RESEARCH STRATEGY

A. SIGNIFICANCE

1. Scientific Rationale for International DTP Genomic Research

Next generation sequencing of patient samples obtained through clinical investigators and biobanks have yielded critical new insights into human biology, thereby promoting the development of new genomic-based health risk assessments, preventive interventions, and innovative therapies. Despite this tremendous scientific progress, traditional approaches to biobanking have proven to be challenging when collecting large volumes of biospecimens and health information from diverse and representative populations.[1] Existing genomic databases are extremely limited in their representation of human ancestry. For example, a 2016 analysis revealed that 81% of subjects included in genome-wide association studies (GWAS) to date have been people of European descent, even though modern societies are heterogeneous.[2]

On a global scale, the existing research model is especially problematic for rare disease research, where cases are defined by their low prevalence, and patients sharing a specific genetic etiology are often geographically distant from physical collection sites.[3] For many rare diseases efficient discovery of causal genes requires seamless aggregation of cases around the world. However, banked samples for rare diseases are often siloed by project and impossible for most researchers to access.[4] Furthermore, given the rarity of certain diseases, even specialist referral centers will not observe more than one case caused by mutations in a particular gene. Obtaining the multiple cases required to demonstrate causality for a new gene requires new approaches, such as having scientists engage in a global partnership with patients, rather than institutions, to collect sufficiently large volumes of either very scarce or representative samples.[5]

Including participants from a large number of countries in genomic research has been difficult because of the various regulatory requirements in each country[1,3,4] that operate to thwart the inclusion of diverse patient populations needed to better understand the molecular underpinnings of disease.[2] Barriers to more inclusive genomic research include prohibitive or unclear regulatory requirements in some countries, lack of international harmonization of research regulation, and a lack of data sharing. Researchers, patient groups, and pharmaceutical companies are all eager to adopt new, internet-based research practices that avoid these traditional obstacles to all-encompassing research.

The investigators on this proposal recently completed an NIH-funded study of the legal and ethical issues raised by international biobank research in 20 countries and proposing harmonized governance to facilitate international collaboration.[6,7] This proposed research is a logical and important follow up. **There is significant interest in developing a direct-to-participant (DTP) research model where scientists can routinely recruit eligible participants beyond their countries' borders via the internet.** However, regulatory bodies governing human subjects research in the vast majority of countries have not yet developed legal standards to facilitate this in practice,[8] and there is great uncertainty surrounding DTP research. By forming an international consortium of experts in law and ethics, scientists, industry leaders, patient representatives, and research administrators, research on this proposed grant will help to better understand the regulatory landscape of 32 countries, fostering greater potential for a global DTP genomic research model.

<u>Online Recruitment</u>

A novel DTP model is emerging that utilizes new technology to facilitate more efficient and representative recruitment for genomic studies. **Population-wide internet access and the proliferation of advocacy groups, social media, and empowered citizen scientists have created a substantial opportunity for the direct linkage of genomic researchers with vast numbers of potential research participants.** Rather than recruiting participants through treating physicians, hospitals, or biobanks at physical collection sites, it is now possible for scientists to recruit, consent, and enroll patients directly using the internet. Typically this involves a single "mega-site" responsible for recruitment, enrollment, management, sequencing, analysis, and follow up of all participants, even

though all interactions with participants are conducted virtually. Recruitment is usually limited to single countries.

From a technical standpoint, this approach is immediately applicable in developed countries, where internet access is widespread, and its utility in developing countries is growing rapidly. In early 2017, worldwide access to the internet is about 40% and by 2020 there will be 6 billion smartphones used by about 70% of the world's population.[9] Researchers can create a study-specific website with targeted recruitment through disease-associated groups, advocates, and patients. In most cases, patients and families complete a self-guided pre-screening questionnaire which allows researchers to determine eligibility. Qualified participants are re-contacted and offered an opportunity to complete an electronic, interactive, informed consent process. A medical records authorization completed as part of the consent process allows researchers to obtain the participant's medical records. Participants who meet all eligibility criteria are sent a sample collection kit to obtain and then ship a blood or saliva sample directly to the researchers.

An illustration of the power of the DTP model is the Metastatic Breast Cancer (MBC) Project at The Broad Institute. Participants are recruited in partnership with breast cancer advocacy organizations, which provides important validation for participants and also raises awareness of the project. One year into the study, more than 2,900 women and men with MBC from all 50 states have joined.[10] Another Broad research project, although not using the DTP model, the Exome Aggregation Consortium (ExAC), is directed by Co-PI Dr. Daniel MacArthur, a pioneer in international genome data aggregation. ExAC is a massive international data sharing effort and a general resource for genetic variation. So far, its website has had over 7 million page views from 137,000 unique users in 176 countries.[11]

