NIH Alzheimer's Disease Centers Panel Recommendations

The Unique Role of Alzheimer's Disease Centers in the NIH Research Portfolio

Alzheimer's Disease Centers (ADCs) are at the nexus of fundamental mechanistic research, clinical trials, population health research and health services research. Over the past 30 years, ADCs have helped set standards and expectations for clinical care by informing translation of scientific advances into clinical practice, conducting research that improves patient care and community based prevention interventions, and contributing to basic scientific discovery. Numerous unique opportunities exist within, across, and outside the ADC program to contribute to the continuous evolution in the AD research landscape. Building on historical strengths and successes, a strategically revised ADC program can facilitate achieving National Plan to address Alzheimer's Disease objectives through increasing flexibility and collaboration by leveraging resources, capabilities and research participants across the network of centers by:

> Studying AD and related dementias (ADRDs) in humans, including use of real world clinical data, to test hypotheses about disease pathogenesis and heterogeneity, risk and protective factors, with the aim of improving diagnosis, prevention and treatment;
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> Accelerating translational research advances from the bench to clinical practice;
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> Developing strategies to address prevention of AD including identification of earliest markers, informing development of candidate trial designs and defining risk/protective factors;
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> Becoming a more cohesive and integrated program to strengthen accessibility and broaden the use of all ADC resources by fostering collaborations with the research community;
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> Establishing an overarching structure across the Center Program to unify goals, ensure that resources are most efficiently utilized, and is suitably flexible to facilitate the ability of the ADC network to respond to a dynamic scientific environment while incorporating the needs of all stakeholders including appropriate representation from the NIA, AD researchers, clinicians, research participants and their families, and other groups with longstanding interests in AD and related dementia research.

Recommendations:

A: Gaps in disease mechanisms and risks:

Expand the set of tools to identify knowledge gaps in disease mechanisms/risks, clinical outcomes and prevention strategies.

Clinical disease is not merely a unidirectional vectorial pathogenesis, but a balance between simultaneous neurodegeneration and resistive compensatory mechanisms, with a net balance of degenerative progression in clinical disease. Compensatory mechanisms that contribute to disease heterogeneity and resilience require prospective consideration in studies designed to elucidate gaps in disease mechanisms, risks and therapeutic target identification. With these considerations:

- Strategically expand efforts to conduct cutting edge research on mechanisms and biomarkers of risk in pre-symptomatic individuals who will progress to dementia in the context of parallel studies in cognitive resilience for the purpose of prioritization and validation of the most promising signals and targets.

- Utilize the breadth of the ADC program to help define the medical, cognitive and functional predictors of decline, compare existing and novel outcome measures, and validate changes in known and/or novel biomarkers of disease progression.

    - Develop new measures of risk, tapping into constructs that are currently measured poorly or incompletely, e.g., lifespan exposures, cognitive reserve/resilience, sleep, daily function, etc.

    - Develop new outcome measures such as innovative cognitive assessments, mHealth (mobile health) approaches, neural function assessments, etc.

- Across the ADC program, identify meaningful indicators for participant stratification and endophenotyping to improve assessment of early signs of pharmacologic and non-pharmacologic therapeutic efficacy and to aid in hypothesis generation for identifying knowledge gaps.

    - Improve interactions between ADC clinical cores and clinical trials through development of new ways to stratify participants, to assess target engagement and to measure outcomes.

    - Ensure recruitment of novel types of cohorts at high risk (age, genetics, co-morbidities, cognitively normal individuals with amyloid- and/or tau-PET positivity, all stratified by race, ethnicity and gender) with careful biomarker characterization.

    - Conduct assessments both prospectively and at intervals during and following interventions to enable validation of diagnostic criteria and treatment effects, including impacts of poly-pharmacy which is a frequent confounding factor in this population.

- Incorporate opportunities to include the development and validation of environmental, wearable, and remote personal monitoring technology for high frequency sampling and naturalistic assessment of disease symptom onset and progression.

