NINDS Strategic Planning Disease Panel
Final Report

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Introduction and Summary

THE TASK

Preventing, curing, and ameliorating the health impact of neurological disorders is the core mission of NINDS. The essential task of the NINDS Strategic Planning Disease Module was to explore how the institute can enhance the impact on disease burden of its research investment across the spectrum of diseases. Although the Basic, Translational, and Clinical Planning Modules together encompassed the breadth of research within the NINDS mandate, and each of these research domains has a crucial impact on progress against neurological diseases, the task of the NINDS Strategic Planning Disease Module was the most directly linked to the mission of the Institute: only the Disease Module approached its mandate from the perspective of the diseases themselves.

THE PROCESS

Story Landis, the Director of NINDS, appointed the panel's members early in 2008. The panel included basic and clinical disease researchers, as well as members of non-governmental organizations (NGO's). Among the members were neurosurgeons and neurologists who treat adults and children with nervous system disorders. NINDS provided extensive information that was compiled for this panel and for the basic, translational, and clinical planning panels. That material included background on the NINDS mission, budget, and organization; descriptions of the institute's initiative process; explanations and examples of how NINDS interacts with other parts of the NIH and beyond; details of translational, clinical, and resource programs; data on disease funding and on the burden of neurological disorders; and information about initiatives, workshops and disease specific plans that NINDS developed since the last strategic plan. The panel interacted through two days of face-to-face meetings supplemented by numerous phone and email exchanges. Discussion among panel members and NINDS program directors at the first meeting was especially useful in illustrating the role of program directors in the current organization and how priority setting and trans-NIH coordination work in practice.

CHALLENGES AND RATIONALE

With respect to its disease responsibilities, NINDS faces formidable challenges. Hundreds of disorders, both common and rare, affect the nervous system. Together, disorders of the nervous system affect people of all ages, cause an enormous burden in lost life, disability, and suffering, and cost billions of dollars each year in medical expenses and reduced productivity. Trauma, infections, toxic exposure, degeneration, inflammation, tumors, gene mutations, systemic illnesses, vascular events, nutritional deficiencies, and adverse effects of treatments for other diseases all can affect the nervous system. Compounding the challenge of confronting these diseases, cellular networks of the brain and spinal cord are intricate in structure, difficult to access, sensitive to intervention, and reluctant to regenerate following damage. To serve its mission, NINDS must balance basic, translational, and clinical research across the full spectrum of neurological disorders, with due consideration to scientific opportunity, public health

need, and finite resources, while sustaining the U.S. basic and clinical neuroscience workforce.

In keeping with the panel's assigned task, the Disease Module report directs attention to changes the institute should consider to better serve its mission. This emphasis on change should not be interpreted as abandonment of enduring principles that have been at the core of NINDS since its inception. NIH has a unique role in supporting basic research, including research that seeks to understand disease mechanisms. Common themes are emerging about what causes diseases and how they progress. These shared mechanisms are key to further progress toward understanding and treating the multiplicity of seemingly separate disorders. NINDS also drives critical aspects of translational and clinical research on neurological disorders. Rare diseases, with small markets, present the most compelling example, but aspects of large market disease research also fall largely to NIH. Some crucial areas that must be addressed – biomarkers, for example – are in the precompetitive domain; that is, the research can expedite therapy development, but too indirectly to reward investment for industry. At the same time, bold therapeutic strategies present risks and long development horizons that are not tolerable for the private sector. NINDS must also nurture critical links among basic, translational and clinical research to ensure that breakthrough findings on mechanisms of disease result in new treatments that reach affected populations and yield better health, without prolonged delays due to 'bottlenecks' in the research continuum. Finally, although the panel will recommend changes in how NINDS sets priorities and evaluates programs, the panel recognizes that the institute must continue to recruit and empower a strong cadre of program directors. Although minimizing administrative costs is important, program directors often have an impact on disease research that is well worth the cost.

Currently, the major drivers of the NINDS research portfolio – the institute's manifest priorities – include unsolicited applications that are reviewed and funded, initiatives developed in response to outside pressures, and the priorities identified by program directors. Investigator-initiated, peer reviewed research forms the largest part of NINDS disease programs, but a portfolio shaped by this process alone does not ensure optimal investment across diseases with respect to scientific opportunity and unmet need. NINDS-funded investigators do not pursue all neurological diseases either in proportion to their biomedical significance or the burden that they impose, nor does the research community quickly take advantage of all new research opportunities that arise from mechanistic advances or technological breakthroughs. Reasons for these shortcomings include the varying experience and organization of different disease communities who advocate and apply for funding, and incomplete knowledge of review panel members about public health priorities and program gaps. A "squeaky wheel" may justifiably provoke external pressures on NINDS directed toward a specific disease, but these external mandates do not always represent the best possible investment. Finally, a talented and dedicated program director can invigorate research on a disease, but the institute cannot afford a program director for each disease.

Recognition of the limitations of the current process by which NINDS sets priorities across diseases guided the recommendations made by the Disease Module. Following discussions at the first meeting, and subsequent discussions among panel members and NINDS staff, the Disease Module established four key priorities and assigned working groups to explore each of these further. As the subgroups discussed recommendations with the larger group, the interrelationships among these topics became increasingly apparent, and a fifth key priority topic related to optimization of treatment (translational-2 research) emerged. The subgroup reports that follow this introduction present detailed recommendations and the logic behind them. What follows here first briefly summarizes the essential recommendations from each subgroup and then highlights common themes and interrelationships among them.

MAJOR RECOMMENDATIONS

The first working group recommended developing a dynamic, biologically clustered, publicly accessible, relational database of neurological diseases. Such a resource would be highly valuable both to NINDS and to the scientific and lay community. The institute might build from the current disease lists to do this, recognizing that the public and government have strong historical ties to current disease names. A list that a) reflects current science, b) can change readily and dynamically in response to new advances, and c) captures in digital, searchable format key categories of disease mechanisms and burden would be optimal. Such a list would greatly facilitate recognition of unknown or untapped connections between diseases, enhance scientists' and the public's capacity to process rapidly accumulating information about diseases and genes, catalyze collaborative research within the research community based on recognition of biological overlap among diseases, raise public awareness about how research on diseases is interrelated, and further the goal of setting priorities across NINDS diseases, as described in the recommendations of the second working group.

The second working group described a new priority-setting process that would be systematic, comprehensive, and data-driven. The two-stage process incorporates a systematic environmental scan (or “landscape”) for unmet scientific opportunity within and across neurological disorders, taking into account the current state of knowledge and ongoing research supported by the NINDS, other institutes, foundations, industry and other groups. The first stage would help determine *within* each disease or disease group what stages of the research continuum might warrant a “push.” The second stage would focus on prioritizing the opportunities *across* diseases.

The third working group developed a prototype for the evaluation of disease initiatives. The group recommended that NINDS develop an evaluation plan for each initiative before it begins, recognizing that evaluation must be tailored to the initiative. Each initiative should clearly state goals and develop quantitative and qualitative outcome measures with input from appropriate outside groups. The evaluation plans should include mechanisms for providing early feedback, an interim assessment using predetermined benchmarks, and a formal review following completion of the initiative or within 5-10 years for continuing programs.

The fourth group explored and recommended opportunity areas for programs to facilitate disease research. The group highlighted the importance of NINDS in encouraging disease consortia. Because technology changes rapidly and often drives progress against disease, the group also recommended that NINDS engage an advisory group to help monitor emerging technological opportunities and develop a program to provide rapid access. Finally, the group described the importance of integrating systems-computational approaches with disease-oriented research.

As the panel's deliberations progressed, translational-2 research emerged as an additional - the fifth - priority topic. The panel concluded that the time is right for NINDS to invest in translational-2 research. Translational-2 research is hypothesis-driven research that identifies and measures barriers to translating clinical trial findings into widespread practice, and develops and tests models and strategies to overcome those barriers, in order to reduce the burden of neurological disease. The key, well-documented observation is that new knowledge from NINDS basic, translational (bench to bedside), and clinical trial research does not guarantee that new knowledge will be translated into improved population health. High quality research on the reasons for the incomplete transfer of new knowledge into practice (translational-2 research) informs efforts to address those barriers, completing the neuroscience research continuum from basic research to optimal health benefit for the public. Translational 2 research for neurological disorders currently receives little support and should become part of the NINDS portfolio.

COMMON THEMES

The substantive recommendations of the working groups overlap in several ways. For example, a biologically informed listing of diseases feeds into a systematic process that assesses the landscape within and across diseases; the opportunities identified through the landscape process will inform potential initiatives, such as consortia, as well as the outcome measures to evaluate initiatives arising from the process; and evaluations of initiatives will assist NINDS in understanding what works best to leverage its resources to meet its mission, including proposed efforts related to emerging technologies, systems approaches, consortia, and other potential high-yield, multi-disciplinary opportunities for enhancing progress in neuroscience research.

A common theme that emerged across virtually all topics is that NINDS should interact with others to accomplish the goals stated in these recommendations. The disease list discussion, for example, noted the importance of access by and contributions from key stakeholders in the NINDS mission, including the scientific community and lay public. Disease landscapes must include what research is supported by others than NIH, and NGOs might make valuable contributions in this respect as well as provide other valuable information to inform and maximize the utility of the priority-setting process. Similarly, crafting outcome measures that reflect goals of new initiatives might profit from input from outside of NINDS. Thus, a technology advisory panel could help the institute react quickly to new opportunities, NGOs might play a valuable role in encouraging disease consortia for clinical trials and biomarker research, and translational 2 research might engage professional societies, NGOs, and perhaps even health care provider

organizations. By engaging NGOs, the scientific community, and other groups with complementary expertise and resources, NINDS may find it easier to adopt and implement some of these ambitious recommendations. Importantly, such engagement would also powerfully foster cooperation, coordination, support, and mutual understanding between NINDS and other groups who are stakeholders in the NINDS mission to prevent and cure these diseases.

NINDS faces difficult choices in the current era. The transparent and systematic priority setting and evaluation processes recommended here should help the institute make good decisions, defend those positions, and assure accountability. An effective process to monitor opportunities across diseases could serve as a counterweight to unjustified external pressures. Rigorous evaluation of initiatives helps the institute to learn what works and to justify, to the scientific community, Congress, and the public, the use of limited resources for targeted purposes.

All working groups were mindful of practical and cultural barriers to implementing recommendations. Thus, the panel focused many of its recommendations on process changes that need not impose prohibitive financial or human resources costs. The most ambitious vision of a biologically clustered disease list might grow gradually, with help from outside participants, while recognizing the outside pressures to preserve historical disease names and reporting. The systematic process for setting priorities across diseases is also presented as a pilot process that could begin on a small scale; that recognizes set-aside funds are not the only way to address priorities; that enhances the current process of program director initiated initiatives rather than replacing it; and that acknowledges that the process itself should be evaluated and revised periodically to ensure that it is efficient and effective. Similarly, evaluations of initiatives need not require a costly outside contract. The panel also discussed compelling reasons why initiation of a relatively modest NINDS translational 2 research program could catalyze further efforts while making an important contribution to the field and the public's health that goes far beyond the direct financial investment.

FUTURE ISSUES

Because all NINDS research is relevant to disease, the disease module was necessarily selective in choosing topics for which it developed recommendations. The panel focused on issues that have an impact across the spectrum of diseases and were not the main focus of other modules. An implicit assumption underlying all key priorities is that NINDS must encourage cross-NIH coordination of disease research. For new initiatives, the panel recommended that in the future this should come early in concept development and be incorporated into the priority setting process. The panel also recognized the importance of other issues that, for practical reasons, were not the focus of recommendations. Among these is improving communication with the public. NINDS must explain better what it does and how it works, and provide more thorough, accessible information about neurological disorders. The recommendations here to improve transparency, enhance accountability, and engage NGOs as partners will help in this regard. Another crucial issue is training the future research workforce. Further consideration of training should explore not only traditional basic, translational, and

clinical workforce issues, but also consider ways to engage neuroscience graduate students (and even younger students) in disease and to support training in translational-2 research. The panel strongly recommends that NINDS adopt these issues in future planning activities.

