Intellectual and Developmental Disabilities (IDD) Branch NICHD

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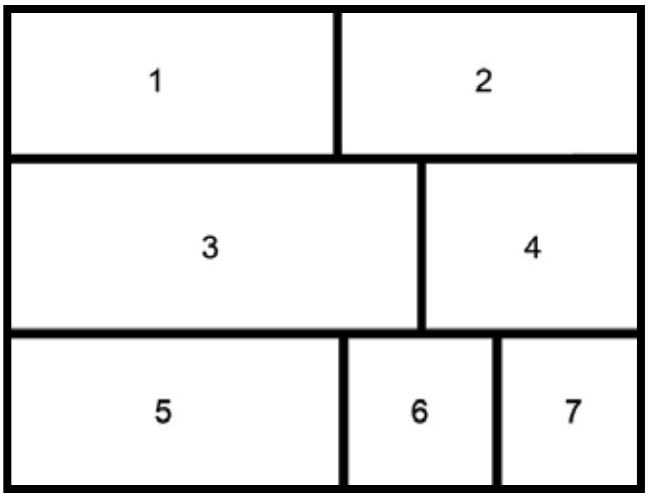

The cover of this report features photos from the life of Eunice Kennedy Shriver, who was instrumental in helping to establish the NICHD, now named in her honor. Most people are aware of Mrs. Shriver's efforts related to Special Olympics and her championing for the rights of those with disabilities. Less well known and especially important to the NICHD, she was equally passionate about the need to study IDD as a way to improve the care of and quality-of-life for those with IDD and their families. Both passions were critical to the establishment of the NICHD, the IDD Branch and its research mission, and the IDD Research Centers Program, which is also now named in her honor. Mrs. Shriver died on August 11, 2009, at the age of 88.

Photos shown are as follows:

1. Mrs. Shriver stands with her arms around two athletes with IDD during a Special Olympics trip to South Africa. (Photo courtesy of Special Olympics)
2. On October 17, 1962, President John F. Kennedy hands his sister, Mrs. Shriver, the pen he used to sign Public Law 87-838, authorizing the establishment of the NICHD to "encourage imaginative research into the complex processes of human development from conception to old age."
3. The first National Advisory Child Health and Human Development Council poses to commemorate its first meeting on November 14, 1963. Mrs. Shriver, fourth from the left in the front row, served a standard tenure on the first Council and took part in Institute-sponsored meetings and conferences for some time thereafter.
4. Mrs. Shriver smiles at her son, Timothy, during the March 2008 event in her honor. During the event, the NICHD officially became the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development. The Institute also renamed its flagship research program as the Eunice Kennedy Shriver IDD Research Centers Program and inducted Mrs. Shriver into the NICHD Hall of Honor.
5. During the Surgeon General's Conference on Health Disparities and Mental Retardation in 2001, Mrs. Shriver poses with a few friends, including (L to R): Dr. Loretta Claiborne, an accomplished and celebrated Special Olympics athlete, member of the Special Olympics International Board of Directors, and passionate advocate for people with IDD; Dr. Duane Alexander, former NICHD Director; then Surgeon General Dr. David Satcher; and Dr. Timothy Shriver, her son and Chairman of Special Olympics. The NICHD played a lead role in the conference, which was planned and carried out with full inclusion of persons with IDD. During the event, Dr. Satcher presented the Surgeon General Medallion Award to Mrs. Shriver for her public health achievements.
6. During "Camp Shriver"—the precursor to the Special Olympics—Mrs. Shriver helps a child into the swimming pool at her Maryland farm, Timberlawn, in 1962. (Photo courtesy of Special Olympics)
7. Mrs. Shriver congratulates an athlete during the 2007 Special Olympics World Games in Shanghai, China. (Photo courtesy of Special Olympics)

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EXECUTIVE SUMMARY

The Intellectual and Developmental Disabilities (IDD) Branch, formerly the Mental Retardation and Developmental Disabilities Branch, within the Center for Developmental Biology and Perinatal Medicine of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), has a longstanding history of providing support for a diverse portfolio of research projects, training programs, and research centers dedicated to promoting the well-being of individuals with IDD. When the Institute was created at the National Institutes of Health (NIH) in 1962 at the request of then-President John F. Kennedy and with the support of congress, one of its primary charges was to encourage investigations in human development throughout the lifespan, with an emphasis on understanding developmental disabilities, including intellectual disabilities (historically referred to as mental retardation). The mission of the IDD Branch is to:

- Develop and support research and research training programs in IDD;
- Administer a program of support for centers for research in IDD;
- Coordinate with university-affiliated programs for IDD with respect to integration of research, training, and service activities; and
- Partner with other federal agencies, organizations, and advocacy groups to advance efforts toward the prevention, diagnosis, treatment, and management of IDD that will improve the quality-of-life for these individuals and their families.

Since its last report to the National Advisory Child Health and Human Development (NACHHD) Council, the Branch has continued its mission through a variety of mechanisms, grants, and contracts. The Branch has also added breadth to its portfolio by expanding traditional efforts to address quality-of-life issues for individuals with IDD, while increasing multidisciplinary and translational research to facilitate the movement of basic research from the bench to the clinic and beyond. The Branch's expanded newborn screening program and the growth of certain cooperative research centers reflect such efforts.

This report highlights advances from Branch-sponsored research, emphasizes major Branch initiatives from the past four years, and outlines areas of future expansion in the field of IDD research.

Branch activities are organized into topical research initiatives, with some areas of programmatic overlap. The following initiatives will be the focus of subsequent sections of this report:

- Eunice Kennedy Shriver IDD Research Centers (IDDRCs)
- Program on Fragile X syndrome (FXS) and associated disorders
- Rare Diseases Cooperative Research Consortia (RDCRC)
- Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers
- Chromosome abnormalities, genetic/genomic syndromes, and epigenetic disorders
- Biochemical and metabolic research
- Research on Autism Spectrum Disorders (ASDs)

- Newborn screening
- Research resources
- Branch-supported training initiatives

The next several sections focus on major accomplishments within each of the areas listed above, with an emphasis on areas for which the Branch has employed collaborative approaches to improve coordination and leverage of resources.

The report concludes with an overview of possible *Future Directions for the Branch* in IDD research. The section describes the discussions of an expert panel of IDD researchers and clinicians assembled as part of the Institute's continued efforts to improve strategic planning and transparency for its components. The expert panel and Branch members gathered to discuss the Branch's existing research portfolio as a way to address the following issues: opportunities in prenatal, perinatal, and postnatal identification of infants and children at risk for developing cognitive impairment; areas, such as adolescent brain development, obesity, and health disparities, in which IDD research has lagged; and promotion of training initiatives. Branch staff and members of the expert panel also discussed a de-emphasis on individual disorders with concomitant support for groups of conditions with common pathways or shared elements as a way to facilitate the ambitious but necessary goal of developing drugs and other cognitive and behavioral interventions to improve the lives of individuals with IDD and their families. The potential to guide the IDD field toward translational applications is enormous and potentially transformative, making this a very exciting time in IDD research.

Biosketches of Branch personnel are listed in *Appendix A*. Funding Opportunity Announcements (FOAs), which reflect areas of programmatic emphasis released by the Branch during the last four years, are listed in *Appendix B*. *Appendix C* lists expert panel members. *Appendix D* describes the various conferences and meetings the Branch supported since the Branch's last report to the NACHHD Council.

INTRODUCTION TO THE BRANCH

Intellectual and developmental disabilities (IDD) represent a significant source of morbidity and mortality among the pediatric population. Intellectual disability is characterized by significant limitations in intellectual functioning and adaptive behavior as expressed in conceptual, social, and practical life skills. These limitations originate before age 18 years. The American Association on Intellectual and Developmental Disabilities describes developmental disabilities more broadly as severe chronic disabilities that can be cognitive, physical, or both, that generally appear before age 22 years, and that are likely to be lifelong. The etiology of IDD is complex, and more than 500 genetic diseases (most individually rare) contribute to this condition; chromosomal disorders, such as Down syndrome, are estimated to account for 5 percent to 19 percent of all IDD cases (Yeargin-Allsopp et al, 2007). The prevalence of severe intellectual disability is estimated as 3 to 4 per 1,000 children and adults, while mild intellectual disability is much more common. IDD significantly impacts the physical, emotional, and financial health

and well-being of the affected individuals and their families. Approximately 17 percent of children in the United States have some type of disability, and about 2 percent of children will require lifelong care for their disability; the associated economic costs of these disabilities are significant (Boyle and Cordero, 2005).