Research Challenges of Rare Disorders

For many disorders, especially rare genetic diseases and cancers, restricting DTP enrollment to the US limits the utility of research because it fails to take advantage of the opportunity to include appropriate participants from around the world. This is despite the fact that the mechanics of the recruitment, enrollment, consent, and sample collection processes are essentially the same for domestic and international research. **Compared with current practices, international DTP enrollment can be more efficient and expeditious, generate more representative and diverse samples, be more participatory and democratic, and lead to scientific discoveries that hold wider relevance for today's modern heterogeneous populations.**

The primary challenge with this approach involves regulation. In many countries, it is illegal for foreign researchers to directly recruit domestic citizens to participate in research and to have biospecimens sent out of the country for research, especially if that research has not been approved by an in-country research ethics committee. From the perspective of researchers, it is logistically untenable to identify and satisfy the separate requirements of regulatory bodies in every country where qualified and willing participants may reside. From the perspective of foreign governments, however, compliance with research laws and regulations is non-negotiable and non-waivable by individual research participants. This position may be traced to several notorious incidents of misconduct by international researchers[12] as well as the economic and dignitary interests of countries concerned about the loss of control over research and the genetic legacy of their population.[13]

In order to address these important barriers to international DTP genomic research, it is necessary to clarify the international legal landscape. To date, there have been no systematic assessments of the legality of international DTP genomic research in the vast majority of countries. **The proposed research project aims to fill this void with an authoritative assessment of the legal issues associated with international DTP genomic research.** We will collect and analyze the information generated by our collaborating experts from 32 countries and provide an assessment of whether it is possible to enable international DTP genomic research in each country while complying with its legal standards and safeguarding the welfare of research participants. We will then develop and widely disseminate policy options setting forth how to overcome existing obstacles.

2. Research Ethics Implications of International DTP Genomic Research

The infrastructure for international DTP genomic research is already in place in developed countries. Global connectivity, through cloud computing, mobile devices, and the "internet of things," sets the stage for the unprecedented generation and international sharing of data for health research. **These technologies are also democratizing research, allowing individuals to generate, manage, and share their own data.** New services, including mHealth apps and direct-to-consumer (DTC) genomic sequencing, put more data in the hands of individuals. Health care providers are establishing policies and infrastructure (portals) to provide patients access to their health data and engage them in shared decision making. Major translational research projects, such as the one million-person Cohort Program (now known as *All of Us*) of the Precision Medicine Initiative in the US,[14] and the U.K. 100,000 Genomes Project[15] plan to provide individuals access to their research data. Commercial entities and genetics laboratories also may be legally required to provide access to health and genomic data results to individuals.

In turn, businesses, researchers, and patient groups are innovating to recruit participants remotely. In addition to the sample collection kits mentioned previously, mobile health research platforms available from Apple (ResearchKit)[16] and Google (ResearchStack)[17] allow researchers to collect data remotely from participants through mHealth apps. Web portals also allow individuals to submit their health information (Sync for Science),[18] genetic test results (GenomeConnect),[19] or genomic data (DNALand)[20] to researchers.

Providers of commercial services (mHealth developers and DTC testing companies), biomedical researchers, and even patient-directed biobanking initiatives will not be content to limit their recruitment within national borders and will seek to solicit participants from around the globe. Indeed, consumer service models, health research, and patient communities all naturally scale internationally. Remote, international collection of data and samples promises to accelerate health research. One example of such research is the Genographic Project, a joint effort of the National Geographic Society and IBM launched in 2005 to map historical migration patterns by collecting and analyzing DNA samples.[21] Although the primary objection to the collection of DNA from diverse populations is that it exploits indigenous populations, more medically oriented, genomic research activities are certain to receive greater legal scrutiny around the world.

In order to launch successfully, international DTP genomic research must comply with internationally recognized legal and ethical protections for individuals, as well as any country-specific laws relating to sovereignty and benefit sharing. Numerous ethical, legal, and social issues must be addressed by international DTP genomic researchers, including the following.

Legal Restrictions

International DTP genomic research may run afoul of various biomedical research laws, genetic-specific laws, data protection laws, biomaterial import/export laws, and consumer protection laws. For example, some countries impose additional consent requirements for the transfer of identifiable (including coded) samples and data across borders, and others forbid such transfers altogether. Even where US researchers strive to comply with applicable norms in other countries, they would need to retain a large cadre of international legal advisers to determine whether their consent practices and other safeguards satisfy the diverse range of national regulatory frameworks. Another important issue is whether companies, researchers, and patient cooperatives may disclaim responsibility for legal compliance, and merely insist that the participant is responsible for "complying with applicable laws."

Unnecessary Barriers to Research and Individual Autonomy

Where international DTP genomic research is prohibited, restricted, or hindered by certain consent requirements and oversight, it may interfere with both progress in research and individual autonomy.

Disproportionate protections of individual privacy or perceived national interests in data can undermine the internationally recognized human right of all citizens to benefit from and participate in the progress of science.[22] In countries where barriers undermine progress in research, future patients suffer. In terms of autonomy, where individuals understand the risks and yet desire to share their samples and data internationally, they should be able to do so. Ethics review restrictions – whether directly (by refusing to permit foreign-based studies) or indirectly (by insisting on additional, local review) – can also restrain individual freedoms and unwittingly contribute to an unethical, practical barrier to research.[23] National prohibitions, conditions, or oversight processes for export of citizens' data or samples similarly restrain individuals' freedom to share with whomever they please.