The subgroup reports recommend changes that will affect how NINDS looks across diseases and sets priorities, how the institute monitors its effectiveness, and what it does to advance disease research. The burden of neurological disorders is large and growing, and NINDS must cope with limited resources, competing demands, and the inherent uncertainties of scientific and medical progress in fulfilling its mission to reduce that burden. The panel members recognize the great promise that disease research presents and are well aware that many innovative strategies to prevent and treat neurological disorders are emerging and moving toward reality. It is therefore important to emphasize the cautious optimism of the panel that NINDS investment in disease research – basic, clinical, and translational – has already provided major benefits to the public and is likely to yield significant further advances in preventing and treating neurological disorders by the time NINDS undertakes its next major strategic plan.

Priority 1 – Disease Module: Develop a revised approach to the current list of NINDS diseases that the Institute can use for new disease-based initiatives and programs.

(Scott Pomeroy, Lucie Bruijn, Stephen Back, John Park and Henry Paulson)

The Priority 1 Working Group was charged with reviewing the current NINDS classification and listing of diseases. Working Group members convened by phone conference on November 11, 2008, and followed up this meeting with email communications. Preliminary recommendations were presented to the Disease Module Panel at the second in-person meeting on January 14th, 2009. Based on fruitful discussions among panel members, the recommendations of Priority 1 Working Group were finalized as outlined below.

Though we begin our report with these final recommendations, we strongly encourage the reader to explore fully the subsequent sections on history of the current NINDS disease list, reasons for updating the list database, a suggested prototype for such a list, and potential challenges to creating a modernized list.

Recommendations

1. Develop a clinically and biologically clustered, web-based, relational disease list database that builds from an edited form of the current disease list. If properly executed, the new disease list could streamline the way in which NINDS inventories, analyzes and publicizes its research portfolio

-The disease list should link specific diseases to a variety of biologically and historically based categories as outlined above.

-The disease list will be most useful if it is readily accessible to NINDS staff, the lay public and the scientific community. The primary mission of NINDS – to understand and cure neurological diseases – is best served by making this list broadly available.

-Developing an accurate, informative, searchable and expandable disease list will be challenging given the inherent complexity of neurological diseases. NINDS should marshal the expertise of a diverse panel of scientists, clinicians, database experts and lay persons to create a disease database resource of maximal utility.

-Partnering with companies and groups with expertise in search algorithms (e.g. Google) could prove useful in developing a disease list database for the 21st century.

2. Make the database publicly accessible and devise a plan to disseminate it.

-Before launching the disease list, NINDS should be ready to publicize it so that the list is used appropriately by its intended audiences and to allow feedback on its utility to refine it in an ongoing fashion.

-Elements of such a plan might include: 1) an article on the NINDS website with a link to the list; 2) development and posting of a user's manual; 3) e-mail alert to all past and current grant applicants and grantees; 4) notification of the various scientific and clinical professional organizations, disease foundations and neuroscience-oriented departments in institutes and universities; and 5) generation of a Wikipedia page describing the disease list to ensure a prominent presence on internet search engines.

3. Dynamically update the disease list, once developed.

-For the disease list to be successful, NINDS must dedicate an annual effort toward its maintenance given the continued growth in our understanding of disease mechanisms. With the right stewardship, the list database should grow in importance to NINDS internally as well as to the scientific, medical, and lay communities.

Existing NINDS Disease List

NINDS covers a vast array of diseases within its research portfolio, estimated by some at roughly 600 diseases. Clearly not all of these are included or reflected in the current list of diseases used by NINDS for reporting purposes (*Appendix 1*). The development of this NINDS disease list presumably was driven by various forces over time: historically established disease entities; changes brought on by the advocacy of lay groups and other outside pressures; and new disease or categories of disease informed by molecular genetic discoveries. As new insights into disease mechanisms are uncovered, the NINDS disease portfolio increasingly accumulates additional "new" diseases (e.g., the profusion of distinct genetic entities in neurodegenerative and paroxysmal disorders). At the same time, NINDS is witnessing a conceptual consolidation of diseases into new categories as pathogenic processes are found to be shared among what had been thought to be unrelated disorders (e.g., Huntington disease, a motor neuron disease and numerous hereditary ataxias all caused by polyglutamine expansion). While in many cases these new disease categories may be obvious to select members of the scientific and clinical community, they are not reflected in what is now an increasingly antiquated NINDS disease list – essentially, the public face of the NINDS research portfolio. In certain cases, the names of diseases or neurological categories on this list may even have begun to outlive their utility to the scientific and medical community.

As an example of a more updated, detailed list of neurological diseases, we have included one developed at Boston Children's Hospital and provided to the Working Group by Scott Pomeroy (*Appendix 2*). This list, developed in part for coding purposes, illustrates the wide range of disease and hints at some of the complex relationships among neurological diseases. This list is not included with any intention that it serve as the model for how NINDS could update their current list. Rather, it is included merely to highlight the complexity of neurological diseases that NINDS' efforts must take into account as it works to improve its disease list.

Rationale for change

Members of the Disease Module and Priority 1 Working Group reached a general and enthusiastic consensus: developing a biologically clustered, publicly accessible, relational database of diseases would be highly valuable to NINDS and to the scientific and lay community. Comments from NINDS staff also made it clear that there is interest among NINDS staff in modernizing the existing list. Such modernization should take into account new molecular and pathological advances and emphasize shared pathomechanisms across diseases.

Advantages to the neuroscience community of biologically based clustering of neurological diseases include the following:

1) Facilitate recognition of unknown/untapped connections between diseases.

2) Enhance scientists' and the public's capacity to process rapidly accumulating information about diseases and genes

3) Help the lay public navigate NINDS web site in search of disease information.

4) Catalyze collaborative research within the research community based on recognition of biological overlap among diseases.

5) Raise awareness of disease foundations, which often focus on one or a few diseases, to ongoing research on biologically related diseases that may be of unanticipated relevance to a particular disease foundation.

6) Dovetail with the goal of setting priorities across NINDS diseases, as described in the recommendations of Priority 2 Working Group.

Similar to large data set analyses that recently have begun to uncover previously unrecognized connections between genes or proteins, parallel efforts to cluster diseases based on their underlying genes, proteins or cellular pathways almost certainly will identify unexpected connections across diseases. These newly identified connections in turn may suggest common routes to disease understanding or to rational therapies.

Recognition of the biological connections across diseases is still in its early phases. Developing a biologically based disease list as soon as possible will allow NINDS to enter at the "ground level," thereby quickly enhancing the Institute's ability to help researchers identify untapped avenues of research discovery that cross cut diseases. This effort would enhance NINDS's capacity to develop an increasingly accurate neurological "disease-ome" in which scientists and the public alike can assess neighboring/related diseases based on the pathways they share.

Nod to history

The Priority 1 Working Group was mindful of that fact that the public and government entities have strong historical ties to particular disease names. Thus, any "new" list developed by NINDS/NIH to facilitate disease-related research cannot, and should not, simply replace the existing historical list of disease names. Perhaps, instead, a new biologically based listing should represent a second level, or higher order, categorization that complements the existing historically established disease list. Despite the importance of historical listing, however, a few disease names may warrant "retiring" from the existing list.

Some limitations to working group

The expertise of the Working Group covers only a fraction of all the diseases within the NINDS portfolio. Thus, the Working Group (or even the full Disease Module) is not well positioned to create this new list. Rather, we can make recommendations to NINDS for effective strategies through which such a list could be created and maintained so that it is optimally accessible to NINDS staff, the public and scientists.

The disease classification/scheme recommended by us is inherently dynamic and in some sense will never be "finished." As science advances, new connections among diseases -- and even new diseases --surely will be found. Accordingly, it will be important that a straightforward mechanism is put in place to maintain and update this relational database.

A new disease database resource prototype

We propose that NINDS develop a new disease classification approach consisting of a dynamic, relational database that allows clustering of diseases by key basic and clinical characteristics and is publicly accessible. A prototype is an Excel spreadsheet comprising an list of NINDS diseases, accompanied by a series of columns extending rightward that correspond to various biologically meaningful categories and disease-specific data on burden (i.e., incidence, prevalence,

morbidity/mortality). Creating such a resource will not be easy: it will need to take into account the remarkable range of mechanistic and pathological complexity among various neurological diseases. While for some diseases, creating the data entry might be relatively straightforward, for others it will be a challenge. To give just a few examples: 1) for a given disease more than one pathogenic mechanism may be in play (e.g. Alzheimer's disease might involve protein misfolding, synaptopathy, inflammation, and glial impairment); 2) many similar diseases can be caused by different mutations in dissimilar genes (eg., hereditary ataxias, spastic paraplegias, and neuropathies); or 3) a "disease" can be a catch-all "wastebasket" term corresponding to dozens of disorders (e.g. cerebral palsy). Such a spreadsheet also would allow NINDS to develop separate types of biological and clinical classifications while also remaining anchored to historical categories (e.g. pediatric vs. adult diseases). Such a spreadsheet would inherently be a dynamic document that would expand over time to include disease genes and proteins.

As a framework for enhancing the current NINDS disease list, Priority 1 Working group offers a prototype: an expandable Excel file that uses, as its base, the existing disease list (preferably a suitably edited list of diseases). T he spreadsheet would place this disease list in relation to various "categories" including proposed pathomechanisms (etiology), cell types involved, and susceptible region(s) of the neuroaxis, among others. This excel disease database prototype is included as *Appendix 3.*

In the simplest version, there might only be 2 "sheets" to the spreadsheet, one designated "Categories" and the other "Diseases." The Categories sheet is an outline/menu that lists the various categories by which to classify a disease and the possible choices within each category. The Diseases sheet would be the entry point to the list. Each disease (rows) should be assigned a value within each category (columns) with the option of having more than one value for a given category. The true value of such a listing would be as a web-based, searchable, and "sortable" database that users can query. For each disease, one could click on each box to the right of a particular disease and get a drop down menu from which to make choices. There would also be an "Other" option to add free form data. One could identify diseases that share implicated cell type, pathomechanism, age of onset, mode of inheritance, gene classification, etc..

It might be appropriate to place disease genes and genetic risk factors in a separate category, a third "sheet" in the data base, in which NINDS staff would have the capacity to list multiple genes for a given disease (e.g., spinocerebellar ataxias, hereditary spastic paraplegias, hereditary neuropathies).

The optimal disease list need not be confined to biological information. For instance, additional columns might outline existing funding for diseases or contain URLs for the various foundations\patient-family groups that exist for many diseases. This would assist the lay public in finding support and aid researchers who wish to gain access to patient groups or to grants offered by foundations.

This disease data set would need to be housed in a web-accessible, relational database. Only in such a context would it prove optimally useful to NINDS staff, the lay public, outside disease foundations and scientists. Importantly, the disease list could be expanded to include disease incidence, public health burden, and current or prior funded efforts. In this manner, this disease list would serve a very important purpose for the development of environmental scans and priority setting for various diseases, as proposed by Working Group 2.

Disease examples: difficult work ahead

As illustrations of how such a relational database might be launched, we provide a few rough outlines for certain diseases: Alzheimer disease (AD), spinocerebellar ataxias (SCAs), and cerebral palsy (CP). These first-pass efforts underscore the inherent challenges to developing a useful biological based disease list, but also hint at the promise this approach may hold for NINDS.

Alzheimer disease (AD): In some respects AD represents a straightforward case for the disease list. It is exclusively an adult onset, purely CNS disorder in which the susceptible brain regions are clearly defined. Likewise, the dual neuropathological hallmarks of AD (amyloid plaques and neurofibrillary tangles) are well accepted -- indeed essential to making the pathological diagnosis. In other respects, however, AD is not so simple and thus illustrates some of the challenges that will surface when a new list is created. For example, AD is both hereditary and nonhereditary: AD exists as a familial form caused by dominant-acting mutations and as a later onset, sporadic form in which genetic risk factors play an important role yet are not causal. The new list should take this into account. Moreover, classification of disease genes/proteins for AD will require at least three categories: classically defined disease genes (APP, presenilins 1 and 2), genetic risk factors (a growing group, with ApoE4 being most significant), and other implicated gene products that, while clearly important in AD, are more closely and directly linked to other dementias (e.g. tau in frontotemporal dementia). While most scientists accept that abnormal accumulation of amyloidogenic proteins is the primary route to pathogenesis, this consensus does not account for the emerging recognition of AD as a synaptopathy in which inflammatory pathways likely play a significant role. Finally, neurons degenerate in AD but clearly other cell populations in the brain are also affected. Thus, deciding which pathomechansim or involved cell type is "primary" versus "secondary" may be difficult in AD and even harder in other diseases.

