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A platform for discovery: The University of Pennsylvania Integrated Neurodegenerative Disease Biobank

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Abstract

Neurodegenerative diseases (NDs) are defined by the accumulation of abnormal protein deposits in the central nervous system (CNS), and only neuropathological examination enables a definitive diagnosis. Brain banks and their associated scientific programs have shaped the actual knowledge of NDs, identifying and characterizing the CNS deposits that define new diseases, formulating staging schemes, and establishing correlations between neuropathological changes and clinical features. However, brain banks have evolved to accommodate the banking of biofluids as well as DNA and RNA samples. Moreover, the value of biobanks is greatly enhanced if they link all the multidimensional clinical and laboratory information of each case, which is accomplished, optimally, using systematic and standardized operating procedures, and in the framework of multidisciplinary teams with the support of a flexible and user-friendly database system that facilitates the sharing of information of all the teams in the network. We describe a biobanking system that is a platform for discovery research at the Center for Neurodegenerative Disease Research at the University of Pennsylvania.

Keywords

Cerebrospinal fluid; Plasma; Serum; Autopsy; Neurodegeneration; Alzheimer's Disease; Dementia; Genetics; Parkinson's Disease; Frontotemporal lobar degeneration

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1. Introduction

The term *neurodegenerative disease* (ND) encompasses a heterogeneous group of diseases defined by the progressive and relentless degeneration of selectively vulnerable populations of neurons and glia that are almost always associated with the deposition of abnormal proteins, usually as amyloid, in the central nervous system (CNS) that mainly manifest clinically as cognitive, movement, language, and behavioral disorders, and/or motor neuron disease. The most common diseases are classified in the following groups: Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD) resulting from tau immunoreactive deposits or FTLD resulting from transactive response (TAR) DNA binding protein 43 immunoreactive deposits (FTLD-TDP-43), amyotrophic lateral sclerosis (ALS), synucleinopathies resulting from the deposition of pathological α-synuclein, and prion diseases. The neuropathological hallmarks of these diseases are identified as a result of the study of brain and DNA samples, and biobanks enable the collection of tissue and biofluid samples to accelerate the discovery of pathological subtypes and DNA to make associations between certain pathological subtypes with specific genetic abnormalities [1–6]. The discovery of the proteins and genes linked to the formation of the CNS deposits shaped the classification of NDs by establishing the diagnostic criteria for different NDs [7–13]. Although NDs such as AD, FTLD, and Parkinson's disease (PD) have characteristic clinical phenotypes that define them, there is some phenotypic heterogeneity. Therefore, clinicopathological correlation varies based on the phenotype [14] and neuropathological assessment is still the gold standard for definitive diagnosis of NDs. In addition, it is common to find coincident ND diagnoses at the pathological level [14]. Cerebrospinal fluid (CSF) levels of amyloid-β and total and phosphorylated tau correlate with deposition of abnormal proteins in the brain in AD [15] and can predict accurately an underlying AD pathology [14]. However, there are currently no reproducible and accurate molecular diagnostic biomarkers for synucleinopathies [e1] and FTLD [e2] whereas plasma amyloid-β levels have not proved useful for diagnostic classification of AD [16]. Moreover, positron emission tomography and single photon emission computed tomography can detect the dopaminergic deficit even at premotor stages of PD [17], and amyloid positron emission tomographic imaging correlates with fibrillar amyloid brain deposits [18,e3]. These advances notwithstanding, it remains a great challenge to predict the ultimate pathological diagnosis while patients are living. Nevertheless, achieving an accurate diagnosis in life is particularly important because there are many clinical drug trials designed to target a specific molecular mechanism or pathological protein that, if successful, will enable targeted therapy for NDs to delay the onset or the halt progression of disease. Because biofluids are easily accessible from living patients, a great deal of effort is focused on finding ways to extract diagnostic information from them. The emergence of new technologies that are able to screen for several proteins [19,e4] in biofluids, such as CSF and plasma, has led to further interest in these samples and to the establishment of biofluid banks that allow the testing of these new technologies in well-characterized recruited cohorts. However, to maximize the utility of biofluid samples for the evaluation of new biomarkers, the subjects from which they were obtained must have a reliable and accurate clinical and neuropathological diagnosis.