    - Evaluate their use as enrollment criteria and as outcome measures in interventional studies (pharmacologic and non-pharmacologic), and for additional contributions to diagnosis and treatment over usual clinical measures.

- Foster education and support of research participants and families to ensure that clinical endpoints are important and clinically meaningful, both in novel prevention studies as well as treatment in established disease.

    - Enable input on patient-oriented outcomes and quality-of-life measures in evaluations of optimal care practices.

    - Develop programs for ongoing feedback from research participants as sources of learning and information for ADCs to improve bilateral communications.

- Because mixed dementias are more common than pure AD, enhance opportunities to describe the co-occurrence of neurodegenerative and other pathologies (particularly vascular pathology, but also others to ensure that complex etiologies are captured for study) from preclinical asymptomatic stages to dementia and death, utilizing structural/functional imaging, biomarkers and neuropathology.

B: Clinical research capacities: Clinical research remains the central activity of each ADC, and has the fundamental purpose of enabling human-based and translational research on AD and related dementias.

- Convene a panel of experts, comprised of ADC Directors and individuals external to ADCs, to provide advice and identify the most important research goals that will capitalize on the combined assets across the ADCs to address the objective of preventing and effectively treating Alzheimer's disease by 2025. The panel's activities will:

    - Establish a center-wide goal for the overall population of participants, including sample size and recruitment strategies of different subpopulations reflecting appropriate ranges of ethnic, racial and cultural diversity, and across clinical stages of disease (from pre-symptomatic to advanced) using good epidemiological principles across the ADC network.

    - Streamline as much as possible the standardized data collection to meet the scientific goals and promote increased opportunities for additional synergistic work. Analyze the Uniform Data Set to determine which variables provide the most meaningful contributions for AD and related dementias, while developing capacities to merge UDS requirements with local data collection scales and measures to enable enhanced longitudinal and cross-sectional research.

    - Consider neuropsychological tools that will contribute to identification and understanding of cognitive and behavioral aspects of mixed dementias, disease sub-types and disease heterogeneity.

    - Periodically evaluate standardized procedures applicable to clinical practice, including: accepted clinical and psychometric measures, biomarkers (imaging, tissue/fluids), longitudinal observation, innovative assessment tools, methods to acquire brain autopsies, and CLIA certification for sharing of relevant data with research participants and families.

    - Consider engagement of families, community partners, and professionals to develop further research on dementia care services including neuropsychiatric challenges, with a focus on improving services to patients and caregivers across the spectrum of disease. Incorporate focus on special needs for caregivers in cases of mixed dementias and/or ADRDs such as FTD and DLB, which often create significant unique challenges that differ from those in AD. Establish independent panels of advisors from the public to evaluate impact.

    - Receive regular reports from ADCs on progress made toward achieving these aims, and on changes that have been implemented when deemed necessary.

- Utilize high quality data collected during clinical care to leverage real world clinical information, as feasible, into research data to evaluate cross-correlations between research tools and clinical methods, to study the utility of biomarkers and other diagnostic measures, to reduce duplication of effort, and to enable caregiver research. This will provide opportunities for additional analyses overall, while also reducing research participant burden and research costs.

    - Encourage research participant consent to provide access to their clinical records in order to augment research efficiency.

    - If a diagnostic clinic is present, coordinate data collection efforts to streamline cross-referrals for clinical care and research participation.

    - Solicit feedback from community and health system referring physicians with consideration of quality assurance, process evaluation and cost-utility measures to inform and improve these activities.

- While it is recognized that each Center will recruit research participants that best serve the scientific goals and research agenda/demography of the specific center, and focus data collection on the variables that are most scientifically relevant to their prioritized objectives, NIA should create a centralized recruitment facilitator that will aid the clinical research and clinical trial efforts across centers in the following ways:

    - Expand research in the areas of recruitment and retention in AD and ADRD, including autopsy consent. Further develop tailored recruitment strategies and related materials, including brochures, videos, online content, pre-post event assessments, etc., that can be adapted individually at each center.

