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Commentary

Down syndrome: Issues to consider in a national registry, research database and biobank

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ABSTRACT

As the quality of life for individuals with Down syndrome continues to improve due to anticipatory healthcare, early intervention, mainstreaming in schools, and increased expectations, the lack of basic information regarding individuals with Down syndrome is being recognized, and the need to facilitate research through a national registry, research database and biobank is being discussed. We believe that there should not be ownership of the samples and information, but instead prefer stewardship of the samples and information to benefit the participants who provided them. We endorse a model with data and sample managers and a research review board to interface between the investigators and participants. Information and samples would be coded, and only a few data managers would know the relationship between the codes and identifying information. Research results once published should be included in an online newsletter. If appropriate, individual results should be shared with participants. A Down syndrome registry, research database and biobank should be accountable to participants, families, medical care providers, government, and funding sources.

The number of individuals with Down syndrome is increasing based on a number of factors [1]. More older women are having children. More women are declining prenatal testing and/or choosing to continue pregnancies after a test indicating increased possibility of having an infant with Down syndrome. The life expectancy of individuals with Down syndrome is increasing. As the quality of life for individuals with Down syndrome continues to improve due to anticipatory healthcare, early intervention, mainstreaming in schools, and increased expectations, the lack of basic information regarding individuals with Down syndrome is being recognized, and the need to facilitate research through a national registry, research database and biobank is being discussed [2]. Types of research that will change clinical practice include clinical trials, evidence-base for best practices, outcomes, research into causes of co-morbidities (e.g. sleep apnea, autism and early onset Alzheimer disease), and identification of diagnostic associations and therapeutic targets (e.g. increased risk of infection).

1. Ownership

One of the first items to be considered is ownership of the information and samples. There are two points of view [3]. One perspective is held by the universities and the courts as seen in decisions such as Moore v. the Regents of the University of California, Greenberg v. Miami Children's Hospital, and Catalona v. Washington University. This point of view holds that samples and any accompanying information is owned by the university. The other viewpoint, held by U.S. Health and Human Services (HHS) and professional organizations, is that the participant retains ownership of the samples and the information. These groups emphasize the role of universities and other institutions as stewards of the samples and information to benefit the participants who provided them.

A recent settlement in Arizona (Havasupai v. Arizona State University) recognized ownership of the samples by the participants and the remaining samples were returned to the Havasupai for a tribal ceremony and burial [4]. This case also involved information about the participants allegedly taken from their medical records without the individual's or the tribe's knowledge. The Havasupai argued that they had consented to research on Type II diabetes. The tribe was concerned that the researchers also studied schizophrenia and migration of tribal ancestors from Asia. The members of the tribe were very upset that the researchers conducted these additional studies without the knowledge or permission of the Havasupai.

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2. Registries

Registries represent organized collections of uniform information on individuals with specific conditions. There are at least three different types of registries. One is a contact registry, which is a list of individuals interested in participating in research and their contact information. Another is a research data registry that contains an organized collection of health and other information that can be mined by investigators. A third type is an outcome registry that is organized with the intent of identifying factors that improve clinical outcomes.

3. Goals for a Down syndrome contact registry

Participants and their families need to understand how their personal information will be used and how their privacy will be protected. This is in contrast to some researchers who seem to prefer a directory with name and contact information that they can access at will. This could lead to constant harassment of individuals with Down syndrome and their families by researchers who may, or may not, have approval from their Institutional Review Board for Human Subjects (IRB), adequate funding to complete their research, research design and methods that are powerful enough to find a difference if there is one, and/or a plan for data collection, secure storage and analysis.

These considerations led Sharon Terry and PXE International to act as intermediaries between researchers and potential participants with pseudoxanthoma elasticum [3]. Sharon Terry replicated this model with the Genetic Alliance for many other disorders [5].

We prefer a model where researchers would not be able to contact participants directly and would receive coded information so they would not be able to identify participants. To gain access to data, researchers would submit to a review board within the registry their IRB approval, funding, and research plan. The board would have the power to grant or deny access to the registry. Approved researchers would have to agree to provide group results to participants, medical care providers and government agencies, for example, in the form of an online newsletter hosted on the program's website. Group data would be included in the newsletter after peer-reviewed publication of the data. Researchers would agree to acknowledge the registry in their presentations and publications, and to provide copies of their presentations and publications to the review board. If they do not, then future access to the registry would be denied. If the individual data from the project would be useful to a participant, then the researcher would need to agree to provide individual data to the review board. The review board would determine whether or not to include these data as part of the registry and/or to share these data with the participant after peer-reviewed publication. The information would be presented by an appropriate medical professional selected by the review board, for example, a physician if the data included the effectiveness of a medication or a genetic counselor if the information included genetic predisposition.

4. Who should operate the Down syndrome registry

The registry should be hosted, but not owned, by the group managing the registry. The host should be considered the steward of the registry with the information “owned” by each participant. The registry should be managed to benefit participants, and to provide information to participants, medical care providers and government agencies. The management of the registry needs to be accountable to the research review board and the funding source(s).

Participants should be able to stop their involvement in the registry at any time and to remove their information from the registry if they desire to do so. Information from participants should be updated on a regular basis, perhaps annually.

