PARKINSON'S PROGRESSION MARKERS INITIATIVE

Play a Part in Parkinson's Research

Parkinson's Progression Markers Initiative (PPMI)
Pathology Core

Core Leaders

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Overview

The goal of the Parkinson's Progression Markers Initiative (PPMI) is to help researchers develop improved treatments for Parkinson disease (PD). As part of the PPMI study, participants complete regular study visits and extensive data and biological specimens are collected for research studies. The donation of brain tissue at the time of death is another important way for PPMI participants to help research. Post-mortem (after death) analysis of brain tissue can provide researchers the unique opportunity to compare the data and samples that have been collected in the longitudinal PPMI study with the post-mortem analysis of brain tissue. These studies will help PD researchers further their understanding of the disease and its progression.

As part of the PPMI study, the Michael J Fox Foundation is collaborating with Indiana University and Stanford University to establish the PPMI Pathology Core. The PPMI Pathology Core will work directly with PPMI participants to explain the importance of brain tissue donation for future research studies. The PPMI Pathology Core will answer all questions from the PPMI participant and their family members regarding the logistics of brain tissue donation, and will provide literature to address common religious and family concerns about brain tissue donation and its impact on funeral preparations.

For over twenty years, the team at Indiana University led by Dr. Tatiana Foroud, has worked with research participants and their family members to plan brain tissue donation. This experienced team has helped coordinate the donation of brain tissue from over 500 research participants located throughout the United States. They have developed extensive protocols that ensure that the brain tissue can be removed rapidly and following a strict protocol as quickly as possible following the death of the research participant. The neuropathologist at Stanford University, Dr. Thomas Montine, is a world recognized neuropathologist who specializes in the study of neurodegenerative disorders including Parkinson's disease and Alzheimer's disease. He has published extensively in this area and has also developed protocols that are widely used by other neuropathologists in the evaluation of brain tissue to determine pathogenesis. Drs. Foroud and Montine have worked together in several studies and will continue this successful collaboration as part of the PPMI Pathology Core.

The PPMI Pathology Core team at Indiana University will work with the PPMI participants to coordinate and plan all aspects of brain tissue donation. A finalized brain tissue donation plan will be prepared. It will be shared and stored on file by the family, the funeral home, the nursing home, if appropriate, and the local brain removal team (i.e. pathology team), who will complete the brain tissue collection. These detailed plans will be confirmed on an annual basis by the PPMI Pathology Core at Indiana University. Careful and detailed advance planning is critical if the brain tissue is to be removed rapidly, ensuring its maximal value for research studies.

At the time of death, the PPMI participant's family will call the PPMI Pathology Core at Indiana University to inform them that their loved one has passed away. Immediately, the brain tissue donation plan will be implemented. After the brain tissue has been removed, it will be sent to the PPMI Pathology Core at Stanford University. The neuropathologist at Stanford University will carefully examine the brain to determine whether there are changes consistent with Parkinson's disease, as well as other disorders. Following this careful examination, the PPMI Pathology Core at Indiana University will generate a summary that will be provided to the PPMI participant's designated legally authorized representative.

Similar to the other types of biological samples collected as part of a PPMI study visit, such as blood, cerebrospinal fluid, etc, the brain tissue samples will be made available to approved researchers. The implementation of the PPMI Pathology Core further expands the range of biospecimens available to researchers seeking to understand the trajectory of PD progression from the preclinical phase through symptomatic disease onset, disease progression and death. PPMI is relatively unique because of the inclusion of different groups of participants, including idiopathic PD and healthy controls, as well as those with and without PD who carry genetic mutations in key risk genes.