In 2016, the Council for International Organizations of Medical Sciences (CIOMS), in collaboration with the World Health Organization (WHO), published its International Ethical Guidelines for Health-Related Research Involving Humans. The guidelines, applicable to research in low- and middle-income countries, contain restrictions on research using biospecimens that may be appropriate for traditional research, but will make DTP genomic research in numerous countries impractical: "Biological materials and related data should only be collected and stored in collaboration with local health authorities. The governance structure of such collection should have representation of the original setting. If the specimens and data are stored outside the original setting, there should be provisions to return all materials to that setting and share possible results and benefits." [24,25]

Given these inherent tensions, there is a potential for significant variation in policies concerning international DTP genomic research. **Widespread variance in legal provisions for international DTP research can impede scientific progress almost as much as an outright ban on research.** Even where a national regulatory framework is permissive or silent, countries may adopt new regulations to protect their citizens' privacy and national economic interests in the future. To avoid restrictive policies, it is essential that international DTP genomic research proceed in a legal and ethical manner that accommodates the societal benefits of research and the necessary protections of research participants.

Informed Consent

It is an internationally recognized ethical and legal principle that consent to research must be adequately informed,[26,27] but there is no comparable international consensus on whether remote, online consent meets the regulatory standards that require informed consent. For US studies engaged in human subject research under HHS or FDA regulations, the FDA and OHRP have issued guidance on online consent.[28] For many other countries, traditional informed consent may seem inconsistent with DTP research for the following reasons. First, the consent process is different when it is mediated by a website or app, rather than a human being. Second, the bilateral nature of signing a written consent (where the formality of signing indicates to people that they are entering into a formal relationship) is weakened online, where people are conditioned to click through consents or sign online without careful or complete reading. Third, self-guided consent makes it more difficult for the researcher to assess the contextual vulnerability of the participant, or for the participant to ask for more information. Fourth, countries may have different standards for the lawful age of consent or who may act as a guardian or personal representative. Certain DTP research studies conducted by the Broad Institute seek to resolve many of these problems by having a video conference with each individual or family during the informed consent process. This proposed research will explore the degree to which individual countries require oversight of online research consent, including consent processes for individual studies.

Privacy and Security

Ensuring that health information is kept confidential and that privacy is protected across global networks requires adequate security. Privacy and security concerns arise when health information is collected remotely because the information has to be transmitted across a complex network of organizations and technology platforms. The facilitation of international transfer of data is important, as evidenced by the January 2017 OECD Recommendation of the Council on Health Data Governance.[29]

Yet, the following concerns arise when information is sent internationally. Laws of foreign countries may not provide the same level of privacy protection, and privacy protection may not be uniform across all sectors in all countries; foreign security requirements or oversight by privacy authorities may be lax or restrictive; legal exceptions allowing access by third parties and law enforcement without consent may be broader; and participants attempting to enforce rights in samples and information under foreign laws may encounter legal and practical challenges. These risks also undermine informed consent because the complex networks and distinctions between legal regimes make it difficult to ensure that individuals will be adequately informed of how their health information will be protected, who will have access to it, and what it will be used for.

Communication to Participants: Risks and Regulations

Participation in biobanking can be a longitudinal transaction and data can flow in both directions. Consumer services offer information and interpretation services to participants. Researchers may return general and individual research results, incidental findings, or raw research data to participants as per the consent agreement. Consumer protection laws and public health regulations may, however, establish what information should or may be provided to individuals in a given country, and under what conditions. The public health benefits, risks, and costs of communicating information may vary across countries with different health systems. International DTP genomic research could involve international liability risks for all parties, and even where these are known, it may not be possible to disclaim all such risks in countries where a waiver of health risk is illegal.

National Sovereignty and Benefit Sharing

Every research project involving international DTP genomic research implicates the laws of various countries, international agreements, and several different local IRBs or equivalents. Research laws and regulations attempt to ensure the welfare of research participants by regulating the conduct of researchers. **If the laws or regulations of countries involved in DTP genomic research differ or are silent in one jurisdiction,[13] it is not yet established whether the laws of the country of the researchers or research participants should apply.** Furthermore, the rationale for regulations on specimen and data collection and sharing, if stated, may be characterized as attempting to protect the country's unique genetic resources from exploitation, to secure intellectual property rights or other benefits for the country of origin, or to safeguard the rights of sample donors, including privacy, once the samples leave the jurisdiction. It will be a challenge to respect these concerns in the face of conflicting laws.