Last, genetic discoveries for NDs have accelerated efforts to delineate molecular mechanisms of NDs. Pathogenic gene mutations and genetic risk variants have been identified for NDs in both small and large collaborative studies. Tissue and DNA samples stored in biobanks [20–22,e5] have enabled these discoveries. Because genetic risk factors for neurodegenerative diseases are better studied and combined with biomarker data, this will lead to new models for diagnosis and prognosis.

Although the number of autopsies worldwide is declining [23,24], families and patients support autopsy-based research altruistically [25–27], and autopsies have a recognized educational and teaching purpose [28]. In addition, still in this century a significant number of autopsies detect clinically important missed diagnoses, although the rate of autopsy-detected diagnostic errors has declined (including nonneurological cause of death) [29]. This is even more important in the case of NDs that show, overall, a clinicopathological correlation of 81% in specialized centers [14]. One of the most important factors for the success of autopsy programs is the clinician's attitude toward autopsies [28]. Therefore, the creation of AD centers and Udall Parkinson's Disease Centers in the United States, and other initiatives in Europe [e6] and Australia [e7], is enabling researchers to access standardized, high-quality samples from patients with NDs in collaboration with clinicians. Recently, our group proposed a model for comprehensive AD centers that would not be limited only to the study of AD but would also include the study of PD, FTLD, ALS, and vascular dementia [30], because of their frequent overlap [14,31], using a multidisciplinary, patient-oriented clinical and basic research strategy. To be able to take advantage of all the new technologies and to build onto the archive of biosamples and information, the Center for Neurodegenerative Disease Research (CNDR) at the University of Pennsylvania (UPenn) established the Neuropathology, Biomarker, and Genetics Biobank (NBGB) as well as the Integrated Neurodegenerative Disease Database (INDD) to monitor biosamples and data collection. In this article, we describe the integrative approach of this biobank together with the different clinical centers [30] that gather clinical data, and genetic and biofluid samples and brains of well-characterized, longitudinally monitored patients with different NDs at UPenn (Fig. 1). In addition, we describe the different basic research, translational, and clinical studies that are developed in this framework.

2. Integrated Neurodegenerative Disease Database

The INDD integrates the information from the NBGB and all the clinical centers involved in the study of NDs at UPenn [32]. Although the different clinical centers have used their own identifiers (IDs) historically, each subject in the database has been assigned a unique universal anonymized ID (IN-DDID). Briefly, the INDD is a relational database implemented with Microsoft SQL Server (version 2008; Microsoft Corporation, Redmond, WA, USA). To offer easy access to members of the different UPenn research groups or cores, a Web-driven online database was created using Microsoft ASP.NET MVC 3 technology along with HTML (HyperText Markup Language) and JavaScript for the user interface. Further details on the INDD structure are described in detail in Xie and colleagues [32]; centers interested in implementing a similar system can contact the corresponding author for further information.

The directors of each of the biosample core areas form a biosample request review committee that evaluates and grants access to the INDD on request from UPenn researchers and research assistants working with them. The access permission also specifies the level of access granted. Users have to undergo Health Insurance Portability and Accountability Act training and be included in the corresponding institutional review board-approved protocols to gain access to the database. After they meet the necessary requirements, researchers are authenticated, and different levels of data access to the tables of the databases are granted to them. The INDD has several security measures, and two systems for regular, periodic backup are also implemented [32]. To ensure the entry of the data is accurate, there is double entry of randomly selected data, and 10% of the original source records are checked quarterly. There are also consistency checks and hard and soft stops, which have been described previously [32]. There are five data tables (autopsy, microscopic study, inventory, genetics, and biofluids) that are used for input, visualization, and extraction of data from the NBGB, as described in the corresponding sections that follow.