    - Enable ADCs to recruit, to the degree possible, individuals from specific populations (e.g., ethnic, racial, social groups, high cardiovascular risk load, etc.) that are accessible in a local context from both clinical and community settings, with the goal of strengthening the diversity of the overall population across all Centers.

    - Ensure inclusion of research participants across the Center network that represent the full range of disease, including those eligible for primary and secondary prevention up to those in the moderate to late stages of the disease in order to inform symptomatic therapeutic development at later disease stages, and support research participants through autopsy acquisition.

    - Support opportunities to identify disease- or performance-related multi-morbidities, pre-dementia cases and risk/protective factors amenable for prevention and treatment interventions, widening the scope of the ADC network research to collaborate with already well-described epidemiologic cohorts and/or initiate new cohort studies.

    - Seek opportunities to extend outreach by incorporating caregivers into research, where appropriate.

    - Encourage recruitment of staff, scientists and trainees that represent a range of racial and ethnic diversity that aligns with the local research participant demography.

    - Establish educational programs for primary care providers including nurse practitioners and physician assistants about AD and ADRD clinical trials and recruitment strategies to enable better cross-communication and engagement with ADC efforts.

        - Capitalize on technology-based training options to provide wide-spread educational opportunities (e.g., ECHO Dementia Program for telemedicine networking).

        - Work with people and their physicians in providing understandable information about their assessments and the use of tools that are pragmatic in the clinical arena and more likely to be utilized outside of research.

    - Improve and share evaluation methods (e.g., pre-post event assessments) to determine return on investment for recruitment efforts.

- Conduct studies to validate novel and emerging endpoints with the aim of comparison to clinical and pathological gold standards of diagnostic criteria, evaluation procedures, and clinical follow-up.

    - Through ongoing longitudinal studies, enhance deep phenotyping with clinical, cognitive, behavioral, functional, imaging and biomarker characterization, with submission of high-quality data to NACC.

- Incorporate digital biomarkers (e.g., wearable and passive sensing, computer use monitoring) into clinical assessment working in collaboration with relevant NIH (e.g., CART) and industry entities.

- Refer well-characterized participants into ADC projects, clinical trials and other research studies.

- Establish a "meta-registry" across ADCs of people willing to participate in future research studies, including: 1) a sizeable group of well characterized potential research participants, and 2) minimally evaluated "trial ready" individuals who could participate in therapeutic trials aimed at specific disease stages or conditions.

    - Expand interactions and integration with existing registries and matching services, e.g., Trial Match, Brain Health Registry, Alzheimer's Prevention Registry, etc.

    - Develop approaches to recruit and maintain these registries across centers, as well as to assure that registry research participants are not overburdened.

    - Explore opportunities to facilitate community based trials, in addition to highly selected and potentially biased clinical populations.

    - Utilize the registry to facilitate rapid enrollment in clinical studies.

C. Maximize value of neuropathology expertise across ADCs: Autopsy continues to be an invaluable component of ADC activities, providing a national resource for expertise in the pathology of neurodegenerative diseases. Postmortem examination remains the gold standard by which to: confirm diagnostic criteria and clinical diagnoses, understand the prevalence of dementia subtypes including those with mixed pathologies, validate imaging and biofluid biomarkers, evaluate therapeutic response, and identify the major therapeutic targets for AD and ADRDs.

- Maximize post-mortem rates across the ADC network, particularly for clinically well-characterized research participants (including those from other research studies and clinical trials) and those of particular interest (e.g., unique populations and rare clinical presentations for future understanding of atypical sub-types that may not be currently recognized).

    - Improve autopsy consent processes for research broadly, to help achieve diversity.

    - Survey availability across the ADC network and NACC to identify gaps in available autopsy material from cognitively normal individuals with useful prior clinical characterization. Augment approaches to increase this resource as deemed necessary, e.g., through establishing interactions with local medical examiners, etc.

- Prioritize post-mortem evaluations according to those that are optimal, mandatory and then optional recognizing that neuropathology is a limited resource and cannot be applied to all research participants.

