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Analysis of Biospecimen Demand and Utilization of Samples from the National Amyotrophic Lateral Sclerosis Biorepository

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Abstract

Amyotrophic lateral sclerosis (ALS) is a rare neurological condition affecting upper and lower motor neurons. The National ALS Biorepository (referred to as the Biorepository) was initiated in 2015, with biospecimen collection beginning in 2017, as a repository for biospecimens for future ALS research. To help ensure the usefulness of the Biorepository, a biospecimen demand analysis is conducted on an annual basis, as well as an analysis of the utilization of the Biorepository.
To determine the types of biospecimens to be collected for the Biorepository, an in-depth initial examination occurred followed by ongoing biospecimen demand and utilization analyses. The initial examination included input from an expert panel, discussions with ALS research experts, review of other ALS biorepositories, assessment of biospecimen demand, and analysis of the biospecimen types historically used in ALS research. Of all biospecimen types reported in the literature, the most frequently used were DNA, postmortem spinal cord, blood, and cerebrospinal fluid; while the frequently reported types of biospecimens used in ALS-related grants were induced pluripotent stem cells, brain, blood, and spinal cord. Continuous analysis of potential sample demand and tissues collected, based on an analysis of the literature and funded grants, and actual sample requests can assist the Biorepository in ensuring that the appropriate samples are available for researchers when they are needed.

Keywords

biorepository; biospecimen; utilization

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Introduction

Amyotrophic lateral sclerosis (ALS) is a rare neurological condition affecting upper and lower motor neurons. Currently, there are no known causes, although the familial form of ALS accounts for 5%–10% of cases.[1] In the United States, ALS prevalence is estimated around 5.2 per 100,000 population,[2] with higher rates of cases among older, male, white, and non-Hispanic individuals.[3] There are two Food and Drug Administration approved medications for the treatment of ALS; otherwise, treatment relies on supportive care.[4]

In 2009, the Agency for Toxic Substances and Disease Registry (ATSDR) initiated the National ALS Registry (Registry) to better describe the epidemiology of ALS in the United States and its potential risk factors.[5] The Registry collects population-based data on the prevalence of ALS using national administrative databases and online self-enrollment. To better understand risk-factors (e.g., occupational, employment histories, and family history) associated with ALS and disease progression, the Registry also includes data collected from patients who voluntarily enroll via a web portal to complete online surveys.

Because ALS is rare, it remains challenging to identify sufficiently large groups of individuals for studies. However, the past 20 years have seen scientific and technological advances have expanded the range and quantity of biological information available for ALS research.[6] One strategy to improve our ability to answer many of the underlying ALS research questions (e.g., what is the cause of ALS?) is to collect and store biospecimens from persons with ALS. Having an adequately stocked biorepository of desired samples helps expedite and facilitate the research process.

To address this need, ATSDR contracted with McKing Consulting Corporation in 2011 to design and pilot test the National ALS Biorepository (hereafter referred to as the “Biorepository”) as a repository for biospecimens for future ALS research and a complementary research facet of the Registry. Samples are available to ALS researchers throughout the world in both academic institutions and pharmaceutical companies. When requesting samples from the Biorepository, researchers may also request complementary epidemiological data. Protocol development for the Biorepository was initiated in 2015, with biospecimen collection beginning in 2017. (https://www.atsdr.cdc.gov/features/als-biorepository/index.html). Individuals enrolled in the Registry are eligible to provide samples to the Biorepository through in-home biospecimen collection and/or postmortem collection.

Avoiding underutilization of a biorepository is significant for ethical and financial reasons.[7] The biorepository community has indicated a concern about biospecimen under-utilization.[7–10] Reasons for this underutilization may include deficiencies in the biorepository design or model, biospecimen quality assurance, strategic planning, or marketing.[11]

One important strategy to ensure effective utilization of a biorepository’s collections is to perform market research to determine the demand for biospecimens and to continue to monitor the demand. Biorepositories can help researchers advance our understanding of treating, curing, and preventing disease; especially when the disease is rare or infrequently occurring. However, a biorepository's usefulness may be limited by its design and biospecimen availability. If the biorepository does not have the types or quantities of samples needed by researchers, its effectiveness will be limited.