SCA: In the updated disease list, SCA would likely be listed as a “disease” though it actually is a large group of dominantly inherited ataxias. Presently, the SCA’s comprise at least 29 distinct genetic causes of spinocerebellar degeneration. There is marked heterogeneity across these disorders and, in some cases, even within a disorder due to differences in mutational severity. Some SCA’s are more “pure” cerebellar ataxia with selective loss of Purkinje cells, while others affect a much broader swath of the CNS. A subset of SCA’s share a possible pathomechanism: at least six are caused by similar CAG repeat expansions that encode polyglutamine expansions in the disease proteins. The updated disease list somehow will need to reflect this diversity among the SCA’s while also illustrating common features among a subset of ataxias. An ideal list would include details about each SCA; that is, the “disease” term SCA could be expanded, if the user so desired, to the full panel of diseases comprising this group of ataxias.

CP:

CP is a particular challenge to classify since it is, in a sense, a "waste basket" diagnosis that broadly subsumes many conditions ranging from hypoxia-ischemia to post-traumatic or post-infectious brain injury. Thus, in CP the presentations are varied as are the patient populations affected. Consequently, funding for CP research by NINDS is probably greatly underestimated– this is not a minor issue because NINDS does periodically get criticized for underfunding this major collection of disorders relative to much rarer adult conditions. Hence, the new classification scheme needs to include a way to track these “messy” disorders, of which CP is far from the only one.

Appendix 1: NINDS Disease Coding Categories for Reporting

ALS
Alzheimer's Disease
Aneurysm
Aphasia
Ataxia Telangiecstasia
Ataxia, Friedreich's
Ataxias, Hereditary
Attention Deficit Disorder (ADD)
Autism
Autoimmune Disease
Batten Disease
Brain Cancer
Cerebral Palsy
Cerebrovascular
Charcot Marie Tooth Syndrome
Chronic Fatigue Syndrome
Coma Research
Creutzfeldt-Jakob
Depression
Developmental Disorders
Diabetes
Down Syndrome
Drug Abuse
Duchenne/ Becker Muscular Dystrophy
Dyslexia
Dystonia
Epilepsy
Fabry's Disease
Fasiocapulohumeral Muscular Dystrophy
Fibromyalgia
Fragile X Syndrome
Frontotemporal Dementia (FTD)
Gaucher's Disease
Guillain Barre Syndrome
Headache
Headache, Migraine
Herpes I
HIV/AIDS
Huntington's Disease
Hydrocephalus
Infant Mortality/ (LBW)
Infectious Diseases
Infectious Diseases not AIDS
Injury - Trauma, (Head and Spine)
Injury - Traumatic brain injury
Leukodystrophy
Lipid Storage Disorders
Lupus
Lyme Disease
Lymphoma
Mental - Anxiety Disorders
Mental Retardation
Mucopolysaccharidoses (MPS)
Multiple Sclerosis
Multiple System Atrophy (MSA)
Muscular Dystrophy
Myasthenia Gravis
Myotonic Dystrophy
Narcolepsy
Neurodegenerative
Neuroendocrine and Autonomic Nervous System
Neurofibromatosis
Neuropathy
Niemann-Pick
Obesity
Pain Conditions, Chronic
Parkinson's Disease
Pediatric
Pediatric AIDS
Pick's Disease
Post-polio Syndrome
Progressive Supranuclear Palsy
Reflex Sympathetic Dystrophy Syndrome
Restless Legs Syndrome
Rett's Syndrome
Schizophrenia
Sexually Transmitted Diseases/Herpes
Sickle Cell Disease
Sleep Disorders
Spina Bifida
Spinal Cord Injury
Spinal Muscular Atrophy
Spinocerebellar Ataxias
Stroke
Sudden Infant Death Syndrome
Syringomyelia
Tay Sachs Disease
Temporomandibular Joint Disorder (TMJ)
Tourette Syndrome
Transmission Spongiform Encephalopathy
Tropical Diseases
Tuberous Sclerosis
Vascular Dementia

Appendix 2: (see online version for full disease list; only the first two pages are shown here)

CHILDREN'S HOSPITAL BOSTON DEPARTMENT OF NEUROLOGY

INTERNAL DIAGNOSIS CLASSIFICATION SYSTEM

Major Categories:

1. EPILEPSY
2.0 HEADACHE
3.0 DEVELOPMENTAL, LANGUAGE AND BEHAVIORAL DISORDERS
4.0 ACUTE & CHRONIC ACQUIRED DISORDERS
5.00 NEUROMUSCULAR DIAGNOSES
6.00 CEREBRAL PALSY
7.0 MOVEMENT/MOTOR DISORDERS
8.0 HEAD GROWTH/SHAPE
9.0 SYMPTOMS AND SIGNS (If no specific diagnosis)
10.0 SLEEP DISORDERS
11.0 GENETIC DIAGNOSES AND SYNDROMES
12.0 BRAIN MALFORMATIONS/DYSGENESIS
13.0 VASCULAR MALFORMATIONS
14.0 METABOLIC DISORDERS
15.0 IMMUNOLOGY/DEMYELINATING DISORDERS
16.0 CNS AND PNS TUMORS
17.00 CRANIAL NERVE AND NEURO-OPHTHALMOLOGY DISORDERS

Detail:

Internal Code	ICD9 Code	Internal Description
1.0 EPILEPSY		
1.1		**Neonatal & infantile epilepsy syndromes**
1.1.010	779.0	Neonatal Seizures, Non-Intract
1.1.011	779.0	Neonatal Seizures, Intract
1.1.020	779.0	Benign Familial Neonatal Seizures, Non-Intract
1.1.021	779.0	Benign Familial Neonatal Seizures, Intract
1.1.030	779.0	Benign Non-Familial Neonatal Seizures, Non-Intract
1.1.031	779.0	Benign Non-Familial Neonatal Seizures, Intract
1.1.040	345.10	EME--Early Myoclonic Encephalopathy, Non-Intract
1.1.041	345.11	EME--Early Myoclonic Encephalopathy, Intract
1.1.050	345.10	EIEE--Early Infantile Epileptic Encephalopathy--Ohtahara Syndrome, Non-Intract
1.1.051	345.11	EIEE--Early Infantile Epileptic Encephalopathy--Ohtahara Syndrome,

		Intract
1.1.060	345.60	West Syndrome--Infantile Spasms, Non-Intract
1.1.061	345.61	West Syndrome--Infantile Spasms, Intract
1.1.070	345.10	Benign Myoclonic Epilepsy In Infancy, Non-Intract
1.1.071	345.11	Benign Myoclonic Epilepsy In Infancy, Intract
1.1.080	345.10	Severe Myoclonic Epilepsy In Infancy--Dravet Syndrome, Non-Intract
1.1.081	345.11	Severe Myoclonic Epilepsy In Infancy--Dravet Syndrome, Intract
1.1.090	345.50	Migrating Partial Seizures Of Early Infancy, Non-Intract
1.1.091	345.51	Migrating Partial Seizures Of Early Infancy, Intract
1.1.100	780.59	Neonatal Sleep Myoclonus (Non-Epileptic)
1.2		**Childhood Epilepsy Syndromes**
1.2.010	345.50	Benign Childhood Epilepsy With Centrotemporal Spikes, Non-Intract (Rolandic)
1.2.011	345.51	Benign Childhood Epilepsy With Centrotemporal Spikes, Intract (Rolandic)
1.2.020	345.50	Benign Childhood Occipital Epilepsy--Early Onset, Non-Intract
1.2.021	345.51	Benign Childhood Occipital Epilepsy--Early Onset, Intract
1.2.030	345.50	Benign Childhood Occipital Epilepsy--Late Onset (Gastaut Type) , Non-Intract
1.2.031	345.51	Benign Childhood Occipital Epilepsy--Late Onset (Gastaut Type), Intract
1.2.040	345.50	Benign Focal Epilepsy Of Childhood (Other), Non-Intract
1.2.041	345.51	Benign Focal Epilepsy Of Childhood (Other), Intract
1.2.100	345.40	Temporal Lobe Epilepsy, Non-Intract
1.2.101	345.41	Temporal Lobe Epilepsy, Intract
1.2.110	345.40	Temporal Lobe Epilepsy, With Mesial Temporal Sclerosis, Non-Intract
1.2.111	345.41	Temporal Lobe Epilepsy, With Mesial Temporal Sclerosis, Intract
1.2.120	345.40	Frontal Lobe Epilepsy (Non-Familial), Non-Intract
1.2.121	345.41	Frontal Lobe Epilepsy (Non-Familial), Intract
1.2.130	345.40	Occipital Lobe Epilepsy (Non-Benign), Non-Intract
1.2.131	345.41	Occipital Lobe Epilepsy (Non-Benign), Intract
1.2.140	345.40	Other Extratemporal Epilepsy, Non-Intract
1.2.141	345.41	Other Extratemporal Epilepsy, Intract
1.2.150	345.40	(Probably) Symptomatic Multifocal Epilepsy, Non-Intract
1.2.151	345.41	(Probably) Symptomatic Multifocal Epilepsy, Intract
1.2.200	345.10	Lennox-Gastaut Syndrome, Non-Intract
1.2.201	345.11	Lennox-Gastaut Syndrome, Intract
1.2.210	345.10	Epilepsy With Myoclonic-Astatic Seizures (Doose), Non-Intract
1.2.211	345.11	Epilepsy With Myoclonic-Astatic Seizures (Doose), Intract

Appendix 3: Categories

	A	B	C	D	E	F	G	H
1	Name	Incidence	NINDS Funding	Cardinal Manisfestation	Etiology	Lesion Location	Cell Type	Subcellular Location
2		#	#	Cerebellar	Degenerative	Basal Ganglia	Astrocyte	Cytoplasm
3				Consciousness	Demyelinating	Cerebral Cortex	Ependymal cell	Cytoskeleton
4				Learning and Memory	Infectious	Medulla	Meninges	Golgi apparatus
5				Motor	Inflammatory	Meninges	Microglia	Lysosome
6				Pain	Metabolic	Midbrain	Muscle	Membrane proteins
7				Psychiatric	Neoplastic	Muscle	Neural Stem Cell	Mitochondria
8				Sensory (non-pain)	Nutritional	Peripheral Nerve	Neuron	Nucleus
9				Speech	Toxic	Pons	Oligodendrocyte	Plasma membrane
10				None	Traumatic	Spinal Cord	Vascular	Unknown
11				Unknown	Unknown	Subcortical WM	Unknown	Other
12				Other	Other	Ventricular System	Other	
13						Cerebellum		
14						Unknown		
15						Other		

Priority 2 – Disease Module: Develop a method for Obtaining an Environmental Scan or "Landscape" for Unmet Scientific Opportunity for Targeted Diseases.

(Barbara Vickery, Nicholas M. Barbaro, and Cynthia Joyce)

Although we begin our report with recommendations, we strongly encourage that the subsequent section on the analysis of the problem, general principles of priority setting, and the table of conclusions/response be read, to give context and the rationale for these recommendations.

WORKGROUP RECOMMENDATIONS:

1. Communicate high-level NINDS support for new priority-setting process that incorporates a systematic environmental scan for unmet scientific opportunity within and across neurologic diseases. NINDS leadership should communicate to its staff within the institute, colleagues at other institutes and at other federal agencies engaged in supporting neuroscience research, and stakeholders in academics, advocacy organizations, and pharma, that it plans to put in place a data-driven, ongoing process for priority setting, that the process will request input from stakeholders, and that the process and its impact will be periodically re-evaluated - and revised, as needed – in an ongoing fashion.