- Build on existing efforts through NACC to establish a central, publicly interfacing database registry of all stored and banked autopsy materials related to ADC research participants (including the diagnostic slides and paraffin tissue blocks in pathology department archives and wet and frozen banked tissue).

    - Establish transparent guidelines for acceptance, retention, and sharing of tissue and data for research purposes to eliminate barriers and facilitate broad access to samples for research.

- Assess scientific value of late stage brains in freezers, both current and future. Develop a protocol for addressing any excesses, while maintaining those that are of value to other researchers.

- Establish mechanisms for digital slide scanning and electronic image sharing/analysis of neuropathologically characterized tissue sections.

- For all autopsy cases (not just those with UDS), facilitate DNA extraction, and collection of biosamples (brain and biofluids for molecular multi-omics profiling) for storage through NCRAD when this is not already available through existing processes.

- Continually evolve standard protocols of assessment and tissue banking, in parallel with advancing clinical and biomarker research, through ongoing communication with imagers, clinicians, clinical trialists and experts in other disciplines.

    - Modify prioritized regions for anatomical sampling to match ROIs based on emerging PET targets (i.e., tau-PET and other novel PET targets as they are developed) and ROIs associated with specific therapeutic targets such as locus ceruleus for adrenergic therapies, dorsal raphe for serotonergic therapies, etc.

    - Establish interactions with therapeutic trial sponsors (academic and industrial) to obtain autopsy tissue from therapeutic studies (both pharmacologic and non-pharmacologic) to evaluate pathological signals of outcomes (both responders and non-responders) for post-hoc analyses of subject appropriateness, adverse effects, confounding co-morbidities and target engagement.

- Encourage application of novel innovations in quantitative neuropathology technologies/methods of assessment as they develop, beyond the standard diagnostic approach.

- Expand opportunities for autopsies beyond UDS and clinical core participants when they facilitate AD and ADRD research, including representation of a broad population of cognitively normal and impaired individuals.

- Establish and publicize a cost structure for neuropathology services that allows other ADCs, non-ADC research programs and families access to their neuropathology expertise, including services that neuropathology cores can provide.

- Create opportunities for the training of neuropathologists in the sub-field of neurodegenerative disease research.

D: Translational research: Accelerate translational research across the spectrum of AD, ADRDs and mixed dementias using healthy cognitive aging and cognitive resilience as comparators, with a strong focus on understanding disease heterogeneity. Promote ADCs as a critical resource for disruptive and transformative translational research.

Drug discovery and preclinical drug development components:

- Increase bidirectional communication between ADCs and NIA translational research program directors to ensure ADCs are aware, and take advantage of, NIA and trans-NIH translational efforts, including new initiatives on cognitive resilience to AD risk and drug repurposing/combination therapy development. Encourage NIA translational program directors to incorporate clinical assets afforded by the ADCs that will strengthen these translational programs.

- Utilize novel animal models generated by NIA translational center (and other similar efforts) for target and/or biomarker validation. Support incorporation of clinically evaluated biomarkers into animal studies to improve predictive value and cross-validate target pathways between animals and human studies.

- Explore linkages with other emerging initiatives relevant to rapid progression of druggable pathways, e.g., LINCS and Tox21.

- Support approaches for the development of lead compounds, repurposing of existing drugs, combination therapies, and for novel interventions for the prevention and/or treatment of AD and ADRDs:

    - Leverage NIA and NCATS translational programs and partnerships for promoting access to drugs off the shelf from pharma and other sources to probe novel pathways and explore surrogate outcome measures where feasible in preclinical models, and to support cross-validation (or demonstrate lack thereof) in human trial bio-samples.

    - Translate results from NIA's genetics and translational programs (e.g., ADGC, ADSP, AMP-AD, etc.) to inform target validation studies.

    - Expand collection of additional biomaterial for the full range of -omics studies to a larger scale, as is being done with AMP-AD.