An example of how the database is updated constantly and of how new features are added is the recent inclusion of two searchengines totheINDD. The firstoneis based on Structured Query Language and enables users to save their own specific queries, modify them, and update them every time if needed. In addition, a new querying system based on the same online Web user interface called INQuery has been implemented for researchers to assist them with their database queries, including selecting different fields fromtables and merging data automatically. Subjects can be selected based on a clinical core or NBGB basis, or on a predefined list of IDs. All the generated data are exported into Excel format for further research use.

3. Recruitment of patients and sample collection across clinical cores

Because of the labor, cost, and logistic implications associated with autopsy procedures, the NBGB selects subjects who are followed in the clinical centers, have detailed clinical information, and, in most cases, additional biofluid, neuroimaging, and genetic data/samples to be included in the brain donation program. The Alzheimer’s Disease Core Center (ADCC), the Penn Memory Center, the Frontotemporal Degeneration Center, the ALS Center, the Parkinson’s Disease and Movement Disorder Clinic, and the Penn Udall Center for Parkinson’s Research each have protocols approved by the institutional review board to recruit patients, along with their clinical data, into research studies. In addition, these centers invite patients to participate in the brain donation program. Although the table fields that contain the clinical and demographic information from the different clinical centers differ, the recent integration of the National Alzheimer’s Coordinating Center FTLD module for use in the National Institute on Aging-funded AD centers will help increase the overlap between the data gathered by this core and the AD centers. Consensus meetings have been held to establish a set of common diagnoses categories to be used. Plasma and CSF samples are collected in the individual clinical cores as described previously [33,34]. In addition, the ADCC and the Penn Memory Center have collected serum samples.

4. Processing, tracking, and storing samples by the biofluids section

Biofluid samples are collected up to 3:00 PM during working hours to ensure that samples are processed after they are obtained the same day. Processing of plasma and CSF in the NBGB follows the same standard operating procedures (SOPs) as the Alzheimer's Disease Neuroimaging Initiative (ADNI) [35]. For CSF sampling, 4 hours of fasting is required, although it is not required for blood samples. CSF is collected using clear polypropylene tubes and aliquoted into 0.5-mL samples in 1.5-mL cryogenic tubes after collection without a centrifugation step. Plasma and serum samples are obtained using Lavander top K2 ethylenediaminetetraacetic acid (EDTA) tubes (BD Vacutainer, Franklin Lanes, NJ, USA) and serum separation (SST) tubes (BD Vacutainer, Franklin Lanes, NJ, USA), respectively. Samples are centrifuged at 3000*g* (equal to 1962 rcf) for 15 minutes at 4°C, and plasma samples are aliquoted into 2.0-mL polypropylene cryovials (Corning cryovials, Acton, MA, USA) fitted with a silicone washer to ensure an air-tight seal. CSF is aliquoted immediately without undergoing centrifugation. Samples from the frontotemporal degeneration and ALS centers are sent to the CNDR for processing after sampling, whereas the ADCC, the Parkinson's Disease and Movement Disorder Clinic, and the Penn Udall Center for Parkinson's Research all process their own samples and send them already aliquoted and in sealed containers with dry ice. For further details on the SOPs for CSF and other biofluid collection and storage, please see the Alzheimer's Disease Neuroimaging Initiative SOPs which are the same as those used in the CNDR.

Tubes are labeled with center, processing date, INDDID, tube number (unique for each vial banked), and sample type (CSF, plasma, or serum). The INDD contains the number and type of available aliquots from each sample (CSF, plasma, or serum), day of sampling, the INDDID, sample ID, and the physical location of the samples. The aliquots are stored at −80°C in freezers dedicated specifically for banking human biofluid samples. These freezers have alarm settings to monitor temperature (high alarm at −70°C, low alarm at −90°C). Freezers are connected to a Sensaphone to alert caretakers if the freezers' temperature is compromised so samples can be moved to another location.