To help ensure the usefulness of the Biorepository, a biospecimen demand analysis is conducted on an annual basis, as well as an analysis of the utilization of the Biorepository.

Materials and Methods

To determine what types of biospecimens should be collected for the Biorepository, the authors used several methods, including an in-depth initial examination followed by ongoing biospecimen demand and utilization analyses. Qualitative data collection (e.g., expert panel discussions, discussions with ALS research experts, review of other ALS biorepositories) provided the initial framework for the analysis. Annually thereafter, the authors conducted content analysis reviews of publicly available reports and information sources to determine biospecimens used in newly published research as well as funded grants.

The initial examination began in March 2015 following the ALS Biorepository Pilot Study.[6] At that time, an expert panel was convened to review preliminary data from the ALS Biorepository Pilot Study and develop recommendations for long-term biorepository implementation. This group of experts met to discuss the type of samples to be collected and what processing and quality assurance testing should be performed. The discussions were transcribed, reviewed, and summarized and the most agreed-upon recommendations were retained.

The future direction of ALS research and the anticipated need for biospecimens were discussed with thirteen individuals representing key groups and leaders in the field through informal phone calls following a semistructured interview guide. These individuals comprised a diverse group of experts and leaders in the field, including a wide range of ALS researchers and consortium leaders, funding agency staff, federal employees, and advocacy group representatives. The interviews were transcribed and analyzed for key themes regarding biospecimen demand.

Through web searches, the authors identified and collected qualitative information from eight other biorepositories (Table 1) and sources of biospecimens from ALS patients. Biorepository managers were asked through informal telephone calls about the types and numbers of requests and biospecimens provided, with the overall goal of identifying gaps. Biorepositories that may provide biospecimens from ALS patients for research were identified from the web and other sources. Managers from those biorepositories were asked about the numbers and types of requests for biospecimens from ALS patients that were received and filled. Data were analyzed by types of biospecimens, types of data provided, and frequency of requests.

Initially and on an ongoing annual basis, the authors, ATSDR contracted researchers, analyzed abstracts from peer-reviewed literature to identify the types of biospecimens from ALS patients most frequently used. The authors searched PubMed using the following search criteria: "amyotrophic lateral sclerosis samples," human, English only, and the appropriate year(s). The initial biospecimen demand analysis began in November 2015, capturing the previous 5 years of articles, with annual updates conducted thereafter. The authors individually reviewed the resulting abstracts for relevance and some were eliminated (e.g., review articles, studies not using human biospecimens, or meta-analyses of other studies). The authors then coded the remaining articles to represent the type of biospecimen used by researchers in the study. These data were aggregated and analyzed on an annual basis.

In addition, the authors conducted an annual search through the National Institutes of Health's (NIH) Research Portfolio Online Reporting Tools RePORTER database[12] to identify newly funded projects on ALS that mentioned the use of the various types of biospecimens in fiscal years 2015 through 2019. This approach has the advantage of providing a more current assessment of biospecimen utilization than the literature search, given the lag time between the time a study is performed and when the results of the study are published. In addition, this approach helps us to determine what samples are being used regardless of whether or not the study findings were ever published, thus minimizing a potential publication bias.

Grants were searched based on the following criteria: award type, year, and ALS and any of the following terms: blood, serum, saliva, plasma, urine, DNA, RNA, brain, spinal cord, cerebrospinal fluid (CSF), muscle, skin, bone, hair, and nails. The list of grants was reviewed for relevance and those who did not use human biospecimens for ALS research were eliminated. The authors reviewed the abstracts of the remaining grants to identify what biospecimen type(s) would be used. Each abstract was coded to indicate each type of biospecimen used in the study. The frequency of biospecimen type was tabulated and reported. These approaches together identified the frequency at which the use of different types of biospecimens were reported in the published literature as well as newly funded ALS projects.