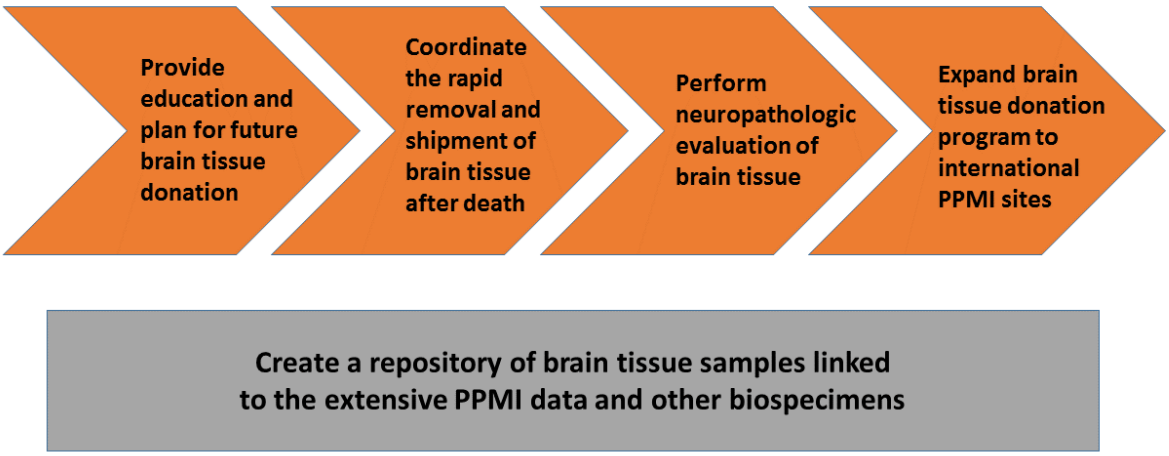

Figure 1: Overview of the PPMI Pathology Core

APPROACH

Aim 1: Assist all interested PPMI participants to develop detailed plans for brain tissue donation at the time of death.

The PPMI Pathology Core at Indiana University will lead efforts related to PPMI participant engagement and participation in the brain tissue donation program. The group at Indiana University will prepare lay materials explaining the importance of evaluation of brain tissue to the study of Parkinson's disease. These materials can be provided by the PPMI site staff to PPMI participants seen in person and can also be sent by mail or email to PPMI participants who are no longer being seen in person at the PPMI site.

To improve efficiency and help families work rapidly with the PPMI Pathology Core, PPMI participants will be encouraged to complete all required planning forms online. As with all studies, the PPMI Pathology Core staff are always available to answer questions by phone and participants can also chose to complete all forms on paper. Information will be gathered to ensure that all aspects of the brain removal can be pre-planned. All the details for the brain tissue removal (where the brain tissue will be removed and who will remove the brain tissue) will be put in writing for the PPMI participant and their family or legally authorized representative. Such preplanning reduces the stress for the family. At the time of death, the participant's family need only call the PPMI Pathology Core team, who will then initiate the steps outlined in the brain tissue donation plan.

The PPMI Pathology Core team at Indiana University will reconfirm all details of the brain tissue donation plan on a yearly basis. An email or letter (as the participant prefers) will be sent to the PPMI participant and their legally authorized representative summarizing the brain donation plan. The PPMI participant and/or their legally authorized representative will be asked to confirm (electronically or on paper) the PPMI participant's residence and the planned funeral home. If any changes have occurred, this can be reported either through an online form or a paper form mailed back to the PPMI Pathology Core at Indiana University. On an annual basis, the team at Indiana University will also reconfirm the willingness of the local brain removal team (i.e. pathology team) to participate in the brain removal. As part of the annual confirmation, the pathology team will also receive the PPMI brain removal protocol and will be asked to reconfirm the availability of the previously shipped brain tissue removal supplies. If necessary, the team at Indiana University will alter the brain donation plans to accommodate changes in residence, funeral home, brain removal team, etc. All changes will be put in writing and sent to the family, nursing home, funeral home and pathology team for their record.

Prior Experience: The team at Indiana University has planned brain donation for study participants located throughout the United States for many years. As part of the NIH-funded Parkinson's Research: The Organized Genetics Initiative (PROGENI), a total of 145 completed brain donations were planned and executed by the PROGENI study team. An additional 118 brain donations were planned, but were cancelled, when NIH funding ended. As part of NIH-funded Alzheimer disease studies, a total of 403 individuals executed a brain donation planned by the National Cell Repository for Alzheimer Disease (NCRAD) or Late Onset Alzheimer Disease (LOAD) study teams. Another 100 individuals currently have a brain donation plan in place. Reviewing information from the NCRAD/LOAD studies, over 200 different brain removal teams have been used throughout the United States.

Aim 2: Coordinate the rapid removal and shipment of brain tissue after death.

If the health of the PPMI participant begins to deteriorate and/or if the PPMI participant dies, a family member or the legally authorized representative is asked to immediately contact the PPMI Pathology Core team at Indiana University. If this occurs outside of normal business hours or a holiday, the study team will still be accessible by pager The team at Indiana University will reconfirm all details of the brain donation plan. The team will then ensure that everyone involved in the brain removal is informed when the PPMI participant dies.

At that point, the team at Indiana University will work closely with the local brain removal team (i.e. pathology team) to ensure that the PPMI brain removal protocol is completed properly. Brain tissue begins to undergo irrevocable changes once an individual dies. Minimizing the time required to remove the brain tissue allows the PPMI study to maximize the information that can be learned from the valuable brain tissue. Therefore, the focus of the PPMI Pathology Core is to remove the brain tissue within 8 hours of the time of death. If that is not possible, then the brain tissue is placed in formalin, which stops any further brain tissue decay, but limits the scope of studies that can be performed with the brain tissue. Once removed, the brain tissue will be shipped by the local brain removal team to the PPMI Pathology Core at Stanford University for neuropathological evaluation.