5. Nucleic acid banking and genotyping

Peripheral blood or saliva is collected from all consenting living individuals for extraction of DNA. Blood in PAXgene RNA preservative tubes (BD, Sparks, MD, USA) is collected from selected individuals from families with known genetic mutations for extraction of total RNA. Blood and saliva samples for DNA are transported to the genetics laboratory and are stored at 4°C until extraction; RNA tubes are frozen at −80°C until needed. In addition, DNA is extracted from all frozen brain tissues collected in the NBGC. DNA and RNA extractions are performed with commercial reagents using manual or semiautomated procedures. Extracted nucleic acid samples are stored at −30°C (DNA) or −80°C (RNA). Sample receipt and testing are tracked using the workflow module of a custom-designed Progeny Laboratory Information Management System relational database (version 8.2.06; Progeny Software, LLC, South Bend, IN). Sample information—such as source, quality, quantity, and storage location—is uploaded into the Progeny database and linked to the individual in the database. Each individual in Progeny is linked to a global database

individual by the IN-DDID. In the majority of cases, a third-generation pedigree is obtained by a genetic counselor to document any family history of NDs and ethnicity. Individuals in the Progeny database can be added to a pedigree so that the relationship between different individuals in a family and their clinical status can be visualized easily. Interested and available family members of primarily familial cases are offered participation in the research studies.

Using the provided Progeny open database connectivity drivers, an external interface to Progeny's internal database was implemented. This in-house-built interface provides the ability to import the matching clinical data fields from the INDD to the Progeny database and vice versa for genetic information. The importing feature is activated when a user creates a new patient record in Progeny. When a matching patient is found in the clinical databases, all the matching data fields are imported from the clinical database to the Progeny database. This automated transfer of data eliminates errors associated with manual entry. Furthermore, the INDD also transmits data to the Progeny database on a nightly scheduled data push. This feature allows two databases to have the identical data and be in synchrony. This feature prevents mismatched data in two different databases and provides the genetics group access to the most up-to-date clinical and neuropathological diagnoses, because these may change over time with new ND research advances.

The genetics core performs a variety of standard and unique genetic tests to evaluate for pathogenic mutations and genotype risk alleles. Because the genetics core is in a unique setting serving patients with AD, PD, FTLD, and ALS, a Pan-Neurodegenerative Disease-Oriented Risk Allele (PANDORA) panel was designed to provide a method for comprehensive genotyping of relevant common mutations and single nucleotide polymorphism (SNP) risk alleles in a time- and cost-effective manner for all four disease groups. PANDORA, performed on a Sequenom MassAR-RAY instrument, includes 52 single nucleotide genetic variants selected to represent the top hits from published genomewide association studies (GWAS) and the interests of the researchers in the different cores. A targeted next-generation sequencing panel has been designed to screen for known gene mutations/variants and to discover novel mutations in targeted genes.

Genetic testing and genotyping results—for example, apolipoprotein E genotype, microtubule-associated protein tau (MAPT) haplotype, and/or gene mutation status—are entered into custom-designed Progeny fields. The decision of which DNA sequencing or genotyping to perform on each sample is based on prior arrangements (apolipoprotein E for all ADCC cases), case-specific features (familial case), and/or special projects [e8–e10], which are reviewed at a biweekly genetics case conference. Relevant genetic information (sequencing and genotyping) are synchronized nightly to the INDD from Progeny. Only selected individuals from each clinical group have access to the genetic information to limit access to genetic information only to those individuals with a need to know. A genetics table with summary fields of gene sequencing results and SNP genotypes is available in the INQuery system to perform searches in combination with clinical, biomarker, and neuropathological features. In addition, subjects who have been included in previous GWAS studies [21,e11,e12] are identified in the INDD, and a graphic–user interface is being developed to extract specific SNPs for all the subjects. Any presymptomatic (prodromal) at-

risk individuals from families with a known autosomal dominant mutation who wish to learn their genetic status are advised on their intent to access this information. However, this information is then regenerated by clinical testing performed in a Clinical Laboratory Improvement Amendments (CLIA)-certified molecular pathology laboratory at the Hospital of the University of Pennsylvania (HUP).