In light of global inequalities, some forms of international health research are exploitative, as where the research disproportionately benefits the companies, researchers, or people in countries extracting data and samples compared to the participants and their countries. Although sharing samples and data promises to accelerate research, it often disproportionately benefits well-resourced parties able to rapidly analyze data and commercialize results. Unfettered international DTP genomic research may exacerbate inequalities and foster resentment, leading to reactive policy making. To offset this potential unfairness, a variety of benefit sharing arrangements have been established or proposed, such as providing additional benefits to participants and building research capacity in a resource poor country.[30] A consideration of benefit sharing principles is part of the process of analyzing international DTP genomic research.

3. Lessons Learned from Prior Studies

Through our work on the NIH-funded grant, Harmonizing Privacy Laws to Enable International Biobank Research (Harmonizing Grant),[6,7] completed in December 2016, the investigators at the University of Louisville and McGill University have developed a knowledge base of the laws, policies, and cultural considerations relevant to biobank-enabled research in 20 countries. There are some conceptual similarities between international biobank-based research and international DTP genomic research, including policies on informed consent, specimen collection, and privacy and security. Significantly, both research strategies (DTP and biobanks) eliminate the central role of local physician-investigators

or hospitals and place responsibility for sample collection on individuals and biobanks. Besides serving to protect the interests of research participants and researchers, research regulations dealing with international biobanking also consider the effects on national economic and dignitary interests.

Through our work on the Harmonizing Grant our expertise has extended beyond privacy laws, because privacy in biobanking relates to, among other things, consent, anonymization and coding, data security, return of results, and sharing specimens and data with other researchers. These issues also arise in DTP genomic research. Therefore, the proposed research will build on our prior work and apply it in another important, but as yet relatively unexamined, context.

The novelty of the issues and the complexity of international research demand a specially qualified research team. The proposed lead investigators have the experience and expertise to successfully complete this challenging endeavor. A unique resource of this proposed grant is the group of international law and bioethics experts originally brought together for the Harmonizing Grant who have committed to working together again on this new project (see Letters of Support). This core group of experts from 20 countries from the Harmonizing Grant has been supplemented on this new grant application by experts from an additional 12 countries. The rationale for expanding the list of countries is to explore other legal systems without limiting the study to countries conducting or planning biobank research, as was done in our prior study. In fact, because DTP research can more rapidly extend across borders without waiting for local infrastructure to be established, it is especially valuable in low resource countries.

Another aspect of this proposed grant is studying the recommendations and actions of international and governmental organizations focusing on international research, such as the Global Alliance for Genomics and Health, the Public Population Project in Genomics and Society, and H3Africa. The investigators and international consultants have leadership positions in all of these organizations. This proposed study on international DTP genomic research also will consider all relevant documents of these organizations. Especially with regard to international policies, the likelihood of a recommendation being adopted is increased when it is grounded in extant laws or guidelines. **It should be emphasized that our proposed work would complement, rather than conflict with, the efforts of these international research organizations.** In fact, part of the dissemination plan in Aim 3 of the grant involves presentations to and consultations with international research organizations. Letters of Support from such organizations attest to this mutually beneficial relationship.

B. INNOVATION

Although the general approach of analyzing a range of international laws is not novel, the way in which the investigators plan to do so is extraordinary. The proposed grant utilizes an unprecedented network of worldwide experts on the law and ethics of research regulation in a wide range of countries from Africa, Asia, Australia, Europe, and North and South America. Such an ambitious research plan might seem infeasible, except that the PD/PIs already have demonstrated their ability to conduct such complex, international research. In our Harmonizing Grant we demonstrated the feasibility of using a large number of international collaborators to address a standard template of specific questions, which produced consistent data for analysis and development of new strategies for international research. The Harmonizing Grant involved a total of 47 international authors writing 27 full-length articles on the laws of 20 countries, which were published in two special symposium issues of the *Journal of Law, Medicine & Ethics.* We completed this work in two years.

The proposed study builds on this successful framework by expanding the number of countries covered by our collaborating experts from 20 to 32. The increase in number permits even greater country diversity in terms of geography, culture, and legal system. In addition, before submitting a list of questions to our international consultants we will take methodologically rigorous steps to ensure that we have the right questions and that we have identified additional issues for the investigators to study. To do this, we will convene three working groups of leading experts in the following categories: (1) distinguished researchers and related experts from academia, biotech, and the pharmaceutical

industry; (2) independent and patient-directed researchers, citizen scientists, app developers, and mHealth experts; and (3) research regulators, including IRB officials and research ethics regulators from the US and overseas. The working group members also will have a role in critiquing the draft documents written by the investigators, thereby providing a structured feedback loop enabling the investigators to refine their final written products. A separate, four-member international advisory board will serve as a final check on all work products. **The process of engagement with stakeholders in international DTP genomic research to generate actionable findings and policy options for researchers, participants, and regulators is unprecedented.**

C. APPROACH

Aim 1: Convene three expert working groups of researchers and IRB leaders to identify and prioritize the key issues for a standard questionnaire and template to distribute to the study's 32 international experts on country-specific laws and research ethics.