2. Initiate a two-level priority-setting process that is based on unmet scientific opportunity within and across neurologic diseases and is systematic, comprehensive, data-driven, and overlaid on the current NINDS structure. A suggested protocol for steps in each level of this priority-setting process is:

Level I – *WITHIN* disease identification of stage on research continuum most ripe for "push" (and how opportune), for each neurologic disease; primarily a "ground up" approach that takes advantage of information technology systems:

a. Working within the current cluster structure of the institute, every neurologic disease – as mapped directly onto the list of diseases that is developed based on recommendations of the disease classification workgroup - should have a responsible "point person" (program director). The distribution of responsibilities across program directors should be balanced in terms of individual workload, disease needs or complexity, and scientific fit with the program director's expertise.
b. For each disease, the associated program director should be responsible for developing and maintaining a "modified" quad chart including supporting documentation (i.e., sources of information; dates of updates; prototype in Attachment I) on:
    i. Burden of the disease: prevalence/incidence/mortality/ disability (can use initial tabulated summary prepared for panel as core data resource to seed process); data should be abstracted from studies into tables in a standardized format to be developed
    ii. Current level of NINDS funding and other NIH funding, by mechanism and by research phase (basic, translation-1, clinical, translation-2 – see next page)

iii. Current status of funding by other players by research phase
iv. Summary analysis of unmet scientific opportunity for NINDS/NIH support for disease, by research phase; possible 'levers' for traction via NIH/NINDS support on any phase exceeding some threshold of opportunity

We recommend developing a "checklist" tool for scientific opportunity for a given disease or syndrome, for EACH of the four *phases* of neuroscience research continuum:

Basic *Translation-1* *Clinical* *Translation-2*

Figure from Sung NS et al, Central challenges facing the national clinical research enterprise. *JAMA* 2003; 289: 1278-87

The Translational Research Panel has developed an early prototype for Translation-1 research criteria (see Attachment II). Example criteria for basic/mechanism, clinical, and Translation-2 research are shown in Attachment III. Scientific opportunity for a given disease should include research that falls within categories of Prevention and Recognition/Diagnosis, in addition to Treatment.

Development of tools for carrying out this step should be conducted with additional technical support from outside NINDS and with staff in the NINDS Office of Science Planning and Policy, who could become technical advisors to the program directors and facilitators of the new process during and after implementation. (This office's staff are already aligned with program directors as "adjunct members" of clusters).

c. Public comment and input on these disease documents should be broad and should include through Sharepoint (web) posting, proactive contact of relevant advocacy organization(s) by program directors for Scientific/Medical Advisory Board review and comment, and other mechanisms. The process of obtaining such input should be documented in a written protocol and updated as appropriate over time.
d. The NINDS Extramural Science Committee (ESC) should review and refine individual disease quad charts and supporting evidence documents at their annual retreat, identifying trans-NIH areas for appropriate input, and developing a summary compendium of neurologic diseases and levels of burden and of scientific opportunity, and potential NINDS/NIH mechanisms for facilitating this phase of research, for subsequent council review. Program directors and ESC will review these materials not only for initiatives with respect to individual diseases, but also to identify common issues across

diseases to suggest opportunities that are cross-cutting. (NOTE: Program directors should retain flexibility to propose ideas beyond those generated by this mechanism, but these would be reviewed alongside those identified by this mechanism)

Level II – *ACROSS* disease judgments in the priority-setting process

Council should review the summary compendium from ESC and participate in a scientific priority-setting process proven to improve the quality of a group's judgments (for example, a modified Dephi approach). Council's input should be solicited regarding proposed levers or initiatives for NINDS facilitation of the highest rated opportunities.

We recommend using a systematic, research method, such as modified Delphi for council (or another body) to provide ratings to guide final decisions by NINDS leadership. This approach needs a modest level of technical support to initiate the process and enable staff in the Office of Science Planning and Policy to execute the process in an ongoing way in the future. It will be essential to establish criteria for the expert body and what the expert body will rate. Likely criteria would include:

- How great ("ripe") is the level of scientific opportunity or readiness
- How great is the burden that would be alleviated by success in this area of science for this disease:
  - Long-term
  - Short-term
- How ripe is the community (NINDS cannot affect alone)
- The extent to which a proposed NIH initiative (as opposed to other sources of support) could make a difference in advancing the science at this stage (vs other sources of support); i.e., what is the "added value" of NINDS/ trans-NIH contribution relative to those of private sector
- Overall assessment

a. Ratings would then be collated by the Extramural Science Committee and reviewed by director for final decision-making on actions/initiatives judged as highest priority, to implement in that year
b. A broad range of levers could be used but top priorities across the entire range of basic, translation-1, clinical, and translation-2 research phases should be purposefully targeted. The workgroup strongly encourages NINDS to include clinical and translation-2 research in the priority-setting, as results of those phases of research can have huge impact on disease burden in a near timeframe.

3. Plan an initial implementation strategy, and phase in the scope of the priority-setting process over several years. We recommend a timetable in which an initial set of 10-20 diseases (whatever is deemed feasible under current budget constraints) be

assessed and prioritized in the first year, to work out bugs in the process and to flesh out protocols and tools. The initial implementation would ideally include a spectrum of diseases encompassing both common and rare diseases, representation of diseases perceived likely to have unmet scientific opportunity in each of the four different research phases, and diseases falling entirely within NINDS' purview as well as diseases supported by other institutes in addition to NINDS. In subsequent years, existing disease-specific quad charts and checklists would be updated, and new documents for remaining neurologic diseases developed. The timing of ongoing re-assessments and who internally is responsible for generating which components should be developed internally by NINDS and reviewed with its Council.

4. Track and re-evaluate disease burden, opportunity, dissemination of the priority-setting products, and the implementation plan for the priority-setting process.

A. **Change in disease burden**. We recommend that rather than invest in a comprehensive neurologic disease burden study involving extensive primary data collection at a single point in time, the institute use existing data, and create an online resource of published articles and reports, with data extracted into tabular form in a systematic fashion.
   - The *establishment* of the resource should be planned with professional society, advocacy organization, and healthcare plan/large delivery system participation, could be conducted with outside academic/contract support, and should be modest in scope (i.e., canvas, grade the quality of, and synthesize existing knowledge). Healthcare delivery systems should be involved to leverage advances in accuracy of electronic records and administrative databases.
   - Ongoing "curation" should be hosted by NINDS but be a joint responsibility with private sector stakeholders and professional societies, to whom the product is a resource for all. Contributions could be made by public (organizations or institutions) by posting additional data resources in the form of citations and/or peer-reviewed literature. Internet resources such as wikis make this approach possible and feasible now.
   - The working group perceives that responsibility for "hosting" a compendium of synthesized, high-quality data on disease burden must lie somewhere, and we do not see that any other organization outside of NINDS has the perspective/motivation/need to be responsible for being a repository for these critically important data across neurologic diseases.

B. **Change in scientific opportunity**. Because scientific opportunity is not static, we recommend instituting mechanisms for periodically re-scanning the environment to update the data on and analysis of unmet scientific opportunity within each disease:
   - Encourage input/data from advocacy organizations and other private sector, as well as comments from scientific community. Consider using "blogs" or sharepoint format to update new data on disease burden. Provide guidance on what data are of interest; ask for Scientific Advisory Boards of disease organizations to provide updates/corrections from literature etc.

- Create a protocol for internal implementation of ongoing surveillance for these data, both 'who' does the action, and 'how often.' The protocol might include:
  - key articles of new discoveries that may potentially 'trigger' a formal re-assessment, as identified from keyword searches in PubMed, RSS feeds to staff from different disease areas, new evidence-based practice center and professional society guideline reports, etc.
  - knowledge of program staff based on their interactions with researchers and exposure to progress in a field,
  - review of interim and final reports from academic researchers receiving funds from NINDS for relevant research,
  - interviews of staff from other NIH institutes with related disease responsibilities
- Create a "reward"/clarify expectations for successfully accomplishing this work internally at NINDS, especially with respect to program directors.

C. **Periodic evaluation of impact of dissemination of the compendium of data and analysis on burden and unmet scientific opportunity**. To be of value, a modest investment of effort in the design and implementation, including set-up of an accessible repository of the synthesized data, must be established. NINDS should track and publicly report the data summaries produced for each disease and the results of the prioritization efforts. Tracking should include how well disease communities spontaneously address priority opportunities vs the use of NINDS initiatives, and those evaluation results should be communicated to the public.

D. **Evaluation of the priority-setting process itself.** An ongoing or *formative evaluation* should be planned and resources and technical expertise identified to conduct this modest evaluation to:
  - document the process that is initially implemented, and
  - enable review and feedback on both the process and "outcomes" (i.e., success in identifying and pushing scientifically ripe opportunities with potential for high health impact) over time

  in order to *continuously revise and improve the process* over time.

5. Maximize efficiency in use of federal resources by pursuing trans-NIH collaboration and involvement. The workgroup felt strongly that given the need to leverage scarce resources for advancing our knowledge about causes and treatment of neurologic diseases, it was essential to systematically – rather than the current ad hoc approach - engage other institutes who have historically supported neurologic disease research in collaboration early in the priority-setting process, and identify whether there are any "lessons learned" from these other institutes around priority setting.

A. A strategy should be developed – involving staff in the development of the strategy and communicating the protocol that is developed widely across staff - for collaborating **early** in the priority-setting process across the main NIH institutes who also fund research in neurologic diseases. Support for developing this early-stage strategy across institutes should be initiated by NINDS leadership to counterparts at the other institutes.

B. To provide data to inform judgments about prioritizing across the spectrum of research, we recommend interviewing staff and leadership from other institutes (NCI, NHLBI) to understand how they view and whether they evaluate their balance of research investment.

THE PROBLEM: CURRENT APPROACH AND GAPS

NINDS Mission and Research Scope

- "reduce the burden of neurological disease through research"
- Institute conducts research across the spectrum of basic, translational, and clinical research, and from rare to common diseases

History of Strategic Planning and Overall Context of Priority Setting

- Last strategic plan to "identify research opportunities, gaps, and priorities to which it should respond" was in 1999; two major changes in internal operations occurred in the timeframe after 1999:
    - Generation of a number of initiatives afterwards compared to before; NINDS went from one of the less 'proactive' in terms of generation of initiatives (especially those with set-asides) to about 100 over the last decade, a number likely in the mid-range across institutes
    - Re-organization in structure to clusters with "flattening" of hierarchy among program directors within clusters
- From 1999 to 2003 there were substantial increases in NINDS appropriations; leveling off (or falling against inflation) in last 5 years.
- In FY07, "competing dollar allocations" in the NINDS extramural budget supported investigator-initiated grants (including new investigator grants above payline) relative to the combination of grant solicitation with set-aside funds and high program priority grants by over a 10:1 ratio:
    - ~$280 million for investigator initiated grants including new investigator grants above the payline
    - ~$24 million allocated about equally to grant solicitations with set-aside funds and to high program priority grants

Current approach to priority setting ('rationally determining disease investment') at NINDS:

- At present, very small proportion of dollar allocations by NINDS for "set-asides" or "high program priority grants"; most research funding is to R01s that come in outside of specific announcements and that are scored highest by review committees of independent scientists
- Regarding the process of generating initiatives (leading to RFA or PA, usually <u>without</u> set-aside):

    a. <u>**Concept Origination*</u>

    "The concept for a new initiative can originate from a strategic plan, workshop, congressional mandate, executive order, discussions among staff and with grantees, or the Institute director. Any program director and certain other staff may suggest an initiative with a translational focus."

    <u>**Early Concept Development*</u>

    "Usually, an individual program director takes the lead in developing an initiative concept. The lead program director seeks informal input from colleagues within NINDS and from other Institutes and Centers

that may have interest in collaborating. Initiative concepts are sometimes fleshed out by internal working groups."
*discussion at division of extramural research retreat
*concept clearance by NINDS council
*extramural science committee review (leadership, program directors); meet twice yearly
*feedback from CSR on language/wording
*final decision among choices - director

b. panel heard at July meeting that not infrequently, a working group is Congressionally mandated, sometimes prompted by advocacy groups; there is no "systematic" approach currently in place to assess scientific gaps or opportunities within and across all neurologic diseases.