6. Brain and spinal cord processing and storage

As described earlier, patients with NDs are recruited into the autopsy program by the different clinical cores. An informed consent is signed by the patient and/or legal guardian of the patient [36]. When the deceased patient is in the Philadelphia area, the brain and spinal cord extraction is undertaken at the HUP morgue. Information is provided to the families with instructions that the funeral director or nursing home should contact HUP pathology staff to arrange transportation to the hospital as soon as feasible. Several phone numbers are provided so families are able to reach laboratory staff 24 hours a day, 365 days a year. At time of death, a HUP medical doctor contacts the family to obtain final consent of tissue donation for research purposes. The funeral director then works with the family to arrange transport to and from the hospital.

When the patient resides in the region of the HUP, HUP pathology assistants are available for brain removal at local hospitals or funeral homes for transport of the brain back to the HUP autopsy suite. Patients who lived outside the region are considered remote autopsies. A national company (Regional Pathology and Autopsy Services, Oakland, CA) is contacted to hire a local pathologist. In these cases, a brain removal and shipping protocol is provided to the private pathologist, who separates the cerebral hemispheres. The left hemisphere and brain stem are immersed in 10% neutral buffered formalin for 2 weeks whereas the right hemisphere is sliced coronally and frozen before shipment to the CNDR. Although previously the whole spinal cord was obtained for ALS cases only, in the new informed consent all patients are asked to donate the brain and spinal cord independent of clinical diagnosis.

The autopsy-related information is contained in two tables in the INDD. The first one contains the demographic, macroscopic, and diagnostic data (Table EA1). Most of the fields included in this table are drop-down menus to avoid typing errors or the use of nonstandardized categories. The final clinical diagnosis is established and confirmed at the time of death by the clinician who monitored the patient. To use standardized diagnostic categories across the different clinical cores, a consensus meeting of all the directors of the clinical cores is periodically held to revise a common set of diagnostic categories across centers. The second autopsy data table in the INDD contains the semiquantitative scores for all the areas included in the routine research diagnostic workup (Table EA2), with fields for additional neocortical, subcortical, brainstem, and spinal cord areas.

The sampling procedure is performed by a prosector and an assistant. The prosector is responsible for the brain dissection and writing the gross report under the guidance of a board-certified neuropathologist. The assistant prepares and presents the specimen containers during the dissection and records the prosector’s observations for later entry to

the database. After demographic information, brain weight and postmortem interval (defined as the time between death of the patient and the autopsy procedure) are obtained, and the brain is examined for any macroscopic lesions. The circle of Willis and the basilar artery are examined, and the extent as well as the severity of atherosclerotic changes are noted using a semiquantitative scale. The surface pH of the brain in the frontal and occipital cortex is measured and recorded at this time as a quality control measure of the samples [37,38]. The brainstem is separated from the hemispheres with a cut between the superior and inferior corpora quadrigemina and then the hemispheres are separated with a cut along the interhemispheric fissure. At this point, pictures of medial and lateral aspects of the hemispheres and the rostral view of the brainstem and cerebellum are taken. In addition, any abnormal macroscopic findings are also documented. Cortical and subcortical samples are taken from the left hemisphere for odd-numbered autopsy cases, whereas the right hemisphere is selected in cases with even autopsy numbers. In cases with an asymmetric involvement, sampling may be changed or may become bilateral. Sampled areas are detailed in Table EA2; all areas are fixed using 10% neutral buffered formalin for one set of blocks, and 70% ethanol with 150 mmol NaCl for another set of blocks. This dual-fixative approach takes into account the fact that some epitopes or proteins are sensitive differentially to cross-linking vs. other denaturing fixatives [39–41]. Before cutting, the following areas are marked with ink to facilitate sampling and tissue bagging at later stages: the primary motor cortex is marked in black, the primary sensory cortex is marked in green, and the angular gyrus is marked in blue. Then, the selected hemisphere is cut serially into consecutive 1- to 1.5-cm-wide sections, and cortical and subcortical sections are taken (Table EA2). The tissue left from the sampled hemisphere as well as the sections from the contralateral hemisphere (also sectioned in 1- to 1.5–cm-wide sections) are frozen at −80°C. The brainstem is cut every centimeter, and sections for the midbrain (including the substantia nigra), upper pons (including the locus coeruleus), lower pons, and medulla are obtained. The cerebellum is also sectioned serially. A sample containing the dentate nucleus is fixed, and a cerebellar folia block of approximately 36 mm^3 is harvested for DNA extraction in the genetics core. The remaining brainstem and cerebellar tissue are placed on foil-lined stainless steel trays and stored at −80°C overnight. Any focal lesions such as suspected strokes, tumors, or other pathologies are also photographed and sampled. The following day, sections are bagged individually in serially numbered, resealable zipper storage bags, and the areas included in each bag are noted and included in the INDD. When classified, the samples are stored long term in −80°C freezers, and the freezer, shelf, and rack locations are entered in the INDD. The availability of frozen and fixed sections for each case is recorded in the tissue tracking table (Table EA3). The same security measures described for the biofluid samples are implemented in the freezers used for tissue storage. Nevertheless, brains with different diseases are distributed evenly in the different freezers to avoid a thaw that could affect all the samples corresponding to a specific disease. Notably, such an event has not occurred in the more than 25 years of the CNDR brain bank. Also, the day after the autopsy, harvested tissue sections are cassetted and, after another fixing cycle, they are embedded in paraffin and cut into 6- to 10-μm sections for diagnosis. A more detailed description of tissue processing and storing has been described previously by CNDR investigators [39,40] and by other groups [42].