Although "mental retardation" and "intellectual disability" are technically synonymous, intellectual disability is the preferred term among many professional organizations, advocacy groups, and government agencies. This language is considered to be less offensive to persons with IDD, to be more consistent with internationally used terminology, and to align with current professional practices that focus on supports tailored to enhance individuals' functioning (Schalock et al, 2007). To reflect the field's move away from the term "mental retardation" and toward the broader term IDD, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) changed the name of the Branch from the Mental Retardation and Developmental Disabilities Branch to the IDD Branch. Similarly, this document uses the term IDD, not "mental retardation" to describe the relevant conditions. Branch reports and other documents published prior to September 2009 use the older Branch name and terminology.

This change in the Branch name also necessitated a change in its functional statement, now revised to better reflect the Branch's growing number of partnerships with other federal agencies, organizations, and advocacy groups. The revised mission of the IDD Branch is to:

- Develop and support research and research training programs in IDD;
- Administer a program of support for centers for research in IDD;
- Coordinate with university-affiliated programs for IDD with respect to integration of research, training, and service activities; and
- Partner with other federal agencies, organizations, and advocacy groups to advance efforts toward the prevention, diagnosis, treatment, and management of IDD that will improve the quality-of-life for these individuals and their families.

The revised mission also better reflects the Branch's longstanding goals of prevention, diagnosis, treatment, and management of IDD with a focus on improving outcomes for persons with IDD.

In fiscal year 2008, the Branch supported IDD research with a total budget of $106.4 million, which represents a stable investment of approximately $106 million during the four-year reporting period, as well as a decrease in actual or constant dollars when corrected for inflation for that same time period (Figure 1). Among the 236 total Branch-supported projects for fiscal year 2008, most (just less than 50 percent) were research project grants (e.g., R01, R03, R13, R15, R21, and R37 mechanisms), the "bread and butter" of National Institutes of Health (NIH) awards (see Figure 2 and Table 1). One-quarter of Branch funds supported Research Centers grants (P30 and P50 mechanisms), and 13.5 percent of the portfolio supported Program Project grants (P01 mechanism) for multi-investigator projects. Another 3 percent of the Branch's portfolio was devoted to training initiatives, including training programs (Ts), fellowships (Fs), and research career development program awards (Ks). Small business awards (Small Business Innovative Research awards and Small Business Technology Transfer awards), contracts, and cooperative research consortia in rare diseases and muscular dystrophy (U54s) comprised the remainder of the portfolio.

The funding of Branch initiatives also reflects some subtle shifts in programmatic emphasis. For instance, during the four-year reporting period, allocation of funds remained fairly consistent in the following categories of research projects: Biomedical, typically considered basic-science oriented; Behavioral, related to behavioral research studies; and Biobehavioral, a combination of Biomedical and Behavioral (Figure 3). However, when further categorized, a trend of increasing support of Biobehavioral projects with concomitant reduction in support for Biomedical research is apparent. This trend is especially evident when comparing human projects (Figure 4) and animal projects (Figure 5), perhaps reflecting the increased sophistication of testing algorithms to dissect complex behaviors in rodent and other animal models of human developmental disorders.

Another way to evaluate IDD Branch funding trends is to examine the Branch's support for selected disorders during the four-year reporting period. Figure 6 and Figure 7 illustrate these trends for nine different conditions or topics within the Branch's portfolio. The figures indicate fairly consistent support for research related to Fragile X syndrome (FXS), metabolic/ mitochondrial disorders, and Down syndrome, while also showing a steady increase in support for Autism Spectrum Disorders (ASDs), which now represents almost 25 percent of the total Branch portfolio (Figure 6). Conditions such as muscular dystrophy and Rett, Williams, and Prader-Willi syndromes received fairly stable support, while the Branch's commitment to newborn screening increased six-fold during this reporting period (Figure 7).

