even assuming there was international support for this approach (a grandiose assumption), it would likely take years to negotiate and implement such an agreement and, in the interim, potentially valuable genomic research would be significantly delayed. A more expeditious and practical strategy would be to build on existing, country-specific legislation using a two-step process of identifying a generally concordant legislative or regulatory framework and then devising a method for its multilateral application. Every country we studied had already enacted laws regulating research with human subjects based on a similar set of underlying principles. The United Nations Educational, Scientific and Cultural Organization (UNESCO), in its Universal Declaration of Bioethics and Human Rights, specifies the broad criteria for ethics review, including informed consent, privacy/confidentiality, benefit/risk ratio, return of results, protection of the interests of vulnerable persons/communities, and research integrity and safety.[3] Another key, non-governmental document is the Global Alliance for Genomics and Health (GA4GH) Ethics Review Recognition Policy. Designed to regularize international genomic research review, it is based on ethics review policies of 39 countries. The foundational principles are: respect individuals, families, and communities; advance research and scientific knowledge; promote health, wellbeing, and the fair distribution of benefits; and foster trust, integrity, and

[2] Office for Human Research Protections, U.S. Department of Health and Human Services, in *International Compilation of Human Research Standards*, 2020, https://bit.ly/324OSsj (last visited 08/11/2020).

[3] UNESCO, *Universal Declaration of Bioethics and Human Rights*, 2005, https://bit.ly/3g2GH7P (last visited 05/11/2020).

reciprocity.[4] We also reviewed several other sources, including the World Medical Association's Declaration of Helsinki[5] and the Council for International Organizations of Medical Sciences (CIOMS)-World Health Organization (WHO) International Ethical Guidelines for Biomedical Research Involving Human Subjects.[6]

We drew from these important documents and other sources additional principles with international applicability. First is the requirement of establishing an independent, external body to perform research ethics review. In the United States, this is called an institutional review board because review is conducted largely within a single institution. In much of the world these bodies are called research ethics committees. Second is the growing trend to have single-site ethics review for multi-site studies, as multiple ethics reviews tend to cause needless delay without advancing the welfare of research participants. In the United States, as of 2019, single-site or "central" IRB review is required for multi-site studies.[7] Third is recognition that international DTP genomic research is low risk. Participants typically spit into a vial or swab the inside of their cheeks (or merely supply data), and there is no intervention or alteration of their medical care. Fourth is acknowledgment that DTP genomic research, especially for rare disorders, is overwhelmingly supported by affected individuals and their families. Removing needless burdens on researchers, such as requiring research ethics review in every country, advances the autonomy interests of participants and their caregivers.

Based on these principles, my colleagues and I concluded that the most promising, basic approach would be to have international ethics review undertaken by a single entity (i.e., IRB or REC) in the researcher's country. There were "only" two practical questions. First, why would the home countries of the potential research participants agree to defer to an approval by the researcher's ethics review body? Second, how would the researcher's ethics review body know whether the research protocol would be lawful and ethical in the various countries where participants might be enrolled?

Adequacy Determinations

The next step was to envision how deferral agreements could be reached without reconsidering the issue each time a new research protocol was submitted. We looked to the principle of "adequacy" under the General Data Protection Regulation (GDPR) of the European Union (EU).[8] Article 45 of the GDPR provides that personal data may be exported to a country outside of the EU only if the European Commission (EC) has acknowledged the adequacy of data protection in the recipient country or there are other appropriate safeguards such as contractual provisions or codes of conduct.[9] Adequacy based on the equivalency of another country's laws is determined by reference to the principles noted in the

[4] Global Alliance for Genomics and Health, *Ethics Review Recognition Policy*, 2017, https://bit.ly/3mFIu4f (last visited 05/11/2020).

[5] World Medical Association, *WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects,* 2013, https://bit.ly/3a4knHc (last visited 05/11/2020).

[6] Council for International Organizations of Medical Sciences (CIOMS) and World Health Organization*, International Ethical Guidelines for Health-Related Research Involving Humans*, 2016, https://bit.ly/3t64x6p (last visited 05/11/2020).

[7] 45 C.F.R. § 46.114, b, 1.

[8] Regulation (EU) 2016/679 of the European Parliament and of the Council.

[9] J. WAGNER, *The Transfer of Personal data to Third Countries under the GDPR: When Does a Recipient Country Provide an Adequate Level of Protection?,* in *International Data Privacy Law,* 8, 4, 2018, 318-337.

GDPR that must be satisfied for an adequacy determination by the EU. Two illustrative principles are:

"7. The foreign country's legislation should include basic data protection concepts and remain consistent with the general 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".[10]

Using these criteria, Argentina, Canada, Japan, New Zealand, Switzerland, and other countries have been deemed adequate by the EC for transfer of data from EU countries.[11] My colleagues and I concluded that an analogous regime could be successful for approving international research, especially as applied to DTP genomic research.

Recommendations

We presented our conclusions, rationales, and supporting documents in an article containing the following 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 the 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. 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 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 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.[12]

Conclusion

The symposium issue of a leading journal containing the country reports and recommendations was published at the end of 2019. We organized a series of presentations for researchers, research regulators, patient advocates, and

[10] ARTICLE29 Newsroom – Working Document on Adequacy Referential (Wp254rev.01) – European Commission, https://bit.ly/3wMSA7S (last visited 08/11/2020).

[11] Adequacy Decisions, European Commission, https://bit.ly/2OEommg (last visited 08/11/2020).

[12] M.A. ROTHSTEIN et al., *Legal and Ethical Challenges of International Direct-to-Participant Genomic Research: Conclusions and Recommendations, in Journal of Law, Medicine & Ethics*, 47, 4, 2019, 705-731, 723-724.

international governments for 2020. Unfortunately, the coronavirus pandemic precluded holding these events, which we hope to reschedule for 2021. In any event, I believe our experience in attempting to facilitate international genomic research in a manner consistent with the laws of numerous countries illustrates the range of conceptual and practical issues to be addressed by laws dealing with genetic technologies.

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