The primary objective of Aim 1 is to elicit input and agreement from multiple stakeholder groups on the most pressing legal and ethical challenges facing international DTP genomic research. The purpose is to inform the evidence-based development of the questionnaire that will be distributed in Aim 2. The working group members will be encouraged to report on their previous experiences with DTP research. Issues such as recruitment obstacles, inclusion and exclusion strategies, informed consent, privacy, return of results, data sharing, and IRB policies are important to the investigators as they compile their findings and policy options. Therefore, the Aim 1 working groups will not only be an important link to Aim 2 (international survey), but also to Aim 3 (conclusions and policy options).

We have assembled three expert working groups, which we will convene in a series of in-person meetings to systematically identify and prioritize questionnaire topics. Each working group will include 7-13 members who are leaders in their fields, and were chosen to provide diverse views. Letters of Support have been obtained from all of the individuals listed below.

Working Group 1 consists primarily of researchers from the academic, biotech, and pharmaceutical spheres. It will meet at the Broad Institute in Cambridge, MA. Dr. Daniel MacArthur of the Broad Institute is a co-investigator on this project.

Working Group 1 – Researchers I – November 2017, Broad Institute, Cambridge, MA

Michelle Agee	23andMe	Thomas M. Morgan	Novartis
Mark Barnes	Ropes & Gray, LLP	Martin Naley	Cure Forward
Paul R. Billings	Omicia	Olivier F. Noel	DNAsimple, Inc.
Noah Craft	Science 37	Michelle Penny	Biogen
Jeff Eidel	Illumina	Amelia Warner	Global Specimen Solutions
Justin McCarthy	Pfizer		
Alex Mittendorf	Genos	Christina Waters	Rare Science

Working Group 2 consists of independent and patient-directed researchers, citizen scientists, app developers, and mHealth experts. The meeting will take place in Washington, DC. These stakeholders bring distinctive perspectives to international research and regulation, and pose novel challenges for the regulation of research. The following individuals have submitted a Letter of Support.

Working Group 2 – Researchers II – February 2018, Washington, DC

Deborah Estrin	Cornell Tech	Ernesto Ramirez	Fitabase
Steve Hershman	LifeMap Solutions	Sharon F. Terry	Genetic Alliance
Steven Keating	Apple	John T. Wilbanks	Sage Bionetworks
Sally Okun	PatientsLikeMe		

Working Group 3 consists of IRB members and administrators from both academic and independent IRBs, as well as experts in international IRBs or equivalents.

Working Group 3 – IRBs – May 2018, Washington, DC

Rebecca Ballard	Schulman Assoc.	Alana Lucas	Australian Nat'l Med. Res. Council
Jeffrey R. Botkin	Univ. of Utah		
Anne Cambon-Thomsen	INSERM (French Nat'l Health Res. Inst.)	Pearl O'Rourke	Partners Healthcare
		Stephen J. Rosenfeld	Quorum Review
Cami Gearhart	Quorum Review	David Townend	Univ. of Maastricht
David G. Forster	WIRB-Copernicus	Delia Wolf	Harvard Sch. of Pub. Health

All working group members will be reimbursed for travel expenses and will receive a $1,000 honorarium for participating at the in-person meeting and reviewing the draft conclusions and policy options at the end of the grant. All travel arrangements will be handled by the Infinity Conference Group of Herndon, VA.

Working Group process: The working group meetings will be under the direction of the Duke University School of Medicine's Program for Empirical Bioethics, directed by Co-PI Dr. Laura Beskow. The Duke program is one of the nation's foremost academic centers for research ethics studies. We will convene a half-day meeting of each working group, at which we will utilize the Nominal Group Technique (NGT), an established methodology for identifying problems, generating ideas, and determining priorities. NGT entails a structured, face-to-face meeting of experts and offers several important strengths: time efficiency; personal contact and exchange of information; orderly procedures to ensure balanced participation from all group members; and a clear outcome, with in-session completion and discussion of group votes and tallies.[31, 32, 33, 34]

Each meeting will begin with a brief introduction of the overall project and explanation of the purpose of the session. Under the leadership of an experienced moderator, Dr. Kate Brelsford of Duke, we will then implement the four traditional stages of NGT: [31, 32, 33, 34]

(1) Silent generation. We will provide working group members with a worksheet to write down independently (without consultation or discussion with others) all of their ideas when considering these two focal questions: (A) Do you believe that international DTP genomic research raises important legal and ethical issues and, if so, which issues are most important to you? (B) If you were able to ask 32 international experts on research law and ethics about the laws in their countries affecting this type of research, what would you ask them?

(2) Round robin. Next, we will invite working group members to share their ideas, one at a time, until all ideas have been presented. Research staff will record the ideas verbatim in a document projected on a large screen visible to the group. This process will continue until no new ideas are forthcoming. The moderator will ensure that no debate or discussion about individual contributions occurs at this stage, so that each person can voice opinions without others modifying or rejecting his or her view.