- Engage with the pharmaceutical/biotechnology sector in an ongoing manner to explore mutual interests and collaborative opportunities in drug discovery from basic research on target identification/validation through target mechanisms/validation and clinical development.

Clinical research components of translational research:

- Expand interactions with clinical trial and other therapeutic recruitment initiatives (e.g., ADCS, ATRI, GAP, etc.).

- Strengthen support for recruitment challenges being experienced by longitudinal observational studies that impact on developing knowledge of disease pathogenesis (e.g., ADNI).

- Expand biomarker and clinical data, including potentially confounding issues related to poly-pharmacy as well as real-world data that can be gathered with environmental and wearable sensor technologies, for hypothesis generation and validation as treatment responses in interventional studies.

- Identify and recruit high-risk populations in pre-symptomatic stages of potentially incipient disease for prevention initiatives.

- Include sufficient numbers of underserved populations and populations with unique risk/protective factors to embrace the heterogeneity inherent to AD, ADRDs and co-morbidities.

- Engage with local communities that are representative of the racial, ethnic, socioeconomic and cultural composition of their referral area to establish relevance across diverse populations.

- Establish expertise in implementation and dissemination research and access to well-coordinated community-based health care systems and clinics that will expedite conduct of studies for rapid adoption of evidence-based research findings into clinical practice.

Biomarker validation, endophenotyping and standardization:

- Participate in, and provide leadership in ongoing efforts to refine uniform SOPs for biomarkers that have demonstrated promise (e.g., imaging, CSF assays, RNAseq, genetic loci, including autopsy criteria) as disease progression markers.

- Incorporate novel biomarker exploration and validation (e.g., MRS, EEG/neurophysiology, novel imaging, metabolomics/ proteomics, continuous monitoring utilizing novel technologies, etc.) across studies of disease continuum. Ensure that such studies are conducted longitudinally in addition to cross-sectionally.

- Develop potential biomarkers for "related disorders" in addition to AD so that preclinical cases may be identified for possible intervention (e.g., alpha-Synuclein, TDP-43, etc.).

- Explore the utilization of biomarkers to drive novel clinical trial design, e.g., as surrogate outcomes in adaptive trials and for clinical subject enrichment strategies.

- Study the utility of various combinations of biomarkers in the above contexts using advanced statistical and analytical techniques.

- Establish panels of experts in innovative techniques and/or biomarker assays to consider whether/when standardization is appropriate within the ADC program.

- Characterize research participants (i.e., clinical core participants) using biomarker data to the most complete extent possible, especially for methods that are well accepted and standardized but also to provide evidence for the relevance of emerging novel biomarkers.

- Incorporate biomarker outcomes into responder analyses in clinical trials to establish potential relationships between biomarker movement and clinical outcomes in individuals who are responsive to therapies as potential theragnostic markers of treatment effects.

- In reporting novel biomarkers, clarify the purpose of the biomarker, experimental design and analytical methods to enable replication and validation.

- Prepare for rapid response to new reports of biomarkers to enable quick tests and replication using either samples acquired at a single Center or a cross-center collaborative model.

E: Cross-ADC interactions/networking: Transform existing Centers into a more coherent network that facilitates interactions and optimizes utilization of unique resources/capabilities contributed by individual ADCs that will enable more rapid development of knowledge related to disease progression, outcomes for people with AD/ADRD, and biomarker development.

- Develop a detailed central inventory database (not central repository) of the specimens, resources, capabilities and technologies of the individual ADCs and post this inventory to a searchable website so that qualified investigators throughout the AD/ADRD field can rapidly evaluate best sources of research materials.

- Increase the flexibility by which ADCs fulfill core requirements, with the possibility of synergistic sharing of competencies across the ADC network e.g.:

- All centers perform autopsies, but in cases where qualified neuropathologists may be lacking, provide an option of shared neuropathology expertise until such gaps are filled.

- Establish sub-networks of centers with strengths in specific thematic areas, i.e., ADRD-related modules (FTD, DLB, epidemiology, mHealth, bioinformatics, translational science, etc.) to create synergies and opportunities to expand more broadly across the full ADC network.