To track the request and utilization of biospecimens from the Biorepository, a proprietary database was established using Microsoft Access™. This database records such items as type and amount of biospecimen requested, institution making the request, and what type of research will be conducted. The database was mined for all biospecimen requests between December 2016 and April 30, 2020.

Results

During the initial design phase of the ALS Biorepository, key themes emerged during consultations with leaders in the field.

Expert Panel recommendations

The Expert Panel reviewed the biospecimens collected during the initial pilot study and made several recommendations. The experts recommended the extraction of DNA and RNA from blood tubes and the expansion of the number of saliva collections to increase the number of DNA samples. Regarding postmortem collections, the Expert Panel recommended the continuation of brain, spinal cord, and CSF collections but the discontinuation of skin, muscle, and bone collection. The Expert Panel also recommended that ATSDR conduct regular market research to determine what type of biospecimens ALS researchers are interested in using, based on current research and technology. They also recommended the annual update to drive what types of samples are collected and how they are collected. As discussed subsequently in this article, one result of this annual update was the addition of the extraction of peripheral blood mononuclear cells (PBMCs) from blood (that can be used to create induced pluripotent stem cells [iPSCs]) once the technology became available.

Interviews with ALS research experts

According to the 2015 interviews with ALS research experts, the most pressing research issues often included genetic research. Such topics included genetic etiology of the disease, conducting whole-genome and -exome sequencing, identifying genes that predict the rate of progression, and conducting biomarker discovery studies. Other topics of interest included identifying disease subtypes, conducting environmental studies, developing models to study ALS in the laboratory, and identifying potential therapeutic targets. These experts also indicated postmortem brain, spinal cord, and CSF would be the most important to collect.

Information from other biorepositories

Eleven biorepositories were identified that collect, store, and/or distribute biospecimens from ALS patients for research; qualitative information and descriptions about the biorepository were collected from eight. The three nonparticipating biorepositories did not respond to our inquires in time to be included in the research activities. Different types of samples are available from each; samples include postmortem tissues, DNA, blood, serum, plasma, and others. Based on the discussions with managers of biorepositories that may collect and distribute biospecimens from ALS patients to the research community, the numbers of requests for biospecimens from ALS patients is generally relatively small, ranging from several per month to several per year, depending on the purpose and nature of the repository. Most requests are for a small number of samples for pilot studies (<10 patient samples); however, some researchers are requesting very large numbers of patient samples for genomic analyses.

Sample demand analysis

Upon completion of the combined peer-reviewed literature search for the time period 2010–2020, 248 articles were identified, of which 203 were determined to be relevant to the analysis. On average, 20 relevant articles were identified per year (2010–2020). Of all biospecimen types reported in the articles, the most frequently used were DNA, postmortem spinal cord, blood, and CSF (Table 2). Other types of biospecimens identified in the literature included postmortem spinal cord, iPSCs, plasma, and serum. Approximately one-half (96/203) of the total number of articles identified as using samples from ALS patients reported research using some type of postmortem specimen, with the most frequently used postmortem tissues being brain and spinal cord.

The search of the NIH RePORTER database over the period 2015–2020 identified 218 newly funded grants during that time period, which reported using some type of human biospecimens for ALS research (Table 3). Some grants used multiple biospecimen types from ALS patients. The most frequently reported types were iPSCs, brain, blood, and spinal cord. In several grants, it was unclear what types of biospecimens were being used. Since 2016, there have been no reports of muscle, saliva, urine, nerves, or feces usage in the abstracts of funded grants.

Sample utilization

As of May 1, 2020, the Biorepository contains over 70,000 samples collected during the time period May 15, 2013 to April 30, 2020 and provided by 1378 unique individuals (Table 4). All samples are sent to a central laboratory, which provide the collection materials and process them according to our established standard protocol. Since December 2016, 8741 samples from the Biorepository have been distributed to 14 unique research teams. Table 4 shows how many researchers requested samples and how many aliquots of the samples were distributed. Sample types distributed include brain, DNA, fingernails, hair, human primary cells, peripheral blood monocytes (PBMCs), plasma, serum, spinal cord, urine, urine with sulfamic acid (to keep the mercury in a reduced state for future analysis), and whole blood (Table 4). To date, all sample requests submitted to ATSDR have been approved. The approval process includes validating that the study is scientifically rigorous with appropriate methods, that the work is ALS-related with value to the ALS community, and that the samples requested are available in the Biorepository. Only one sample request was not fulfilled because the researcher could not be located after the request was approved.