(3) Clarification. Once all ideas have been listed, working group members can seek verbal explanations or further details from one another, with the goal of confirming a common understanding of the ideas. Again, the moderator will ensure the discussion is not dominated by one person or turn toward judgment or criticism. With agreement from all participants, ideas may be grouped together, altered, or eliminated, with edits made to the document projected on the screen to reflect the final list.

(4) Voting. We will then ask working group members to select individually their top five ideas from the final list, and to rank each one on a worksheet. To preserve the anonymity of individual scoring, the research team will collect the worksheets and, during a short break in the session, compile all the rankings in an Excel spreadsheet. The spreadsheet will be pre-populated with formulas to calculate, for each idea, the number of votes received (number of participants who selected the idea in their top five) and the sum of scores assigned. The spreadsheet can be quickly sorted by these factors, reflecting the priorities of the group, and immediately reported back. The moderator will facilitate group discussion of

these aggregate results, followed by one more round of voting to allow participants to revise their selections and rankings based on the discussion.

Toward the end of each meeting, time will be dedicated for PD/PI Professor Mark A. Rothstein to lead a discussion of participants' first-hand experiences conducting DTP research, including the specific challenges faced, how they were addressed, and ways in which this research project can facilitate research while respecting and protecting the rights of participants.

We will conclude the NGT session by asking working group members to fill out an evaluation form assessing the quality of the process, rating aspects such as facilitation, equality of participation, participant engagement, and respect.[35]

Questionnaire development: The three working groups are likely to be concerned about similar issues, but it is unlikely that their views will align perfectly. The investigator team will review the priority topics from each of the working groups and draft a set of specific questions to be presented to the 32 international experts. Our aim is to keep the questionnaire to a reasonable length and therefore anticipate the final version will consist of approximately 10 questions. In addition, because of the complex and likely patchwork nature of international laws and ethics in this arena, it will be important to afford our experts an opportunity to provide us with a more general description of the legal and ethical conditions for DTP genomic research in their country. Thus, we will also ask each country expert to draft a 250-500 word description of the current state of research ethics and law in their country and the likely steps their country will take in the next 10 years regarding international DTP genomic research.

Once the questions have been drafted, we will pilot test the questionnaire and general question with our four-member international advisory board and make refinements to ensure that all questions are understood as intended and can be reasonably answered. The International Advisory Board consists of the following four distinguished members, each of whom has submitted a Letter of Support.

Ruth Chadwick	Univ. of Cardiff (UK)
Ellen Wright Clayton	Vanderbilt Univ. (US)
Jantina DeVries	Univ. of Cape Town (South Africa)
Daryl Pullman	Univ. of Newfoundland (Canada)

After the International Advisory Board comments have been received, the study investigators will meet at the University of Louisville, for a one-day meeting to finalize the questionnaire and general question for distribution. We will also use this meeting to plan for the implementation of Aim 2. In general, when deciding on questions for submission to our international collaborators we will consider the importance of the issue to international DTP genomic research, the likelihood that the issue pertains to all of the countries, the perceived ability of the experts to answer the question, and whether the question involves issues that are likely to persist for an extended period of time.

Aim 2: Distribute the questionnaires to the international experts, consult with and advise them as they prepare their responses to the questionnaires and summaries of country-specific legal and ethical issues, compile and analyze the responses, and draft conclusions and policy options.

The questionnaire will be implemented online using Qualtrics survey software, available to the Duke team through a university-wide site license. This software, which Dr. Beskow has used successfully on numerous occasions, will allow us to build static content (e.g., descriptive text, graphics) and employ a variety of standard and specialty question types, including a text box for the general question and a file upload feature for respondents to provide supporting documentation. Using Qualtrics, we can generate personalized invitations and reminders, provide a unique link to each expert consultant, and compile matrices of the responses. We will also provide the expert consultants with the option of completing the questions as a Word document.

All international consultants will receive a $1,000 honorarium. Letters of Support from all of the countries are included. Some countries will use two or more experts to provide answers to the questions. The 32 countries and lead expert for each country are as follows.

Australia	Don Chalmers	Univ. of Tasmania
Brazil	Suelie Dallari	Univ. of Sao Paolo
Canada	Yann Joly	McGill University
China	Haidan Chen	Zhejiang Univ.
Denmark	Mette Hartlev	Univ. of Copenhagen
Egypt	Iman Gouda Farahat	Egypt Nat'l Cancer Inst.
Estonia	Liis Leitalu	Univ. of Tartu
Finland	Sirpa Soini	Nat'l Inst. for Health & Welfare
France	Emmanuelle Rial-Sebbag	INSERM (Nat'l Health Research Institute)
Germany	Nils Hoppe	Hannover Univ.
Greece	Maria Bottis	Ionian Univ.
India	Sachin Chaturvedi	Research & Info. System for Devel. Countries
Israel	Gil Siegal	Univ. of Virginia
Italy	Stefania Negri	Univ. of Salerno
Japan	Ryoko Hatanaka	Univ. of Tokyo
Mexico	Lourdes Motta	UNAM (Mexican National University)
Netherlands	Aart Hendriks	Leiden Univ.
Nigeria	Obi Nnamuchi	Univ. of Nigeria
Peru	Rosario Isasi	Univ. of Miami
Poland	Dorota Krekora-Zajac	Univ. of Warsaw
Qatar	Eman Sadoun	Qatar Ministry of Pub. Health
Singapore	Calvin Ho Wai Loon	Nat'l Univ. of Singapore
South Africa	Pamela Andanda	Univ. of Witwatersrand
South Korea	Won Bok Lee	Ewha Law School
Spain	Pilar Nicolas	Deusto Univ.
Sweden	Titti Mattsson	Lund Univ.
Switzerland	Dominique Sprumont	Univ. of Neuchatel
Taiwan	Chien-Te Fan	National Tsing Hua Univ.
Uganda	Obi Nnamuchi	Univ. of Nigeria
United Kingdom	Jane Kaye	Univ. of Oxford
United States	Heather L. Harrell	Univ. of Louisville
Vietnam	Thai Cuong Nguyen	Ho Chi Minh Univ.