The remainder of the report highlights the science advances sponsored by the IDD Branch during the past four years. Although there are some areas of programmatic overlap, Branch activities are organized into the following topical research initiatives: Eunice Kennedy Shriver IDD Research Centers (IDDRCs); program on FXS and associated disorders; Rare Diseases Cooperative Research Consortia (RDCRC); Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers; chromosome abnormalities, genetic/genomic syndromes, and epigenetic disorders; biochemical and metabolic research; research on ASDs; newborn screening; research resources; and Branch-supported training initiatives. These sections describe the Branch's activities with a focus on major accomplishments of each initiative. The final section of this report describes possible *Future Directions for the Branch*.

Biosketches of Branch personnel are listed in *Appendix A*. Funding Opportunity Announcements (FOAs), which reflect areas of programmatic emphasis, released by the Branch during the last four years are listed in *Appendix B*. *Appendix C* lists expert panel members. *Appendix D* describes the various conferences and meetings the Branch supported since the Branch's last report to the National Advisory Child Health and Human Development (NACHHD) Council.

EUNICE KENNEDY SHRIVER IDD RESEARCH CENTERS (IDDRCS)

Congressional mandate established the IDDRCs (formerly the Mental Retardation and Developmental Disabilities Research Centers), the flagship program of the NICHD, one year after the Institute's founding in the early 1960s. These centers were to provide facilities and support for research in IDD and to develop university-affiliated programs for training personnel to care for individuals with IDD. In 2008, when an Act of Congress changed the name of the Institute to the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the NICHD's leadership also renamed its flagship centers program in her honor as the Eunice Kennedy Shriver IDDRCs. The focus of the program is to support researchers whose goals are to understand the causes of and to develop treatments for IDD. During the last 40 years, the Centers' activities have made dramatic strides in achieving these goals.

Currently, 14 funded sites and one site under a no-cost extension located at universities and children's hospitals throughout the country comprise the Eunice Kennedy Shriver IDDRCs (Figure 8). Many of these Centers are at institutions that also support University Centers for Excellence in Developmental Disabilities Education, Research, and Service (UCEDDs), which represent 67 sites located in every state in the country. Quite a few Centers also overlap with the 38 Leadership Education in Neurodevelopmental and Related Disabilities (LEND) programs, which are funded through the Maternal and Child Health Bureau of the Health Resources and Services Administration (HRSA) to provide interdisciplinary leadership training. Thus, these three programs—the Eunice Kennedy Shriver IDDRCs, UCEDDs, and LENDs—function synergistically at many sites to promote IDD-related research, service, and training. A P30 grant mechanism funds the Eunice Kennedy Shriver IDDRCs in the form of core infrastructure that supports independently funded, IDD-relevant projects and new program development projects, the latter of which represent a small portion of the overall budget expenditure within an individual Center. As a result, the IDDRCs primarily provide research support services for investigators rather than directly funding research projects.

The Centers differ from each other in many aspects, including their scientific focus, size, lifespan, and history. Although these differences impart a unique quality to each Center, the Eunice Kennedy Shriver IDDRCs share common features that are discernible and important, including their ability to leverage resources from their host institutions, private donors, and other sources to facilitate growth. Each Center presently supports between 45 and 166 projects and at least 20 to more than 70 principal investigators (PIs), who receive funding from a variety of sources. This diversity allows the Centers to support substantially more projects and affiliates than would be possible using NICHD support alone. In fact, between fiscal year 2005 and fiscal year 2008, the IDDRCs expanded the total number of projects supported by their cores from approximately 1,000 to 1,200, in spite of nearly flat funding provided to the program from the NICHD during that time period. Many of the additional projects receive funding from other NIH Institutes, such as the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute of Mental Health (NIMH), and a number also are supported by non-governmental sources, such as foundations and private research institutions (Figure 9). In addition, IDD Branch staff work closely with the IDDRC directors and/or co-directors at twice-annual meetings and in various one-on-one discussions.