For the routine diagnostic procedure, the sections detailed in Table EA2 are stained with hematoxylineosin to quantify neuron loss and gliosis, and the following primary antibodies are used for the detection of abnormal proteins: nab228 (monoclonal antibody [mAb], 1:8000, generated in CNDR) [43] to detect amyloid deposits and for Thal staging [44], phosphorylated tau PHF-1 (mAb, 1:1000, a gift from Dr. Peter Davies) to detect phosphorylated tau deposits, pS409/410 (mAb, 1:500, a gift from Dr. Manuela Neumann) to detect phosphorylated TDP-43 deposits [3], and Syn303 (mAb, 1:16,000, generated in the CNDR) to detect the presence of pathological conformation of α-synuclein [45]. Primary antibody binding is visualized with the avidin–biotin complex detection method (VECTASTAIN ABC kit; Vector Laboratories, Burlingame, CA) with ImmPACT diamino-benzidine peroxidase substrate (Vector Laboratories) as the chromogen. In addition, thioflavin S is used to grade the presence of neuritic plaques and to determine the Consortium to Establish a Registry for Alzheimer's Disease score [46,47]. All changes are rated using a semiquantitative scale (0 point, no changes; 0.5 point, rare; 1 point, mild; 2 points, moderate; 3 points, severe) and these gradings are introduced in the INDD. Also, for every studied area there is a string field to note any additional comments. All cases are reviewed by a board-certified neuropathologist for quality assurance and accurate grading.

The NBGB holds a training seminar and discussion of the autopsy protocols and procedures every 6 months, and there is a laboratory manual that contains all the sectioning, rating procedures, and bibliographic references for neuropathological diagnosis, and it is updated regularly. Moreover, a small primer that contains all the key sections to guide dissection is used during the dissection.

7. Examples of studies using samples from the NBGB

The framework that has been established during the past two decades in the NBGB has enabled researchers to pursue a large number of diverse studies that address NDs from different approaches. Some of these studies have defined brain deposits that characterized new subgroups of FTLD defined by TDP-43 [3] or fused in sarcoma protein pathologies [2]. These findings have been followed by a clinical and neuropathological characterization. The spectrum of the TDP-43 proteinopathies has been studied further [e13] and FTLD-TDP-43 has been characterized further based on the pattern and morphology of the deposition of TDP-43, which correlates with genetic findings and clinical phenotype [7,48]. The genetics core led a GWAS study based on neuropathologically diagnosed FTLD-TDP-43 cases that identified *TMEM106B* as a risk factor for FTLD-TDP-43 [e12], and the pathway implicated in the disease has been characterized recently by Chen-Plotkin and colleagues [e14]. The recently described *C9orf72* expansion has also shown a characteristic pattern of ubiquilin deposition in patients with ALS and FTLD-TDP-43, as described by Brettschneider and colleagues [e9], and the clinical characteristics have also been reported [e15]. Another example of translational research is the discovery by Cohen and colleagues [49] of how tau acetylation impairs tau–microtubule interactions and promotes pathological tau aggregation, and the following study by Irwin and colleagues [41] that characterized the deposits in AD and cases of FTLD resulting from tau immunoreactive deposits.