Once all of the information is received the investigators will construct a 320-cell matrix incorporating summaries of the answers to 10 questions for 32 countries. This matrix will be constructed by Dr. Heather Harrell of the University of Louisville, who completed the 20-country matrix for the Harmonizing Grant. The matrix will be part of the concluding article by the investigator team to be published in a special symposium issue of the *Journal of Law, Medicine & Ethics*, described under Aim 3. The matrix is an invaluable resource permitting quick access to the law in particular countries as well as facilitating international comparisons.

The investigators will also carefully review the 32 country general descriptions of the current status of research regulation of DTP genomic research. We will prepare a comparative law summary, including identifying which countries: (1) unconditionally prohibit DTP genomic research; (2) condition approval of DTP genomic research on researchers satisfying certain conditions; (3) unconditionally approve DTP genomic research; (4) are unclear about the legality of DTP genomic research; or (5) are silent on the issue.

Of equal importance, we will also prepare assessments of the likely future of DTP genomic research in each country, noting the legal and practical issues that could interfere with participation as well as the specific measures needed to ensure informed consent, privacy, and other key elements of research

ethics. We will then combine these country-specific assessments into a more general, international evaluation.

The next step will be developing a series of policy options. Among the categories of policy options are those that (a) can be adopted unilaterally by either the country of the researchers or the country of the research participants; (b) require bilateral legal agreements; (c) involve regional or larger legal agreements; (d) involve private, international organizations that rely on a commitment to follow agreed-upon best practices; or (e) can be adopted by individual researchers.

After studying all of these data and deliberating on the issues, we will prepare our first draft of the study's conclusions and policy options.

Aim 3: Distribute the draft conclusions and policy options to the three expert working groups, international consultants, and advisory board members, and obtain their feedback; analyze the responses and use them to prepare a final draft; write and publish articles presenting the findings of the study; and disseminate the results in presentations to various groups of stakeholders.

To refine and finalize our draft conclusions and policy options, we will invite detailed feedback from three key sources: (1) members of the three expert working groups; (2) the 32 international consultants; and (3) our four-member international advisory board. Specifically, we will again capitalize on features available in Qualtrics to circulate the draft document and invite comments on each major section via open-ended text boxes. At the same time we distribute the draft conclusions and policy options we will solicit input from these individuals about recommended strategies for dissemination of the completed works.

After all of the comments have been received, the McGill University team, under the direction of PD/PI Dr. Bartha Maria Knoppers, will validate the country-specific materials. This will be a final check by the comparative law experts at McGill to verify the accuracy of all statements and legal references, including statutes and regulations. The entire investigator team will then meet in Montreal to finalize the written work products of the research project. In the unlikely event that the investigators cannot reach consensus, we will involve our international advisory board to help us resolve contested issues. If any minority positions remain, we will duly note those positions in our work products. We also will use the meeting in Montreal to map out plans for dissemination of the conclusions and policy options. The dissemination element of Aim 3 will be met through data sharing, publications, consultations, and presentations.

Data sharing: The PD/PIs are committed to open data sharing throughout the course of this project. Accordingly, all four institutions involved in this research (Louisville, McGill, Broad, and Duke) will use their websites to provide updates (at least semi-annually) on the work of the project and solicit input from interested individuals and entities. For example, reports of the three working group meetings will be published online and the draft questionnaire for the international consultants will be made available online and be open for a one-month comment period. Public presentations and publications of the investigator team will be announced online, and developments in the field, both scientific publications and legal developments, will be posted on these four websites.

Publications: The *Journal of Law, Medicine & Ethics (JLME)* has agreed to publish the key findings of this study in a symposium issue, which will include the detailed matrix of responses to the specific questions addressed by all 32 country consultants, the 250-500 word descriptions of each country's current and likely future legal landscape, and the concluding article drafted by the investigator team in which we will present and thoroughly discuss our conclusions and policy options. *JLME* is a leading interdisciplinary journal in the field of health law, bioethics, and health policy. A Letter of Support from *JLME* is included. Other articles on the study's methodology and case studies on DTP genomic research may be published in *JLME* or other journals.