More than 25 researchers have contacted the Biorepository to inquire about sample procurement and availability; of those, 15 researchers completed an application. Most commonly, researchers requested blood-related samples or postmortem tissues. Overall, the main types of research being conducted include studies of possible environmental risk factors, therapeutics for diseases, and disease progression.

While the types of biospecimens available are provided on the ATSDR website (https://www.cdc.gov/als/ResearchersandClinicians_NatlALSBiorepositry.html), the Biorepository received a few inquiries regarding biospecimens not being collected. These types of biospecimens included liver tissue and postmortem teeth. Researchers also requested additional genetic test results beyond what the Registry has available.

Discussion

Effective biospecimen utilization depends on effective biorepository design. Continuous analysis of potential sample demand and tissues collected, based on an analysis of the literature and funded grants, and actual sample requests can assist the Biorepository in ensuring that the appropriate samples are available for researchers at the time they are needed. Of all biospecimen types reported in the literature and ALS-related grants, researchers most frequently use blood, brain, and spinal cord.

Blood and postmortem tissue continue to be frequently reported as biospecimen types used or planned for use in both the more recent literature and grant awards. The reported frequency of the use of other biospecimen types, such as DNA and RNA, hair, nails, urine, postmortem bone, and skin for fibroblasts, remains very low. The literature search did not identify any studies using urine and there have been no external requests. The decision of what to collect is a combination of specimen demand and analysis findings and the guidance of the expert advisors. Because of the low utilization and literature findings, and, in consultation with experts, hair and nail collections were dropped from the ALS Biorepository in 2016, and urine collection was stopped in 2019.

Beginning in 2017, iPSCs were the most frequently reported biospecimens used in newly funded ALS-related grants. This number continued to increase each year thereafter. As a result of these findings, the isolation and storage of PBMCs, from which iPSCs can be created, began in 2018 for a subset of Biorepository participants. As the popularity of the usage of iPSCs continues, the Biorepository may consider increasing the number of participants sampled for this biospecimen type.

In addition, it appears from these analyses and requests for samples that although researchers are interested in identifying ALS patients with specific genetic mutations, the use of DNA alone in research may have decreased. Therefore, there should be further evaluation of whether it is advantageous to continue saliva collections that produce only DNA samples.

Limitations of the analysis

One of the limitations of this analysis is the fact that only abstracts of the literature and the funded grants were identified and reviewed. Thus, this analysis may not have captured all sample types being utilized in the reported literature or funded grants. In addition, usage trends from our analysis of the literature may lag behind current trends because of the time it takes to bring a study to publication and the retrospective nature of our analysis. Nonetheless, we believe that these approaches suggest some trends in usage that can serve as one measure of assessing the demand for certain types of biospecimens from ALS patients. The COVID-19 pandemic halted collection of new biospecimens in March 2020; collections will continue when it is safe to do so.

Conclusions

The utility of the Biorepository depends on how it adapts to the current and future needs of ALS researchers. Continuing to monitor biospecimen demand and sample utilization will improve the utility of the Biorepository. The Biorepository has used the annual biospecimen demand analysis to adjust biospecimen collection. The Biorepository has discontinued collection of hair, nails, and urine as there has been no recent evidence of researchers using these biospecimen types. While the Biorepository is not collecting these biospecimen types, any previously collected samples are available to researchers. This allows the Biorepository to focus its resources on collecting biospecimens that are in demand for research such as PBMCs to create iPSCs. It is important to continually evaluate how research is changing so that the Biorepository collects and stores the most valuable biospecimen types for research ALS.

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Table 1.