Other studies have sought to characterize neuropathological changes that underlie specific clinical features of NDs, such as dementia in PD [e16] or executive dysfunction, disease progression, and clinical symptoms in ALS [e17,e18]. Biomarker studies have dealt with the differential diagnosis of different NDs using neuropathologically validated diagnoses [14,34], evaluated the importance of coincident neuropathological diagnoses and the bias introduced by the use of a clinical diagnosis in a sample of consecutive neuropathologically validated cases [14], compared different CSF analytical platforms and derived transformation formulas [e19,e20], and investigated the possibility of using magnetic resonance imaging as a surrogate for CSF biomarkers [e21]. The genetics core not only has provided genetic information on the studied patients [e9,e15], but also has collaborated in large, multicenter GWASs [21,e11] and discovered *TARDBP* mutations that linked this gene and its encoded protein TDP-43 to the neurodegenerative process in TDP-43 proteinopathies [e22], as well as the studies described earlier. In addition, biosamples are available to outside investigators (for complete details, see [e23]).

8. Conclusions

In summary, we have presented an integrative approach that exemplifies the multidisciplinary integration of basic, translational, and clinical research teams in a single, dynamic framework centered on the NBGB, which gathers the clinical, biomarker, and autopsy samples and information of well-characterized subjects and enables different teams to gather efficiently large and rich data sets for studies across different NDs.

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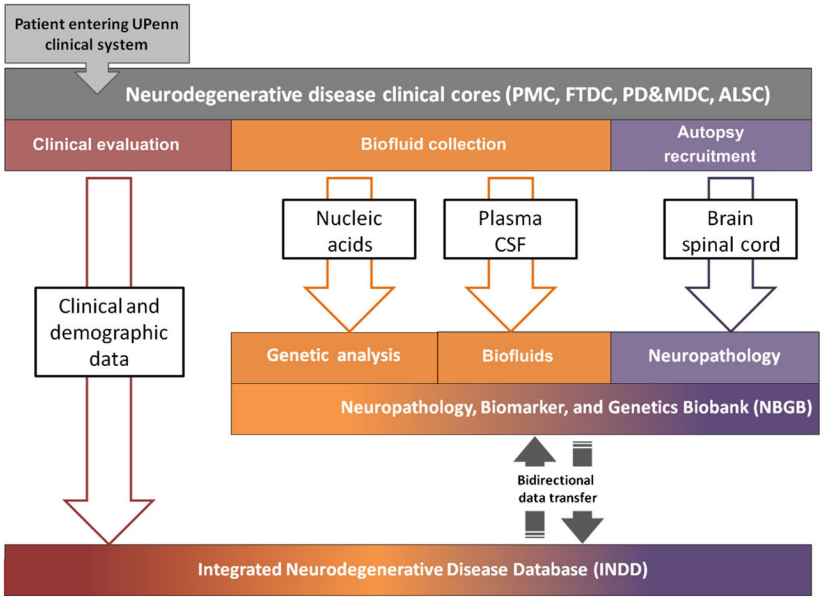

Fig. 1.

Description of clinical, data, and sample integration in the Neuropathology, Biomarker, and Genetics Biobank. UPenn, University of Pennsylvania; PMC, Penn Memory Center; FTDC, Frontotemporal Dementia Center; PD&MDC, Parkinson's Disease and Movement Disorder Clinic; ALSC, Amyotrophic Lateral Sclerosis Center.