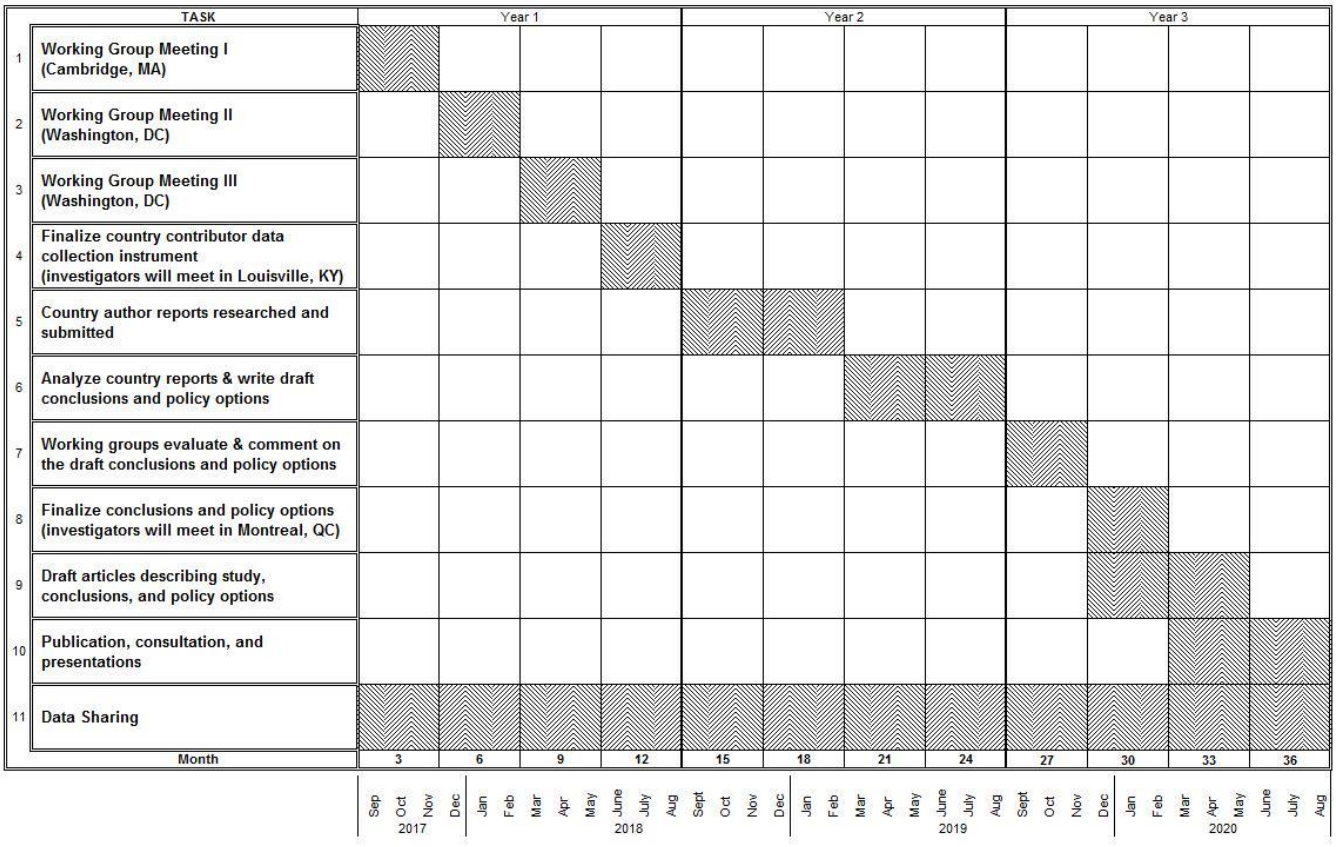
Consultations: Throughout the research and writing process, we will be highly cognizant of the need to integrate our conclusions and policy options with the work of other professional and international

organizations with a stake in this emerging type of research. At the conclusion of the study, we will meet in a variety of fora with leading international organizations to share our results and jointly plan for future endeavors. Some of these groups are the Global Alliance for Genomics and Health, the Public Population Project in Genomics and Society, the American Society of Human Genetics, the European Society of Human Genetics, and H3 Africa. Letters of Support are included with this application.

Presentations: The two lead PD/PIs are internationally renowned and travel and present extensively to academic, professional, industry, and consumer groups. They will use these opportunities to discuss the issues raised by international DTP genomic research with the international community. In fact, they are already scheduled to present the idea behind this grant application at a plenary session of the Global Biobanking meeting in Stockholm, Sweden in September 2017.

We also intend to present our findings at a variety of professional conferences and public meetings, including those of the American Society of Human Genetics, European Society of Human Genetics, Public Responsibility in Medicine & Research, regional meetings of IRB administrators, international research ethics conferences, and government agencies and advisory committees.

D. TIMELINE



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