- Several recent initiatives representing somewhat newer approaches for the institute have been launched/piloted: SMA for translation; trans-NIH initiatives such as muscular dystrophy (original MD Care Act 2001) whose investment more complex and beyond an RFA or PA

Barriers to priority setting/'rationally determining disease investment' at NINDS:

A. Infrastructure of NINDS is Not Aligned with Diseases. *Variable and diffuse representation of different neurologic diseases due to current programmatic structure of Extramural Research Portfolio.*

1. NINDS has six main clusters with teams of program directors and staff; team leaders rotate under the 'flattened' structure
2. Clusters span multiple diseases or functions applicable to multiple diseases (channels, synapses, and neural circuits; neural environment; neurodegeneration; neurogenetics; repair and plasticity; systems and cognitive neuroscience). In addition there are several 'groups', including a *clinical trials* group, and an Office of Translational Research (formerly the Technology Development group) that is principally focused on translation-1 research efforts. Both groups have staff who work with program directors across clusters.
3. Cluster structure is not disease-oriented: one disease can span multiple clusters and program directors; some neurologic diseases have no clear 'home' or are underrepresented in the cluster structure.

B. Sizeable Gaps Exist in Comprehensive Data on Neurologic Disease Burden. No internal source of data on burden of neurologic diseases has been formally maintained or updated at NINDS since 1991, and those data were incomplete and sources undocumented; there is no known external compendium of such data, either. There appears to be no current organizational commitment within the federal government to collect these data.

C. Lack of Templates/Prototypes for Assessing Scientific Opportunity WITHIN a Disease. No formal guide or template has been developed or requirement to systematically evaluate current 'state-of-research-in-a-disease' in terms of ongoing research either funded by NINDS, across institutes, or beyond, in setting up initiatives; neither do there appear to be prototypes or existing templates or checklists

for assessing 'scientific opportunity' from a societal perspective, NIH-perspective, or NINDS-perspective. T-2 research (clinical trial to population) is essentially entirely lacking from current portfolio.

D. Lack of Formal, Transparent Guides and Protocol for Prioritizing Scientific Opportunity ACROSS Diseases. Under current process, the initiative process is driven by the "squeaky wheel" and congressional mandates. While there is a process in place for conducting internal review of potential new initiatives is at twice yearly Division of Extramural Research Retreat and at Extramural Science Committee (institute leadership and select program directors) meetings, a systematic process for reviewing across diseases is not apparent.

E. Key Stakeholder Involvement in Priority-setting is currently ad hoc
   a. *Individual Academic Researcher Investigators*
      i. Reviewers (both CSR and internal to NINDS) have until recently typically rewarded quality of methodology and not significance, for which there have been few review criteria established (until recently); yet bulk of funding by NINDS is according to scoring
      ii. In the application phase, there are no templates or guides for Academic Researchers to provide data to justify significance
      iii. In the progress of final reporting phases, there is no requirement for individual investigators to describe and interpret their findings or suggest next steps along the neuroscience research continuum (bench, translation-1, clinical, translation-2) based on their findings, and no place where these findings are captured for broader review and analysis. This includes lack of a requirement that final reports or competing continuation proposals of basic science research grants explain how the grant has advanced knowledge related to a particular neurologic disease.
      iv. Same investigators rarely have appropriate expertise to carry research forward from one stage to the next
   b. Patient advocacy organization involvement is ad hoc and more likely if initiative comes through a congressional mandate that the organization has encouraged
   c. Unclear when if any industry input in a systematic way; transparency is particularly vital here

F. Lack of a common perception on what "priority-setting" means in terms of resource allocation and autonomy reinforces the status quo and will make instituting change more difficult unless directly addressed.
   a. Some constituents may not understand that the kind of change in priority-setting envisioned is in alignment with investigator-initiated research, focusing on optimizing the priority-setting that already occurs, and employing a wide range of potential levers beyond announcements with set-asides, including:
      i. Announcements without set-asides
      ii. Establishing a dedicated program director
      iii. Sponsoring a workshop

iv. Engaging in an in-depth strategic planning more in-depth for a particular disease
v. Exploring trans-NIH interest/support
vi. Others, such as ones identified in Priority #4 recommendations

b. Currently, there are no clear procedures for gauging success of initiative process nor incentives for implementing a new process.

G. Trans-NIH Initiatives Appear to be Even More Ad Hoc

a. Unclear what if any are incentives to collaborate in priority-setting across institutes, yet 2/3 of neuroscience research funding occurs within other institutes
b. While institutes share solicitation initiatives, typically these are not collaborative early in the priority-setting process but are shared with counterparts across institutes once they are already developed, to ascertain whether another institute wishes to "sign on"
c. Early-stage initiatives, when they occur, typically are in the context of either a congressional mandate or due to ad hoc relationships of program directors with individuals they know at other institutes
d. Unknown whether any other institute employs a systematic priority-setting process to scan across diseases, or any ongoing evaluation of their priority-setting process. Cluster organization of NINDS may be somewhat unique across institutes and create unique challenges for comprehensive assessment across diseases, relative to institutes that have a more disease-oriented structure.

GENERAL PRINCIPLES OF PRIORITY-SETTING:

- A change in the current priority-setting process should include:
  - Comprehensive scanning across diseases
  - Structured ascertainment of data on burden and unmet scientific opportunity
  - Ongoing surveillance and re-assessment in a systematic fashion
  - Transparency of data collection, synthesis, and analysis
  - Engagement of stakeholders from academia, advocacy organizations, pharma, healthcare delivery systems, and other government agencies/institutes to provide input and commentary, and to use the products of the priority-setting process
- Priority-setting for this purpose conceptually must occur at two levels that require different tools, protocols, and perspectives, as well as distinct commitments and incentives to be successful:
  - *Within* a disease or disease group, what 'stage' or stages of the neuroscience research continuum is (are) ripest for a 'push', i.e., what is the status of scientific knowledge (broadly defined, i.e., basic, translation-1, clinical, translation-2) for improving the health of people with, better recognizing, or preventing that disease?
    1. The article by LeRoy and colleagues (Leroy JL et al., Current priorities in health research funding and lack of impact on the number of child deaths per year. *American Journal of Public Health*

2007;97:219-223) describes a formal, quantitative, modeling approach to analyzing the relative impact of investment in new research on childhood mortality that is focused on better medical technologies versus directed toward new knowledge on how to disseminate technologies already proven effective.

2. This within-disease assessment will generally be from a broad societal perspective, but national vs. global perspectives may differ. For example, there may be high recognition of epilepsy in the US, with greater opportunity for improving health across persons with epilepsy in the US through discovery of drugs having novel mechanisms, such as those immune to drug-resistance (translation-1 research). In contrast, in third world countries, studies of ways to improve recognition of untreated epilepsy (for which inexpensive drugs are available but underused) represent the greatest opportunity for improving the health of the population with epilepsy (translation-2 research).

Basic Translation-1 Clinical Translation-2

Figure from Sung NS et al, Central challenges facing the national clinical research enterprise. *JAMA* 2003; 289: 1278-87

3. It requires scientific expertise to evaluate the need for tools to enable subsequent "discovery research." Critical path assessments can help with this. The people completing the evaluation tool need to have a good understanding of the research continuum. Program directors are well-positioned to take the lead in conducting this type of analysis, and in providing input into the tool itself.

- *Across* neurologic diseases, how should NINDS initiatives be prioritized?
  1. This level of priority-setting includes not only assessment of burden and of opportunity across diseases (with data provided from the level 1 analysis above), but NINDS/NIH-perspective on opportunity. That is, what is the unique/added value contribution of investing federal support into research or facilitation of research, beyond private or industry support.
  2. This level of priority-setting should ideally rely much more heavily on coordination of effort with other institutes (NIMH, NIA, NIDA, NEI, NICHD) for diseases not exclusively in NINDS domain.
  3. This level of priority setting should rely on systematic, transparent evidence collection and analysis, and employ feasible, established research methods for optimizing the quality of judgments by groups.

- Priority setting can be supported by quantitative data on prevalence, cost, estimates of health impact, etc., but at both levels described above – especially level 2 - such priority-setting involves judgment. There are well-described and extensively applied techniques from the social sciences on formalizing and optimizing the outputs of group judgments that would improve the quality and transparency of the priority setting process
- Use of data synthesized in a formal way and transparency in the priority-setting process is critical for credibility and sustainability for a public sector institute.
- As there is not clearly any prototype for a priority-setting process like this, there needs to be an ongoing or *formative evaluation* planned from the beginning, to
    - document the process that is initially implemented, and
    - enable review and feedback on both the process and "outcomes" (i.e., success in identifying and pushing scientifically ripe opportunities with potential for high health impact) over time

  in order to *continuously revise and improve the process* over time.
- Priority-setting involves a change in "culture" of the way private and academic stakeholders share information and provide advisory input to NINDS, as well as NINDS needing "buy-in" with other institutes who are the main other contributors to funding neuroscience research.
- Putting in place a change in the approach to priority-setting will require "buy-in" of and alignment of expectations of key staff within the institute, particularly program directors, as well as strong support and follow-through from institute leadership.
- Priority setting that aims to assess unmet scientific opportunity across the spectrum of research requires objective analysis of the balance of investment across the research spectrum to meet the institute's mission.

CONCLUSION	RESPONSE
For a given disease, success in strategic planning on priority-setting investments should ***change*** opportunity and even burden over time.	Priority-setting is not static or one-time, but needs to be a process that allows for ongoing scanning for changing scientific opportunity and burden. Will require some modest ongoing investment of resources and expertise, a change in "culture", and a revision of relationships with stakeholders to do this.
Priority-setting inherently involves judgments, as comparative 'burden' and 'unmet scientific opportunity' are only partially quantifiable and both constructs do not fall together on one metric.	Process should be used that is data-driven, standardized, transparent, brings to the table a range of perspectives, and minimizes dominance of individual influences.
Academics emphasizes and rewards becoming experts in one aspect or phase of the research continuum, and generally academicians have little incentive to analyze the impact or implications of their research within the broader continuum, or the expertise to conduct more than one aspect of research in the continuum.	Need to address this either by requiring an analysis of the implications of a study's findings for advancing knowledge about a neurologic disease from those who are funded, or by planning to do this internally at the Institute on a periodic basis and in a systematic way. Need to brainstorm recognitions and incentives for successful research that leads to another phase of research in which that investigator may not be engaged or positioned to compete for funding.
Priority-setting is most likely to be considered acceptable and successful if the input from a variety of stakeholders and perspectives is obtained (in an organized way) in the process.	Include members from academia, pharma, advocacy organizations, NINDS, and other relevant NIH institutes in proactive, ongoing priority-setting tasks. Change culture to view obtaining input from all stakeholder groups for information-gathering and in selected, formalized aspects of the priority-setting process that minimizes dominance of individual stakeholders. Make all advisory procedures and content transparent. Will need to obtain high-level support at NIH for trans-institute cooperation in the priority-setting process.
One key data element for making judgments about priority setting in neuroscience research is health burden of individual neurologic diseases, and an organizational commitment to setting up and maintaining a continuously updated, publicly accessible compendium is needed.	Within HHS, NINDS may be best suited to take the lead in a "partnership" responsibility with advocacy organizations, pharma, and healthcare delivery systems for obtaining and maintaining a basic repository of these data resources.
The NINDS mission is framed in terms of disease ("*reduce the burden of neurological disease through research*"), and disease-specific goals resonate with the public, who finance research.	Implementing a priority-setting process that comprehensively scans and periodically reports on the unmet scientific opportunity across neurologic diseases in an ongoing way will show that NINDS has done "due diligence" in its mission.
A priority-setting process can be compatible with and in alignment with maintaining investigator-initiated research and complement	Improving the priority-setting process by making it data-driven and transparent across NIH/all other sectors should help neuroscience investigators by

not replace autonomy of NINDS program directors to propose and justify initiatives	making them better informed about fruitful directions for their research, and better able to justify significance to reviewers, who are now required by CSR/NIH to place greater and more explicit emphasis on justification of significance into the proposal-review process. Tools for evaluating unmet scientific opportunity should help program directors generate and justify initiatives.
A priority-setting process can be successfully implemented only with "buy-in" and support at the institute from the directorship and staff, particularly program directors.	Performance incentives need to be aligned to meet this goal.
International and national perspectives on burden and opportunity may differ.	Need to consider this explicitly in the priority-setting process and assess how to balance US vs international perspective.