Although it is difficult to summarize the breadth of research supported by the Eunice Kennedy Shriver IDDRC Program, a number of accomplishments are worth highlighting:

- Three Requests for Applications (RFAs), issued in 2005, 2007, and 2008, solicited competitive continuation and new grant applications. The RFAs spelled out the goals of collaborating, sharing, and translating discoveries in IDD research. These RFAs attracted new applicants to the field, and several successfully competed for research funds.
- The creation, launch, and expansion of a secure Web portal for the Program facilitated collaboration among investigators affiliated with the Eunice Kennedy Shriver IDDRCs. This project lasted three years, ending in 2008. The NICHD funded the work under a subcontract to the Association of University Centers on Disabilities, which hosted and updated the "public" face of the Web portal.
- The Centers are making efforts to integrate several patient registries across all the IDDRCs. This process began with a Participant Registries Meeting, sponsored by the IDDRCs at the University of North Carolina (UNC) and the University of Wisconsin, held at the Waisman Center at the University of Wisconsin in June 2007. The meeting attracted representatives from most IDDRCs, other IDD centers programs (including UCEDDs and LENDs), the Centers for Disease Control and Prevention (CDC), and some advocacy groups (such as the Fragile X Research Foundation, called FRAXA). The two sponsoring IDDRCs initiated a proof-of-principle test to integrate their patient registries and document the process of addressing human-subjects compliance issues and other challenges. Initial efforts will be focused on registering individuals with FXS; registries of those with other disorders will follow.
- The IDDRCs at the Kennedy Krieger Institute (KKI) in Baltimore and at the Children's Hospitals in Washington, D.C., and Philadelphia, Pennsylvania, initiated a Mid-Atlantic Consortium on March 30, 2007, with aims to synergize their efforts on shared research interests, develop collaborative projects, and create cross-institutional training opportunities. The second meeting of this Consortium, which focused on ASD research, occurred on April 27, 2009.
- *Translational Analysis of Chronic Aberrant Behavior across the Life Span*, a program project with a focus on collaboration, received an outstanding score for funding in fiscal year 2009. This program consists of one project at the IDDRCs based at the KKI, the University of Kansas, and the University of Massachusetts and will utilize an IDDRC Core at the University of Massachusetts. This project will share a unique resource, facilitate collaboration among users of three IDDRCs, and translate basic knowledge in behavioral science into treatments for difficult behavior.
- The University of Wisconsin IDDRC organized an interdisciplinary training conference that gathered representatives of all Branch-funded T32 training programs in IDD. The conference's aim was to enhance training opportunities and facilitate synergy. This effort resulted in an R13 application, *Interdisciplinary Training Conference in Intellectual Disabilities*, for support of a mentoring workshop for predoctoral and postdoctoral fellows that will be held in conjunction with the annual Gatlinburg Conference on Research and Theory in IDD, a seminal meeting for investigators in the field.

- In 2005, the IDDRC directors catalogued collaborations among IDDRC affiliates. Since then, the directors have consciously facilitated collaborations among individual investigators, within and across IDDRCs, and with other centers programs, including FXS Centers-within-Centers, to better address research goals.

The fifth-year hiatus in the competition of the Eunice Kennedy Shriver IDDRCs occurred in 2006-2007 and provided an opportune time to contemplate change for the Program. NICHD leadership and IDD Branch staff established several goals for this process, including: encouraging the Centers' leaders to share unique resources, facilitating collaboration among users, and stimulating translation of knowledge about the causes of IDD into interventions; soliciting input from IDDRC directors and their colleagues, patient advocacy groups, and potential funding partners to facilitate restructuring for the continued vitality of the Program; considering a formal evaluation of the P30 funding mechanism as a means of defining and achieving new Program goals; and updating existing and issuing new guidelines that reflect contemporary Program goals. The outcomes of this effort are outlined below:

- The IDD Branch sponsored a workshop entitled *Mental Retardation and Developmental Research Centers Program: Planning for the Fiscal Year 2007 Hiatus and Beyond* in June 2006. Three principal recommendations resulting from the meeting were to retain the P30 funding mechanism, increase monitoring of progress, and make the Program much better known to constituencies, congress, and the public.
- Consequent to the 2006 workshop recommendations, Branch staff organized a meeting on *Community and Public Interest Insights for the Mental Retardation and Developmental Research Centers*, held on March 25, 2007. The purpose of the meeting was to include advocacy groups in Program planning and outreach. Attendees included representatives from advocacy organizations and NICHD staff, including the NICHD Director.
- The steady increase in the number and quality of P30 applications, despite flat funding, is also a significant achievement. This trend reflects the growth of IDD research nationally, the openness and transparency of the Program, and the recognition of the pivotal role that the IDDRC Program plays in promoting and advancing IDD research.