- Reorganize the ADC meetings so that they are thematically driven, and reflect cross-center research that holds the best promise for promoting interaction and advancing the knowledge base. Take advantage of the clinical and scientific expertise across ADCs to define and prioritize knowledge gaps that extend from basic and translational through clinical research.

    - Facilitate collaborative research focused on major unanswered core questions that are best answered by several centers working together.

- Expand collaborative opportunities by establishing Center-based workgroups (optional "Collaboration Cores") to develop and prioritize cross-Center projects with the aim of synergizing and expanding strengths in basic, translational/clinical research and data collection, and to establish cross-center training through clusters/subnetworks. Create "central navigator" mechanisms across "Collaboration Cores" to:

    - Catalogue and make accessible the existing interactions and collaborations.

    - Remove logistical impediments to collaborations such as contracts, material transfer agreements, regulatory and ethics considerations (including utilization of a centralized single IRB), and establish policies for data sharing/ownership, publications/authorship, etc.

- Augment the capacity of NACC to act as the clearinghouse for collaborative information such as available data, cohorts, services and projects seeking collaborators.

    - Facilitate access to the open science research ecosystem to support specimen sharing using existing NIA-funded infrastructure including NCRAD, ADGC, and NIAGADS.

    - Combine/integrate assets (i.e., patient cohorts, data sets, bio-samples, etc.) to afford greater opportunities for more highly powered collaborative studies and meta-analyses. Utilize global data catalogues and data aggregation approaches (e.g., GAAIN, EMIF).

F: Interactions beyond the ADC network: Develop strategic interactions across relevant NIH, VA, other federally supported Center programs, non-governmental organizations, and large epidemiologic studies.

- Promote interactions among multiple Centers programs that address the broad impacts and interplay of cognitive aging, co-morbidities and heterogeneity in disease and resilience to facilitate ongoing thematically focused collaborations and programmatic development, e.g.:

    - ADGC, ARTFL, CTSAs, LEFFTDS, PCORI, Pepper Centers, RCMARs, Roybal, Demography of Aging Centers, Shock, Udall, HRSA's Geriatric Workforce Enhancement Program, The Veterans Administration Geriatric Research Education and Clinical Centers (GRECCs), etc.

    - Build on recently released U24 FOA as foundation for enhanced collaborations across NIA's six Centers programs.

- Enable existing and emerging opportunities for research collaboration among Centers programs.

- Promote the use of common clinical evaluations among ADC and non-AD Centers as well as large epidemiologic studies to facilitate better comparisons and reciprocities among cohorts.

- Standardize collection of biospecimens and clinical data across Centers Programs.

- Adopt a Global Unique Identifier (GUID), as research participants may be shared across studies and Centers.

- Establish collaborative opportunities directly linked to NAPA, ADRD and other planning efforts that have yet to be addressed or require expanded effort.

- Plan joint meetings to address areas of common interest among Centers programs.

- Enhance collaborations with non-governmental organizations.

    - Expand communications between NIH, national/international non-profit organizations and foundations on activities that progress towards common goals.

    - Create additional opportunities for interactions with ADCs through ongoing activities such as participation in ADC meetings, and meeting of ADRD non-governmental organizations.

- Incentivize collaborations between ADCs and epidemiological studies for the development and/or testing of findings from clinical and basic research, e.g,: Religious Orders Study (Rush), Mayo Clinic Study of Aging/Rochester Epi Project, MESA (Wake Forest), Indianapolis Ibadan Study of Health and Aging.

- Enable expansion of opportunities for international collaboration, particularly for rare dementias.

- Develop further innovative mechanisms to foster such collaborations, e.g.:

    - Joint mentoring of fellows, including inter-professional education, trans-disciplinary approaches and cross-training in basic and clinical research.

    - Exchange programs, in which established scientists visit another laboratory to learn a new technique or establish a new collaboration.

    - Novel research partnerships among ADCs and related programs.