Attachment I: Example Neurological Disease X modified Quad Chart for analysis of burden and opportunity for Disease X: [*year generated; year updated*]

i. SUMMARY OF BURDEN OF DISEASE X: (sources of data would be tabulated on subsequent pages)	**ii. CURRENT STATUS OF FUNDING BY OTHER PLAYERS FOR DISEASE X BY RESEARCH PHASE**
Prevalence/Incidence/Mortality/Disability US Prevalence: Global prevalence (3rd world): Incidence (US/global): X% of people > age 60 Y% report disability in daily activities, Z% quit profession **Special considerations** Generally acknowledged as most common { } disorder; progressive	**By Research Phase:** **Basic, mechanism:** Non-profit supports pilot grants and fellowship training in basic research in disease; approx $X annually **Translational-1:** Pharma investment of $Y for 3-5 drug development actions specifically **Clinical:** Non-profit supports pilot grants and fellowship training in clinical research in disease; approx $X annually **Translational-2:** Prof society supported guideline development; AHRQ evidence report on treatment of [type of] symptoms of disease published in [year]
iii. CURRENT STATUS OF NIH FUNDING FOR DISEASE X BY RESEARCH PHASE (sources/amounts would be detailed on subsequent pages) **NIH funding (07) -** NINDS only **NINDS PORTFOLIO/ACTIONS:** **Funding (07) (with subgroups if appl)** No coding category Estimated ~$X million total **By Funding Mechanism: (100%; with %'s)** X# R01 100% relevant (on environmental epidemiology) Intramural program: [name] is active **Program actions:** 200X R13 conference **Clusters:** **By Research Phase:** **Basic, mechanism:** No grants on disease specifically, but [type of] portfolios are relevant. **Translational-1:** No grants on [disease] specifically **Clinical:** Environmental Epidemiology R01 Intramural runs [specify] **Translational-2:** None	**iv. SUMMARY OF UNMET SCIENTIFIC OPPORTUNITY FOR NIH SUPPORT FOR DISEASE X [detailed on subsequent pages for each research phase and categorized into prevention/diagnosis or recognition/treatment]** **Status/Major Prevention AND Diagnosis/Recognition AND Treatment Advance:** {what} was last major clinical advance in each area (when) **Analysis of Unmet Scientific Opportunity By Research Phase and by Category:** **Basic/Mechanism – [CHECKLIST 'READINESS' RATING – Attachment III]** Very high/high/medium/low etc.: [describe if very high] If *very high*, potential levers: [describe] **Translational-1 [CHECKLIST 'READINESS' RATING – Attachment II]** Very high/high/medium/low etc.: [describe if very high] If *very high*, potential levers: [describe] **Clinical [CHECKLIST 'READINESS' RATING – Attachment III]** Very high/high/medium/low etc.: [i.e., VERY HIGH] If *very high*, potential levers: [describe] **Translation-2 [CHECKLIST 'READINESS' RATING – Attachment III]** Very high/high/medium/low etc.: [describe if very high] If *very high*, potential levers: [describe]

Attachment II. Prototype Checklist for Translation-1 Research Opportunity (excerpted from report of Translational Research Panel**)**

CRITERION	RATING OR RESPONSE	SOURCE OR CITATION(S)
The Disease		
The contribution of NINDS to the Focus Disease should be unique and should not be competitive with a well-established effort in pharma or academia. This mandates that the global competitive environment should be critically evaluated and understood. NINDS Focus Diseases will lie in the funding gap between academic and industrial research.		
Biological Target		
The biological target has been clearly associated with human disease. Manipulating the biological target is expected to have a beneficial effect on the Focus Disease		
Ideally, biological targets that are logically related to the target of interest will have proven tractable.		
Tools		
Are there relevant in vitro biochemical or cellular assays that allow one to test for drug effects on the biological target?		
Are there relevant in vivo animal models that predict pharmacologic success against the disease target or a direct effect on the biological target?		
Are there biomarkers that are relevant to the disease?		
Chemical Matter		
Are there chemistry starting points for a discovery program?		
Is there any evidence of structure activity relationships?		
Can a high throughput screen be run in order to discovery chemical matter?		
Biological Matter		
Evidence for target engagement/interdiction		
Evidence for clinically relevant delivery methodology		
Evidence for manufacturing to scale under cGMP		
Long-Term Trajectory		
Timing. Can the disease be addressed in a reasonable amount of time?		
From an economic point of view, will pharma be attracted to a candidate in this disease area no later than clinical proof of concept?		

Resources		
Are there research resources that the proposed translational research program could leverage against (e.g., RAID or others)?		
Milestones		
Does the disease lend itself toward milestone-gated research? Simply stated, translational projects should clearly be on a path to help patients (e.g. entry into clinic, accelerate development via biomarker/patient selection or endpoint, etc).		

Attachment III. Prototype Preliminary Checklists for Research Opportunities: Basic/Etiology, Clinical, Translation-2

NOTE: These "checklist" criteria represent our workgroup's suggestions and an early prototype. Before these checklists can be implemented in the new priority-setting process, a series of steps to develop the tools from these early prototypes to versions that can be implemented in the first round of assessment of neurologic diseases needs to occur. An overview of these steps, analogous to development of a new measurement tool for a research study, is to circulate for input on format, additional criteria, etc in iterations, to increasingly larger groups of experts and stakeholders.

Basic/Etiology:
Pathophysiology is not well-established AND:
*there are epidemiological data suggesting new, unexplored

- environmental leads, or
- genetic leads,
- or potential gene-environmental interactions

that can be used to investigate mechanism

OR
*there are new technologies or resources (i.e., newly-identified families) that can be used to re-explore existing environmental, genetic, physiological, or imaging approaches to elucidating pathophysiology

OR
*there are promising exploratory data to suggest more in-depth investigation (through large-scale epidemiological study) of an environmental or genetic factor

Clinical (some bullet points are adapted from Translational Research Panel report); need to be sure this spans treatment/prevention/recognition:
*For treatment trials, the clinical endpoint is feasibly achieved in the timeframe of the disease or a biomarker measure of disease progression is available that is strongly linked through evidence to disease progression
*a potential treatment is at the point of readiness as evidenced by new issuance of Investigational New Drug (IND) or Investigational Device Exemption (IDE)
*IND or IDE represents new class or mechanism of treatment
*Efficacy study is not a priority for pharma
*Patients are available for or can readily be identified for clinical trials [unless this is the sole criterion lacking for the disease and thus is the recommended area of clinical research or infrastructure development in the form of registries, clinical trial network development, etc]
*Clinical endpoints/outcome measures relevant to the type of study (prevention, recognition/diagnosis, treatment) have a consensus of support and are well-established [unless this is the sole criterion lacking for the disease and thus is the recommended area

of clinical research (natural history, outcome measurement tool development, biomarker development) or infrastructure development in the form of biobanks, etc]

Translation-2 (applies to prevention/treatment/recognition or diagnosis):
*Body of clinical trial or other evidence demonstrates that there are one or more treatments or preventive strategies having high-quality, RCT evidence in support of efficacy OR one or more tools that can potentially improve recognition or diagnosis of a disease

*The potential health impact of implementing these approaches of proven efficacy is large (i.e., clinically important with a smaller group of people, OR affects a large number of people and impact on individuals is modest or large)

*There is evidence of substantial gaps between what is known to be efficacious and current practice, OR there is strong likelihood that current practice patterns are discrepant with best evidence

*Mechanism for lack of diffusion of new evidence is likely to be modifiable through new research findings

*Disparities in health or healthcare are a dominant feature of the incomplete diffusion of the new treatment, approach, or technology

*Quality of care indicators/health outcome measures are well-established [unless this is the sole criterion lacking for the disease and thus is the recommended area of translation-2 research

*For treatments for a given disease, the efficacy of two or more treatments is well-established but *comparative effectiveness* data (both on health and economic outcomes) are lacking

Priority 3 – Working Group: Develop a prototype of an evaluation process that NINDS can use for new disease-based initiatives and programs.

(Susan Axelrod, Kurt Fischbeck, Harry Orr and Timothy A. Pedley)

Process: The full Disease Module Panel met on July 23rd in Bethesda. As a result of that meeting four priorities were established and working groups assigned to each. The Priority 3 working group met by telephone conference call on October 28th with further follow-up by e-mail. We considered the charge as well as benchmarks that could be used to measure success. Input from the entire Disease Module panel and discussion of the final recommendations occurred at a meeting in Washington DC on January 14, 2009. A draft of a final report was circulated to all members of the working group, and all suggestions and changes were incorporated into the final submitted version.

Background: New disease-based initiatives were relatively rare before 1998 (see discussion in Priority 2 for a history of the new program initiative process). In 2005, NINDS Council asked for information regarding setting priorities for new initiatives, and how initiatives were evaluated. At that time, the main reason for the Institute to pursue a new initiative was to 1) advance research in an area where some important gap existed, such as limited understanding of relevant cell biology or disease mechanisms, absence of treatments that altered the course of disease, etc; 2) provide a needed resource or infrastructure; 3) enhance training in a relevant area or further career development of individuals with relevant expertise; and 4) create new mechanisms for advancing research. By numerical count, by far the greatest number of new programs was targeted at addressing an identified science gap.

Part of the 2005 analysis looked at whether new initiatives were successful in meeting their objective. Conclusions were that 1) new investigators for initiatives received a slightly higher percentage of awards (28.3%) than unsolicited applications (24.4%); that initiative awards had a higher percentage of new NINDS investigators (40%) vs unsolicited applications (26%); publications resulting from initiatives had impact factors similar to those resulting from unsolicited grants; and that the number of grant applications and funded grants increased following an initiative in selected areas (e.g. role of Parkin in PD, microarray centers for CNS research, SPOTRIAS awards). It is also worth noting that another important consequence of the SPOTRIAS awards has been an increase in the number of patients enrolled in stroke clinical trials. What has become clear from the 2005 analysis and other observations is that outcome measures specific to a given initiative provided useful data that can be missed by more general analyses.

We reviewed a number of specific initiatives, including the Udall Centers for Parkinson Disease, the Anticonvulsant Screening Program (formerly the Anticonvulsant Drug Development Program), the SMA Project, and the White House Conference on Curing Epilepsy.

Recommendations: Based on information provided by NINDS staff, review of the 2005 analysis and more detailed review of four different types of initiatives, our working group made the following recommendation:

For each new disease-based initiative:

1) ***There should be clear and explicit statements about its purpose and the anticipated goals.***

2) ***Outcome measures, both quantitative and qualitative, should be developed related to those goals, and such measures should be determined before the initiative begins.***

3) ***Input should be sought from appropriate disease-oriented non-profit organizations and other groups outside the NIH that offer relevant expertise .***

4) ***An evaluation plan should be developed that includes mechanisms for providing early feedback, an interim assessment using predetermined benchmarks, and a formal review following completion of the initiative or at 5-10 years out in the case of continuing programs (such as was recently done for the Udall Centers using an outside contractor).***

Benchmarks: These will vary with the initiative and programmatic details, but they should address the following considerations:

1) They should be based on information provided by the "landscape analysis" described in Priority 2.

2) They should be established before implementing the program.

3) They must be measurable (quantitative).

4) They must relate to the stated goals and objectives of the initiative.

5) A final assessment of the initiative, including its perceived success based on achieving prespecified objectives, as well as "lessons learned," should be reported to the Institute Director and NINDS Council.

Examples of Quantitative Outcome Measures: These might include the following comparisons related to individual initiative goals:

1) Increase in the number of a) R01 applications, b) new investigators applying, and c) institutions and investigators involved in research targeted to the disease area.

2) Disease-directed initiatives should enhance interactions between basic scientists and clinicians (including direct involvement between scientists and clinicians) as documented, for example, by co-authored publications.