Access to the registry should be controlled by a research review board that would include membership from participants, medical care providers, researchers and representatives from funding agencies. This control should assure that the resource would be used only for valid projects.

5. Issues of privacy and confidentiality of information in a research database

The managers of the research database should publicize this resource using their website and through presentations at meetings of organizations of families and individuals with Down syndrome and of professionals involved in providing care to individuals with Down syndrome or carrying out research on this condition. Funding for the database could come from government agencies, foundations, and/or fees charged for access to the database by researchers. Costs of the database include collection of the data (medical care providers may require funding to collect information), data verification and entry, research database management, the research review board, information technology, and the website and online newsletter. There should also be redundancy of information storage at multiple sites.

Participants in the research database need to be informed regarding the type of information that will be collected, the kind of studies that will be performed, and how often they will be asked to update their information for the database. This information would be included in the informed consent document.

Each participant should have a unique code number with their unique identifier and a family identifier to indicate their place in the family in relation to their family member with Down syndrome. The relationship between an individual's code number and identifying information should be available to a very limited number of database managers, and should be highly secure, for example with encryption.

If a study is a clinical trial of a drug and it has been approved by the research review committee, the database staff would share the informed consent document with potential participants. If a potential participant has questions for the researcher, the database staff would share the questions with the investigator and provide the researcher's responses to the participant. The investigator would not know who was offered participation in the study and declined. The researcher would only know the identities of those who agreed to participate.

After the results of a clinical trial have been reported in a peer-reviewed journal and in the online newsletter for participants, medical care providers and the government, the research review committee should determine if individual participants should receive their results. If it is determined that they should, then each participant should have the opportunity to accept or decline their results. If they agree to be informed, they should be told whether they received the active drug or a placebo. If they were given the active drug, they should be told whether or not it was effective for them and what dose they received. If they were given the placebo, they should be informed about what a placebo control group is and what the placebo effect is.

The technology/software needs to be flexible to incorporate updated information and new items. It needs to be able to interface with the biobank and to incorporate information from biobank results. In addition, results from imaging are important, even though their storage may be challenging. Storage and processing capacity will be a further challenge as genomic, expression and proteomic data are added to the database.

6. Biobanks

Biobanks are repositories for cells and/or tissues (e.g. blood and immortalized cell lines) or for molecules derived from cells and/or tissues (e.g. DNA and proteins). Information may also be a part of the biobank, including information about participants and how to access the information and samples. A biobank could be developed by an

investigator that is disorder-specific and may be treated as proprietary. The biobanks at the Genetic Alliance are disease specific, and control is maintained by the disorder-specific advocacy group. To access the Genetic Alliance biobanks, investigators must agree that the advocacy groups will control any intellectual property derived from research with the samples. There are two types of biobanks at the Coriell Institute for Medical Research [6]. One type is the open repository that is freely available to any investigator (for example, NIGMS Human Genetic Cell Repository). Another type is the closed repository where an organization works with Coriell to retain control of the biobank, because samples are considered too precious to be made freely available for any investigation.

7. The logistics of biobanks

The benefits of a centralized biobank include improved quality control and economy of scale. However, there should be geographic redundancy with storage at secondary sites to protect valuable specimens. Within a centralized biobank there should also be a redundant storage system with alarms and remote paging of responsible personnel with coverage at all times to prevent loss in the case of power failure.

To protect the privacy of participants, samples need to be coded. The codes need to be the same as those for the research database so samples can be paired with information on the participants. This also facilitates storing the results on the samples in the research database.

Costs of biobanks include the collection and shipping of samples; laboratory and office space; IRB costs; purchase and maintenance of storage freezers and associated supplies; personnel to code the samples, record the samples, prepare the samples, aliquot the samples into multiple containers, retrieve the sample containers as needed for researchers, maintain an inventory of available samples, and secure additional samples as needed; biobank management staff; biobank research review committee; online newsletter containing reports of research results; and provision of individual results when appropriate.

Tissues that should be collected include blood and cell lines for genomics investigators, and remaining tissue after surgery and any necessary pathology studies. Quality control for proteins for proteomics can be an issue and specific collection and shipping protocols need to be in place [7]. The biobank would have standard sample procurement and shipping protocols for each tissue and purpose.

8. IRB issues

Individuals with Down syndrome have been considered to be a vulnerable population, and, therefore, IRBs will examine these initiatives more carefully than for other populations [8]. Individuals with Down syndrome should be asked to provide consent or assent depending on their age and their reading comprehension. Parents would be asked to provide consent for individuals with Down syndrome who were under 18 years of age or if the individual with Down syndrome was unable to do this for themselves.

Consent and assent forms should be translated into the preferred language of the individual with Down syndrome and their parents if their preferred language is not English.

Consent and assent forms should provide the opportunity for the participants to withdraw their sample(s) at any time. They should also have the opportunity to indicate if they would like to receive individual results if the research review committee determines that the data are appropriate for sharing with each participant.

9. Recommendations for a centralized Down syndrome registry, research database, and biobank

A registry, research database, and biobank should function to benefit the individuals with Down syndrome. A research review board should have oversight to insure that investigations are important and well-supported and to determine how results will be distributed to participants.

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