G: Infrastructural supports to enable prior recommendations: Modernize and expand the computer and data analytics systems required to facilitate interactions among the ADCs and broader research community.

NACC, NCRAD, ADGC, GCAD, NIAGADS and AMP-AD have provided invaluable productive benefits to academic work across the ADC landscape and more broadly within the AD/ADRD research field. These NIA-supported initiatives provide a structure on which further developments can be built. Further developments of such infrastructure should enable the following outcomes:

- Leveraging of existing data and computer systems to address the challenge of facilitating access to the rich ADC and related resources for samples and data.

- Provision of a unified federated resource sharing hub to find data and samples, both those common across multiple sites and those that are uniquely located.

- Incentivization for both data producers and data consumers to align with the federated system, and to ensure that the technical infrastructure is developed to support their needs.

- Promotion of access to ADC resources, both within the ADC program and with the larger AD/ADRD research community.

- Access to dynamic developments, i.e., new molecular and imaging data being generated from living and deceased research participants, and new clinical data being constantly updated.

Recommendations:

- Building on existing capacities within NACC and the phenotyping catalog under development at NIAGADS, determine their strengths and limitations in the context of the overall data infrastructural needs, and their further potential to optimize interactions more broadly across the research community.

    - Improve the visibility and use of data available through NACC on clinical core participants at ADCs.

    - Establish approaches for implementing electronic and web-enabled (e.g., tablet-based) data entry at point of contact with research participants, with appropriate considerations of privacy/ethics that will be required for de-identifying personal health information when uploading data to research databases.

    - Establish a task force to develop guidelines for data/sample sharing and review criteria across the ADCs and other collaborators that are consistent with researchers being able to emphasize their areas of interest and strength, but also provide shared resources that will have greater impact across the AD/ADRD research field.

    - Expand utilization of federated database models (such as GAAIN) to enable and incentivize accessible and facile sharing across the ADC network to support cross-Center collaboration and enable meta-analyses across the research community.

        o Consider establishment of a centralized informatics capability involving Centers with appropriate capabilities to interact across the ADC network to enable meta-analyses.

            - Develop a unified digital schema and ontology across ADCs as a shell that interacts with each ADC's database to afford integration of data collection (including biospecimen linking and tracking) in order to streamline access to data and provide opportunities for leveraging existing cohort studies across ADCs and other Centers programs.

            - Ensure adaptability to employ new statistical techniques and to host both existing and new unanticipated high-throughput measurement modalities as they are developed.

    - Make cross-center datasets updatable to leverage ongoing data collection over the course of an analysis.

    - Identify critical meta-data and data descriptors for archiving and sharing.

        o Organize and align with current NIH-activities to enhance creation of an integrated cross-Center coherent dataset that will support more transparent and consistent data

management practices across ADCs. Key use cases might include replication of discoveries to promote reproducibility.

- Assess the use of version control systems (e.g., SVN, GitHub) for archival, monitoring provenance, and incentivizing group use of data, analytical scripts and software.

- Ensure that data subsets and compute cycles be made accessible and computationally available, possibly in a compute cloud setting.

- Ensure that the platform has robust authentication.

- Consider community engagement metrics to identify which among the wide range of possible communities to engage, and to track community usage.

- Attract to these efforts participation of appropriately trained and talented experts in the areas of neuroinformatics and data mining.

- Develop metrics as measure of use, i.e., new discoveries, degree of infrastructural success, etc.

- Building upon efforts to modernize data analytic and bioinformatics capabilities, an effort should be made to modernize and standardize electronic data capture (EDC) and database structure across ADCs to better permit Center-Center and Center-NIH interactions.
  - Encourage the adoption of existing systems such as REDCap or LAVA for data capture and database structure.
  - Discontinue use of antiquated systems that cannot cross-talk with other systems or support big data analytics.
  - Promote data access via standardized EDC for data transfer to and from NACC, NCRAD, ADCG, GCAD and NIAGADS.
- Develop advanced data analytic capabilities (e.g., IBM Watson, Amazon Web Services) at local level.
- Develop a reward system for data/sample generators through frequency of use by others, and data/sample consumers who access data to encourage use and outcomes, with flexibility for generators to decide on co-authorship, review of resulting findings and disclosures (abstracts and publications) to enable cross-prioritization of respective studies.