3) Number and impact of published papers describing breakthrough discoveries in the initiative's disease area.

4) New and novel therapeutic advances as represented by published pre-clinical proof of concept studies, patents, INDs, completed phase 1,2 and 3 clinical trials, and FDA approval of innovative pharmacologic and biologic treatments.

There was some discussion as to whether biologically-based workshops would be helpful in establishing benchmarks, and the consensus was that these could be, depending on the initiative.

Finally, an overall **qualitative analysis** should make some determination as to 1) how the disease has benefitted from a particular initiative especially in terms of "meeting" a previously-identified unmet scientific opportunity; and 2) how the disease initiative has advanced the Institute's goals.

Priority 4 – Disease Module: What are opportunity areas for existing programs?

(Daniel H. Geschwind, Robert H. Brown, John K. Park, Roby Blumenstein)

Our group has identified 4 major areas where clear opportunities exist:

1) Establishment of a technology advisory group

This purpose of this group is to advise program staff, council and the institute director on how best to adopt and integrate new technologies and disciplines into basic, clinical and translational research programs, so as to most efficiently further NINDS' aims.

Why the timing is right:

- Advances in technology in areas such as
    - informatics
    - genomics and genetics
    - nanosciences
    - imaging
    - engineering
    - molecular and systems-computational biology

  all provide exciting opportunities to forward the disease related research agenda of NINDS. For example, such advances could aid in the development of earlier and more accurate diagnoses, biomarkers of disease progression, and, disease mechanism-based treatment strategies.
- However, there is a lag between recognition of these advances and the usual mechanisms, such as organizing workshops and advisory groups, to forward research agendas based on these advances.
- Further, there is a need for integrated thinking around seemingly different technologies or advances, which is not easily accommodated by a group of disparate workshops.

A standing technology advisory committee with rotating members with clinical expertise and experience in the disciplines mentioned above, as well as relevant industry representation, would aid in identifying areas of opportunity for rapid implementation for NINDS. The key will not just be having experts, but experts willing to hear the opinions of others and engage in a productive dialogue.

A specific example of an immediate priority or goal that such an advisory committee could tackle would be to enable the broader adoption of computational or systems level analytic approaches into neurologic disease research. There is a growing realization that some of the most exciting advances in biomedicine will come from the intersection of mathematical/computational approaches and bench biology. Thus disease-related work

that invokes systems level approaches that are truly multidisciplinary represents a key area of emerging opportunity (see recommendation #3 below).

It should be further acknowledged that the need for true multidisciplinary research teams to take advantage of a broad range of technological advances that offer new hope for significant treatment advances in neurological disorders is a major motivation and rationale for the expansion of multi-investigator collaborative grant mechanisms, rather than their reduction or elimination.

2) Rapid Response Infrastructure and Enabling Technologies Support

As recognized in the first recommendation, technology has the potential to drive innovation in disease-related research. One way to allow rapid and fleet-footed implementation of such technologies is via supplements to enable funded groups to harness this new technology. For example, in the area of genomics and genetics, high throughput genotyping and sequencing provide significant opportunities to advance our understanding of disease etiology and identify disease biomarkers. The discovery of previously unappreciated mechanisms of human variation, such as copy number variants (CNV), demands the use of microarray-based approaches to survey whether this form of genetic polymorphism contributes to neurologic disease. Such approaches require new equipment and often require the establishment of core centers of excellence that can serve the community. In some cases, such centers and needs may be optimally developed as cross-institute initiatives, as exemplified by the microarray consortium.

Why is such an initiative needed?

- There are significant barriers to adopting new research approaches and technologies into existing programs. Such barriers include access to the platforms, existing funding mechanisms, and review mechanisms (which may penalize investigators for attempting to enter a new area).
- However, many new approaches and technologies offer the hope and potential for more rapidly advancing our disease-related knowledge and treatment agenda and thus warrant rapid adoption.

New technology can be divided into two basic groupings based on the scope and intensity of the funding need:

- 1) Improvements on existing methods and approaches (e.g. confocal or live microscopy, real time PCR, DNA sequencing) that largely require learning the technique via training, workshops, manufacturer, etc. and for which new funds are needed to purchase the necessary infrastructure
- 2) Entirely new approaches that require intensive collaboration or re-orientation of a lab, in addition to equipment purchases. Examples of this type of need include functional genomics using microarrays or massively parallel sequencing, complex disease genetic association, human imaging, or systems biology/computational approaches.

For the former, supplements or new grants using more standard approaches that fund new equipment and infrastructure required or experiments will likely work. The latter may require new or specifically-targeted mechanisms that should not just fund experiments but also require a clear analytic and follow-up plan, as the analysis of such experiments is where most labs get hung up using new high throughput or highly technical methodologies. These technologies require more long term or intensive interactions among those with expertise, for example in cores, and the investigators and mechanisms to maintain these interactions are needed. This is also an area where the technology advisory group could play an important role. Survey of the research community should also be employed to help inform this process about emerging needs.

Specific programs might include:

A) Focused, rapid turn-around applications for infrastructure, equipment needs, or access to core resources that could be reviewed by staff and overseen by the technology advisory group could be very effective (need type #1).

B) Microarray-center like core facilities run via NIH institutes that address the need for new extensive platforms for research (need type #2).

C) Workshops or pilot grants to promote the kind of multidisciplinary interactions , or cross talk, that is required for integration of systems and computational biology with more established bench science.

In this last example, the concept of focused pilot grants stems from the notion that the R21 mechanism is not optimally effective as it competes with R01s in the same study sections. Rather, small methods (e.g. computational?) or technology-focused grants requiring some cross-disciplinary work on innovative methods, approaches or technologies combined with a disease-relevant question would be helpful. This would differ from the larger Eureka awards or Transformative R01s, as they would be smaller awards. Special study sections likely would be needed to handle these grants effectively.

3) Enable integration of systems-computational approaches with disease-oriented research.

In its broadest sense, systems biology is the analysis of interactions among all key components in a particular tissue, set of brain circuits, organism, etc. over time and in its major states. In its practical sense, it is based on approaches that attempt to put specific genes or gene products in the context of the system being investigated, including multiple levels of complex disease-related phenotypes, so as to understand priorities at a functional level.

Why is such an initiative needed?
The availability of high throughput data generation (e.g. genome) and large datasets (gene sequencing, gene expression, neuroimaging, patient data and outcomes, etc.)

necessitates a high level of computational expertise to optimally exploit the opportunities afforded by these data. Advances in computational power and development of effective methods to understand disease related gene-networks or brain networks now permits such an approach. Integrating systems computational approaches with disease-oriented research will result in a more exhaustive and complete level of hypothesis generation, rather than the current state of the art which often relies exclusively on investigators' intuition and educated guesses. The proper application of systems and computational approaches has such a large potential to accelerate concrete progress in disease understanding and treatment that it warrants separate consideration.

Mechanisms:

Potential specific mechanisms that could be considered include:

- Workshops or other meetings that bring disease researchers together with those thinking at a systems level (see #2C above).
- Support of multidisciplinary, multi-investigator projects integrating computational and bench approaches to disease
- Support of emerging multidisciplinary pilot collaborations to jump start initiatives where such work is in its very early phases.
- Support the necessary computational infrastructure at institutions engaged in disease-oriented research.
- Funding of training programs at participating institutions is likely necessary to galvanize such efforts.

4) Facilitate and Optimize Disease Consortia

Historically, biomedical research has taken place in independent labs or among small groups of investigators collaborating on an informal basis. These disease related efforts often occur in isolation or in groups that do not effectively collaborate with others. Perhaps an even more serious problem is parochialism or boundary setting by those who are working in the field to maintain the status quo. Also, aside from the relatively small number of investigators who conduct both bench and clinical research, basic lab research into the causes of disease is somewhat isolated from patient-facing clinical research into treatments for disease. This has become rate limiting:

- New technology platforms (GWAS, proteomics, micro-array, etc.) require quantities of patient-derived biomaterals and phenotypic that are greater than can be collected by an individual lab;
- The expertise required to collect, process and analyze samples is distributed across multiple investigators and institutions;
- The cost of simply collecting the quantity of raw data required for subsequent analyses is high (i.e., 5,000-10,000 GWA samples); and
- Replication of potentially important scientific findings requires open sharing of reagents, models, and methods;

- Disease consortia allow the collection of morbidity and mortality data across clinical centers and facilitate the optimization of care (per recommendations in Priority #5) for specific disorders. An important example is the consortium developed by the Cystic Fibrosis Foundation.

There are great advantages to having patient biomaterials, phenotype data, reagents, animal models etc. available to the larger community (academic and industry) rather than isolated within one lab or group of investigators. These include the ability to rapidly apply new technologies and test novel hypotheses by those currently outside of a particular field of basic or disease study. The foregoing issues could be addressed by the formation of disease-specific research consortia, and by the requirement that investigator-initiated projects bank their samples and data in a manner that can be made publicly accessible. While consortia may be more likely to succeed if somewhat self-organizing, NINDS could play a role by:

- Convening workshops on best practices for the organization and governance of such consortia;
- Convening initial planning meetings of investigators in specific disease areas interested in forming a consortium;
- Supporting consortia infrastructure or biobanks, such as biological material and reagent repositories (eg, Coriell) and community databases (eg, dbGAP);* [At the very least, sample and phenotyping banking requirements should be integrated into ongoing investigator-initiated research involving human subjects. For example, those studying Parkinson's disease and collecting patient samples, should be required to deposit those samples (cell lines, DNA, serum, RNA, etc) with high quality clinical phenotype data in publicly available databases. One example of such an effort is the NIMH human genetics initiative. In this manner, such activities can operate within or outside of active disease consortia.]
- Creating a funding mechanism for disease consortia activities, or for bio-banking of materials obtained in investigator initiated grants that will yield shared data and biomaterials.
- Adopting and enforcing policies that promote the sharing of data and reagents among disease community investigators. Although there sometimes may be grey zones in this area, requiring specific forms of sample deposition in repositories as a prerequisite for funding would help and is currently done at other institutes such as NIMH. The NINDS should play a role in assuring oversight and accountability.
- Leveraging collaborations with NGOs in all of these areas.

*One example of where the availability of both data and biomaterials has played a large role is in autism, where the AGRE resource (AGRE.org), brought more than 100 new investigators into the field by making biomaterials and related clinical data widely available. A critical element is having adequate phenotype information concurrently available, a criteria which is not met by many current bio-banking initiatives.

Priority 5 - Translational 2 Research : NINDS should attend to translating fruits of its traditional research portfolio into practice

The NINDS mission. The mission of NINDS is to reduce the burden of neurologic disease. Research funding through the NIH represents a societal investment, and the public and elected officials desire evidence that the investment ultimately produces better health in populations having neurologic diseases.

New knowledge from basic, translational (bench to bedside), and clinical trial research does not guarantee "translation" of that new knowledge into improved population health (Sung et al, *JAMA*, 2003). Despite substantial advances in medical science technology and knowledge about mechanisms and models of disease, as well as identification of new treatments of proven efficacy based on findings from randomized controlled trials (RCTs), there are well-documented gaps between findings from this discovery research and actual application of efficacious therapy in routine clinical practice settings. If therapies proven to improve health (under ideal, clinical trial conditions) are not delivered in actual practice to intended target populations or are not correctly implemented, health benefits to populations burdened with the disease do not accrue. Gaps may be manifest as either (1) a low proportion of eligible individuals who do not receive therapies that are known to improve health (McGlynn et al, *NEJM*, 2003), or (2) substantial delays in the diffusion of new knowledge about efficacious therapies (Antman et al, *JAMA*, 1992). In either situation, the consequences can be estimated in terms of reduced population health or avoidable morbidity and mortality.