Prior Experience: The PPMI Pathology Core team at Stanford University has used an 8 hour cut off for obtaining fresh tissue in their brain banking efforts since 2002; this includes the Pacific Udall Center of Excellence for Parkinson's Disease Research and four different Alzheimer's Disease Research Centers. This time point was selected because markers of lipid peroxidation, a sensitive measure of tissue degradation, are significantly increased by a ten hour post mortem delay. Many studies have been published using human tissue from these different banks, and Dr. Montine and his research team have demonstrated high quality preservation of DNA and protein, and moderate preservation of RNA using this cut off. Tissues collected beyond this 8 hour time period will be formalin fixed.

Aim 3: Perform neuropathologic evaluation of brain tissue.

The evaluation of the brain tissue by the PPMI Pathology Core at Stanford University will follow contemporary consensus guidelines and will evaluate 23 regions of the brain, using multiple types of stains in each region. This standardized work up will evaluate synucleinopathies, tauopathies, and usual changes of aging brain including Alzheimer's disease, vascular disease, vascular brain injury, hippocampal sclerosis, and TDP-43 cytoplasmic inclusions. Families of the PPMI participant will receive a letter summarizing the results of the neuropathological evaluation of brain tissue.

Because a uniform protocol is being used in the PPMI Pathology Core at Stanford University, each PPMI subject donating brain tissue will have a detailed report of all results obtained from the tissue evaluation. This information will be sent in a de-identified dataset to the PPMI Informatics Core at the Laboratory of NeuroImaging (LONI) at the University of Southern California (USC).

Aim 4: Create a repository of brain tissue samples.

The PPMI Pathology Core at Stanford University will create a repository (or bank) of samples that will be made available to other researchers. Scientists will be able to request brain tissue. They will also be able to view digitized images of the slides that were evaluated using multiple stains. PPMI and the MJFF have established protocols in place to allow investigators to request brain tissue for research studies. All tissue requests are reviewed by the Biospecimen Review Committee (BRC) and brain tissue will only be distributed to approved investigators.

Aim 5: Expand the PPMI Pathology Core to PPMI Sites outside the United States

Initial efforts of the PPMI Pathology Core are focused on PPMI participants completing their study visits in the United States. However, there are a substantial number of PPMI participants who are enrolled at sites outside the United States. Beginning in Year 2, the PPMI Pathology Core will begin to work with the PPMI sites outside the United States to implement the protocols successfully put into place in the United States.

Because of the variety of languages spoken by the PPMI participants outside the United States as well as the challenges in transporting brain tissue internationally, we do not propose to have brain tissue transported to the PPMI Pathology Core at Stanford University. Instead, we propose to identify neuropathologists known to the international PPMI site investigators who can ensure that they can follow the standardized PPMI Pathology Core protocols implemented by the PPMI Pathology Core at Stanford University.

Efforts will be focused initially on those international PPMI sites with the largest number of enrolled PPMI participants (i.e. Germany, Spain, Israel, Norway) as well as those PPMI sites with unique PPMI participants (Italy, Greece). The PPMI Pathology Core will work closely with each of these groups to implement a brain tissue donation program that can be managed by the PPMI site coordinators. Dr. Montine will also ensure that the neuropathologists at each of these sites can implement the PPMI Pathology Core protocol and can also generate the minimal dataset. Plans for generating digitized images will also be developed with each of these sites.

PPMI Pathology Core Brain Tissue Donation Projections

The goal of the PPMI Pathology Core is to facilitate the donation of brain tissue from all PPMI participants willing to participate in this research protocol. To ensure the ability to rapidly remove brain tissue at the time of death, the PPMI Pathology Core at Indiana University will prepare a plan for all PPMI participants who express interest in this research effort. To date, 321 individuals have indicated that they are interested in considering a brain tissue donation. With the focused effort proposed as part of the PPMI Pathology Core, we expect that the number of individuals who will wish to develop a brain tissue donation plan will continue to increase. It is difficult to predict the number of PPMI participants who will die each year. It is equally challenging to estimate how many will participate in this research effort. However, early indications suggest that when the importance of this initiative is explained, and coordinators take the time to answer all of the participant's questions, a substantial number of participants will be ready to plan a brain tissue donation.

Table 1: PPMI Pathology Core Yearly Projections (US Only)

	Year 1	Year 2	Year 3	Year 4	Year 5
Consent and prepare brain tissue donation plans	250	250	100	100	50
Reconfirm previous brain tissue donation plans	0	250	500	600	700
Complete brain tissue collection and neuropathology	3	10	15	20	25