Other Biorepositories Providing Information to Guide Amyotrophic Lateral Sclerosis Biorepository Design and Demand

VA ALS Brain Bank
The National Registry of Veterans with ALS
NEALS Consortium
NIND Motor neuron Disease Repository (Coriell)
University of Miami Brain Endowment Bank
University of Maryland Brain and Tissue Bank
Cooperative Human Tissue Network
National Disease Research Interchange (NDRI)

Not all biorepositories may be active at the current time.

ALS, amyotrophic lateral sclerosis.

Table 2.

teral Sclerosis Biospecimens by Type Appearing in Literature Reviews, 2010–2020 Numbers of Articles Citing Biospecimen Type

Blood	Bone marrow	Brain (postmortem)	CNS (postmortem)	CSF	CSF (postmortem)	DNA	Hair	iPSC	Muscle biopsies	Muscle (postmortem)	Other cell line	Plasma	RNA	Saliva	Serum	Skin	Spinal cord (postmortem)	Stool	Urine	Unclear
16	1	11	2	21	1	33	1	0	7	2	0	7	0	1	9	1	13	0	0	0
11	0	11	0	11	0	21	0	5	11	2	0	5	0	0	16	5	26	0	0	0
4	1	6	0	4	0	3	0	3	0	0	2	1	2	0	5	0	4	1	1	1
4	0	7	0	5	0	0	0	4	1	0	3	3	0	0	2	0	2	1	0	1
5	0	7	0	4	1	4	0	0	0	0	0	5	0	0	2	1	5	1	0	0
50	2	42	2	44	2	61	1	12	19	4	5	21	2	1	34	7	50	3	1	2

n from living donor unless otherwise noted.

id; iPSC, induced pluripotent stem cell.

Table 3.

Amyotrophic Lateral Sclerosis Biospecimens by Type Appearing in National Institutes of Health RePORTER, Funded in 2010–2020 Numbers of Newly Funded Grants Citing Biospecimen Type Usage

	Total grants	Blood	Brain	CSF	DNA	Hair	iPSC	Muscle	Nerve	Other cell line	Plasma	RNA	Saliva	Serum	Skin	Spinal cord	Stool	Urine	Unclear
2010–2015	80	22	28	12	13	0	17	5	1	0	17	2	1	19	9	13	1	2	0
2016–2017	31	7	7	3	4	0	6	1	0	0	3	0	1	0	2	4	0	0	0
2017–2018	24	5	5	1	1	0	16	0	0	2	0	3	0	0	1	3	0	0	0
2018–2019	32	5	0	1	0	1	21	0	0	4	0	1	0	2	1	0	0	2	3
2019–2020	51	3	16	5	6	0	31	0	0	1	2	0	0	2	1	6	0	1	4
Total	218	42	56	22	24	1	91	6	1	7	22	6	2	23	14	26	1	5	7

Table 4.

Samples in the National Amyotrophic Lateral Sclerosis Biorepository, as of April 30, 2020

Sample type	Current No. of samples in Biorepository	Sample size/aliquots	No. of researchers requesting samples[a]	No. of samples distributed
In-home samples				
Buffy coat	274	1.0mL		
DNA	22,496	2 μg	2	1740
Fingernails	268	10 Nails/vial	1	330
Hair	241	1 Vial	1	330
PBMCs from blood	1450	500,000 Cells/vial	1	350
Plasma	9719	0.5 mL	3	304
RNA	9466	2 μg	—	—
RBC	3850	1.0mL	—	—
Serum	7149	0.5 mL	3	1883
Urine	10,046	1.8 mL	1	1806
Urine with sulfamic acid	690	4.5 mL	1	587
Whole blood	2751	1.8 mL	3	1290
Postmortem samples				
Bone	48	1″ Piece	—	—
Brain	48	Fixed and frozen	3	56
CSF	328	1 cc vials	—	—
Human primary cells from postmortem skin	680	500,000 Cells/vial	2	16
Muscle	49	1″ Piece	—	—
Spinal cord	47	Fixed and frozen	2	49
Total	69,600			8741

[a] Some researchers received more than one sample type, thus count will not add up to the total number of researchers requesting samples (13).

PBMCs, peripheral blood mononuclear cells; RBC, red blood cells.