> Diseases that are the subject of NINDS-supported research are not immune to this kind of shortfall in translation to practice. There are numerous examples of excellent clinical trial research that produced new knowledge which was only incompletely diffused into actual practice. tPA for stroke is one example. NINDS-supported RCTs met high standards for scientific quality and produced results that demonstrated efficacy under certain conditions; findings were published in high-profile journals. However, this therapy – even a decade later – is considerably underused relative to projected numbers of eligible individuals with stroke (Katzan et al, Arch Neurol, 2004). Similarly, recent evidence indicates that optimization of existing care such as nutritional and ventilatory support could have great impact on less common but particularly burdensome diseases such as spinal muscular atrophy and amyotrophic lateral sclerosis. There are many other examples, although documenting these gaps between availability of evidence-based treatments and their actual application to improve health of a population with a given neurologic disease is a relatively underdeveloped body of knowledge relative to cancer (IOM report, Ensuring Quality Cancer Care, 1999) and heart disease (Krumholz et al, Circulation, 2005), for example.

Addressing this problem (a problem which limits the NINDS being able to complete fulfillment of its mission) requires recognition that there are gaps in research. Analogous to research on mechanisms of disease, understanding reasons for lack of/incomplete diffusion of new knowledge on therapies and developing effective strategies for overcoming these barriers requires setting up models, measuring key variables in those models, and designing

interventions that are likely to target and reduce the barriers, then testing whether the hypothesized intervention produces the desired outcome. This kind of research, currently commonly identified as "Translation-2" or "T2" research, "requires different research skills: mastery of the implementation science of fielding and evaluating interventions in real-world settings and of the disciplines that inform the design of those interventions, such as clinical epidemiology and evidence synthesis, communication theory, behavioral science, public policy, financing, organizational theory, system redesign, informatics, and mixed methods/qualitative research." (Woolf, *JAMA*, 2008).

No other research funding agency is training investigators in or supporting T-2 research for neurologic conditions except in an ad hoc fashion. The Agency for Healthcare Research and Quality (AHRQ) has had limited funding over the years, and its support is spread across all medical conditions. Training of investigators with expertise and interest to conduct high-quality T-2 research for neurologic diseases has occurred ad hoc, with those individuals competing for training slots with trainees from other disease disciplines.

Anticipating developments in comparative effectiveness research. It appears likely that federal support for comparative effectiveness research may be forthcoming. It is important to clarify that T2 research is broader in scope than comparative effectiveness research, but comparative effectiveness research falls within the portion of the neuroscience research continuum encompassed by T2 research. Comparative effectiveness research provides rigorous quantitative analysis of the relative health benefits of different treatments (or diagnostic tests) for a *given* disease and patient population; such studies may or may not evaluate relative costs. Study designs can range from systematic reviews of existing literature to randomized trials comparing alternative treatments for which there is uncertainty as to relative benefit. For many neurological diseases, head-to-head comparisons of alternative treatments are infrequently conducted, yet diffusion of new treatments from clinical trials into widespread practice may be limited because of lack of data about the relative clinical benefits of new treatments compared to existing treatment approaches, and lack of data on the benefit among general clinical populations, which differ from highly selected clinical trial samples.

Thus, if anticipated federal investment in comparative effectiveness research comes to fruition, NINDS should be poised to maximally target those resources on disease-focused studies that are consonant with its mission. Implementation of a priority-setting process for research along the full continuum (including T2 research) is recommended elsewhere in the panel's report. A priority setting process that includes a landscape analysis that encompasses T2 research would enable NINDS – with input from other stakeholders – to systematically analyze and justify applying those resources to comparative effectiveness research studies of those neurological diseases for which (a) knowledge is most lacking about the relative health benefit of alternative treatment approaches, and (b) obtaining this knowledge would have a large health impact or could greatly affect diffusion of a superior treatment (or diagnostic test) into routine practice.

WHY THE TIME IS RIGHT FOR T2 NEUROSCIENCE RESEARCH INVESTMENT BY NINDS

1. T2 research has traditionally been conducted in the context of initiatives; thus, investigators in the field are used to responding to initiatives. Initiatives on the part of NINDS are likely to be well-subscribed by highly-qualified investigators prepared to focus on problems that are likely to have a high impact on the health of persons with or at risk for neurological diseases.
2. Other NIH institutes such as NCI and NHLBI have experience in supporting T2 research and thus have established track records to follow in facilitating the research and present opportunities for leveraging resources across institutes.
3. Addressing disparities is already a required investment for NINDS and is an important aspect of T2 research. Many modifiable health disparities are due to disparities in healthcare delivery.
4. Overall investment in T2 research has been estimated as only about 1.5% of total biomedical research funding. While this is generally seen as too low an overall societal investment, support for T2 research in neurological disease is even lower. A relatively small commitment of NINDS funds could have a large impact, and initiation of targeted investments on research questions of likely high-yield/high-importance should not meaningfully change level of support across the current range of research in the institute's portfolio.

RECOMMENDATIONS:

	COST	POTENTIAL IMPACT
Identify or hire a program director with interest and expertise in health services research and ensure direct reporting lines to NINDS leadership, analogous to clinical trials/translation-1 offices. This person should work in close relationship with Office of Science Policy and Planning Staff, across clusters in the disease-specific analyses in the priority-setting process, and in reviewing/collaborating in initiatives/ announcements from other institutes, to ensure advocacy and awareness at NINDS for signing on to T2 research announcements that are relevant and priorities for NINDS.	low to moderate	high
As an outcome of the initial round of the new priority-setting process, launch initiatives for the highest-priority/highest yield areas for T2 neurosciences research. Set specific milestones and measurable objectives for those initiatives within a 3-year timeframe a priori, and track them.	moderate	high
Establish a working group of NINDS staff to develop recommendations for T2 research. Encourage a broad range and number of NINDS staff and leadership to attend a workshop to learn how T2 research fits into their research emphasis and the institute's research mission. Invite staff from other institutes who have engaged in similar initiatives. Invite extramural investigators doing T2 research in neurological disease and IOM- and other nationally recognized health services research thought leaders from outside neurology for perspective.	low	moderate to high
Identify neurological disease advocacy organizations interested in T2 research. Establish relationships with counterparts to the NINDS program director responsible for T2 research to identify opportunities for partnership. Promote the funding and co-sponsorship of initiatives to make standardized morbidity and mortality data available from clinical centers treating specific neurological diseases.	low to moderate	moderate to high
Review advances in T1/clinical trial research funded by NINDS with specific recommendations for T2 research that should be considered in the priority-setting process arising from research in those earlier phases. For example, in some cases, clinical trials should include analysis of barriers to implementation of the results.	low	moderate to high
Identify funded CTSAs that have neurology investigators as major participants and evaluate whether these centers may provide opportunities for T2 research in neurological disease, particularly where community practice settings are already established through those centers.	low	moderate
Modify the K announcements from NINDS to include specific	low to	moderate to

language that invites and acknowledges T2 research as one area in which the institute seeks to develop investigators and support discovery.	moderate	high
Until there is a cadre of senior investigators in neurology health services research, make sure that T2 neuroscience research applications are properly reviewed by directing applications to study sections within the Healthcare Delivery and Methodology IRG at CSR, specifically, the Health Services Organization and Delivery Study Section*, which has experts in the disciplines that comprise T2 research (rather than review committees with neurology but not T2 research expertise).	low	moderate to high
Seek out NIH institutes with common goals (i.e. NHLBI for cardiovascular disease prevention; NCI for brain tumor) and identify ongoing or completed T2 initiatives that NINDS can learn from or collaborate in with minimal investment.	moderate	moderate to high
Interview leadership and key staff at those institutes to learn what worked/what they would do differently to implement the specific T2 initiatives they have put in place. Prepare a report on these findings for internal use and for NINDS council review. Institutes could include NHLBI, NCI, and NIMH.	low	moderate
Compile a list of what evidence reports on neurologic topics have been funded by AHRQ through its evidence-based practice center network, analyze what gaps these reports identify, and work with AHRQ and professional societies like the AAN (through the staff person assigned this topic) to facilitate funding more neurologic topics through this mechanism.	moderate	moderate to high
Ensure that NINDS' new priority-setting process enables the institute to identify and justify funding for comparative effectiveness research studies that target neurological diseases for which there is a dearth of information about the relative clinical benefit of alternative therapies and diagnostic tests, and for which obtaining this new knowledge is likely to have a meaningful impact on current practice. The scope of this research could include anticipated emerging therapies and diagnostic tests from NINDS-supported Translation-1 and clinical research.	low to moderate	moderate to high

***http://cms.csr.nih.gov/PeerReviewMeetings/CSRIRGDescriptionNew/HDMIRG/HSOD.htm**

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Major Recommendations Compiled (all working groups)

Note: Please refer to the working group reports for more detailed recommendations, rationale, and implementation suggestions.

Working group 1: Disease List

1. Develop a clinically and biologically clustered, web-based, relational disease database that builds from an edited form of the current disease list.

2. Make the database publicly accessible, and devise a plan to actively disseminate information about the availability and utility of the disease list resource to the scientific community, the lay public and NGOs, and internally to program directors and other institute staff. Evaluate its utility/value among each target group of users

3. Dynamically update the disease database, once developed.

Working group 2: Environmental scan / Priority Setting

1. Communicate high-level NINDS support for new priority-setting process that incorporates a systematic environmental scan for unmet scientific opportunity within and across neurologic diseases.

2. Initiate a two-level priority-setting process that is based on unmet scientific opportunity within and across neurologic diseases and is systematic, comprehensive, data-driven, and overlaid on the current NINDS structure.

3. Plan an initial implementation strategy, and phase in the scope of the priority-setting process over several years.

4. Track and re-evaluate disease burden, opportunity, dissemination of the priority-setting products, and the implementation plan for the priority-setting process.

5. Maximize efficiency in use of federal resources by pursuing trans-NIH collaboration and involvement.

Working group 3: Evaluation Process

For each new disease-based initiative:

1. There should be clear and explicit statements about its purpose and the anticipated goals.

2. Outcome measures, both quantitative and qualitative, should be developed related to those goals, and such measures should be determined before the initiative begins.

3. Input should be sought from appropriate disease-oriented non-profit organizations and other groups outside the NIH that offer relevant expertise.

4. An evaluation plan should be developed that includes mechanisms for providing early feedback, an interim assessment using predetermined benchmarks, and a formal review following completion of the initiative or at 5-10 years in the case of continuing programs (such as was recently done for the Udall Centers using an outside contractor).

Working group 4: Opportunity Areas

1. Establish a technology advisory group.

2. Develop a program for rapid response infrastructure and enabling technologies support.

3. Enable integration of systems-computational approaches with disease-oriented research.

4. Facilitate and optimize disease consortia.

Translational 2 Research

1. Identify or hire a program director with interest and expertise in health services research and ensure direct reporting lines to NINDS leadership, analogous to clinical trials/translation-1 offices. This is considered to be the most critical, highest impact recommendation of the set of Translational 2 Research recommendations.

2. As an outcome of the initial round of the new priority-setting process, launch initiatives for the highest-priority/highest yield areas for T2 neurosciences research.

3. Make sure that T2 neuroscience research applications are properly reviewed by directing applications to study sections within the Healthcare Delivery and Methodology IRG at CSR, specifically, the Health Services Organization and Delivery Study Section.

4. Seek out NIH institutes with common goals (i.e. NHLBI for cardiovascular disease prevention; NCI for brain tumor) and identify ongoing or completed T2 initiatives that NINDS can learn from or collaborate in with minimal investment.

5. Interview leadership and key staff at those institutes to learn what worked/what they would do differently to implement the specific T2 initiatives they have put in place. Prepare a report on these findings for internal use and for NINDS council review. Institutes could include NHLBI, NCI, and NIMH.

6. Compile a list of what evidence reports on neurologic topics that have been funded by AHRQ through its evidence-based practice center network, analyze what gaps these reports identify, and work with AHRQ and professional societies like the AAN (through the staff person assigned this topic) to facilitate funding more neurologic topics through this mechanism.

7. Ensure that NINDS' new priority-setting process enables the institute to identify and justify funding for comparative effectiveness research studies that target neurological diseases for which there is a dearth of information about the relative clinical benefit of alternative therapies and diagnostic tests, and for which obtaining this new knowledge is likely to have a meaningful impact on current practice. The scope of this research could include anticipated emerging therapies and diagnostic tests from NINDS-supported Translation-1 and clinical research.