- Promote access to ADC resources by non-ADC investigators within same institution, non-ADC institutions and additional Centers programs, and through sharing agreements with the pharmaceutical/biotechnology sector.

  - Within ADC program, align data science training and other activities to ensure effective discovery and use of resources.

  - Beyond ADC program, develop mechanisms to identify and engage investigators who are not associated with ADCs but whose cutting-edge research aligns with the goals of the ADC program.

  - Develop incentives for consistent data management among the data producers and consumers, with opportunities for feedback to enable improvements and more effective data sharing.

- Enable these activities through prospective development of appropriate contractual and ethics-related processes, e.g.:

- Development of templated participant consent agreements with clauses allowing data sharing, utilizing streamlined IRB processes as they are implemented, optimally employing single centralized IRB.

- Development of appropriate multiple data use agreements for access to data.

H: Further development of training programs: Enhance multifaceted training programs focused on improving research and clinical care workforce capacity across the Center network.

Recognizing that training is a critical component of all recommendation sections above and should be integrated within each, develop programs as follows:

- At the personnel level:

    - Identify and address obstacles that differ among various groups of personnel required to staff ADC efforts, i.e., clinicians already in practice, new clinicians, neuropathologists and researchers in both basic and translational disciplines, etc.

    - Facilitate the training of staff/clinicians from racially/ethnically/linguistically/gender diverse backgrounds (e.g., Athena Silver Award in UK – requirement for award is that there are women in all levels of leadership).

    - Expand junior faculty support for career development– transition to independent research careers by increasing pilot studies for early-stage investigators.

    - Create a path for staff scientists by taking advantage of K awards not traditionally used by the ADCs, such as the K25 for computational biologists, and K12 for preparing candidates for full independence.

    - Create focused personnel exchanges among Centers that leverage the broad network expertise.

    - Increase incentivization for development of additional neuropathologists, neuropsychologists, behavioral neurologists, geriatric psychiatrists, and geriatric internists across ADCs.

    - Develop approaches to attract information science specialists with (or who will develop) deep knowledge of AD and ADRD. Establish programmatic and compensation/remuneration incentives with consideration of alternative career paths that such individuals may be pursuing in order to motivate engagement with AD and ADRD research.

- At the programmatic level:

    - Adopt training programs and/or a common course to foster state of the art dementia diagnostic and treatment capabilities as well as cognitive health in aging to increase the workforce caring for older adults with dementia.

        - Seek opportunities to share the training programs/courses widely across various center programs and medical schools by collaborating with HRSA's Geriatric Workforce Enhancement Program, the VA's GRECCs, and others to translate AD and ADRD research into practice and academia through faculty development, integrating dementia content into health professions curricula and continuing education.

- Develop training and incentives for primary care physicians, nurse practitioners, and physician assistants to inform patients about clinical trials and recruitment with Geriatric Workforce Enhancement Program and CMS.

- Incentivize other Centers Program research career development initiatives to use ADC resources and vice versa.

- Develop new programs in team science, including multidisciplinary training that crosses along the lines of NIA's new training and fellowship programs (e.g., disease biology, data science, drug discovery, systems biology including disease modeling, neuropathology, epidemiology, neuroethics, and ethics of data re-use and cloud based analyses). Consider summer boot camps.

- Enhance cross-training of established clinical centers with emerging clinical centers.

- Support administration of training programs, e.g., T32.

- Explore further development of exchange programs (beyond AMP-AD) between basic and clinical scientists within ADCs, with research scientists embedded in the industrial sector (e.g., pharma, biotech, medical device companies, etc.).

    - Establish cross-training programs between ADCs and industry, e.g., rotations for physician-translational scientists for mutual knowledge exchange.