EUNICE KENNEDY SHRIVER IDDRC PROGRAM SCIENCE ADVANCES

Neural Stem Cells (NSCs) and Induced Pluripotent Stem Cells (iPSCs)

The discovery of NSCs in the adult mammalian brain dramatically changed the view of the brain's regenerative potential and raised the possibility of preempting the development of some neurodegenerative (e.g., Alzheimer disease) and neurodevelopmental (e.g., Down syndrome) diseases. Despite intense efforts to identify their origin during the last ten years, NSCs' identity had remained elusive. One group of scientists, supported by the IDDRC at University of California, Los Angeles (UCLA), provided evidence, based on their demonstrated cell surface markers, that the ependymal cells lining the murine brain ventricles are NSCs (Coskun et al, 2008). Characterizing these cells structurally and functionally will be important for developing methods to control their proliferation and differentiation *in situ* before onset of pathogenesis to preempt development of disease.

In another development involving stem cells, new technologies are allowing investigators to take skin fibroblasts from individuals with neurological disorders and reprogram them to become iPSCs, which can then be differentiated into neurological cell types. This cellular reprogramming might provide an opportunity to not only understand fundamental disease mechanisms, but also to screen drugs and other compounds for their potential therapeutic utility. Investigators at the Waisman Center at the University of Wisconsin have generated iPSCs from the skin cells of a child with spinal muscular atrophy (SMA), a genetic neurological disorder resulting from mutations in the *Survival Motor Neuron 1* (*SMN1*) gene that cause SMN protein deficiency and lead to the loss of motor neurons, muscle weakness, paralysis, and death (Ebert et al, 2009). This research showed that the iPSCs can be differentiated into expressing markers of spinal motor neurons by treating them with neurotrophic and other growth factors, and that the cells from the affected child exhibited selective motor neuron degeneration consistent with SMA. Moreover, treatment of the cells with drugs to increase the amount of SMN protein showed a compensatory improvement. These technologies show potential for investigating disorders that affect neurons, which are notoriously difficult to isolate from affected individuals, and the promise of developing therapies to treat them.

Rett Syndrome

Rett syndrome, caused by mutations in the *MECP2* gene, occurs almost exclusively in girls, causing loss of language, cognitive, and fine motor skills around the time they are learning to walk. In boys, who have only one X chromosome compared to girls' two X chromosomes, this deficiency tends to cause death or very severe neurological impairment during infancy. Until recently, scientists believed that the *MECP2* gene was an "off" switch, or silencer, for other genes. But a study performed by IDDRC investigators showed that the gene is an "on" switch for a startlingly large number of genes. A team at the Baylor College of Medicine IDDRC analyzed gene-activity patterns in the brains of both mice with a MeCP2 deficiency and those with an *MeCP2* gene duplication, notated as $MeCP2^{+}$ (Chahrour et al, 2008). Previous studies revealed only subtle differences between the brains of normal and *MeCP2*-mutant mice, but those studies measured gene activity throughout the brain. In this study, the investigators focused on the hypothalamus, a region known to produce hormones that influence growth, mood, and the sleep-wake cycle—all of which are affected in Rett syndrome. Their analysis revealed nearly 2,600 misregulated genes in both mouse models, with opposite patterns. The activity of about 2,200 genes decreased in MeCP2-deficient mice and increased in $MeCP2^{+}$ mice, indicating that MeCP2 is an activator for those genes. Among the genes activated by MeCP2, the researchers found many that encode neuropeptides; however, about 400 genes showed the reverse pattern, indicating that MeCP2 is a repressor for their expression.

These results dramatize the need for a paradigm shift in research on genetically caused IDD from the "one gene-one protein" linear approach to a "gene-protein network" approach. Based on this discovery, researchers could design therapies for Rett syndrome and $MECP2^{+}$ syndrome by targeting the downstream genes affected by MeCP2, but first they would have to know which target genes and which brain regions are most relevant to neurological function in this condition.

Cornelia de Lange Syndrome (CdLS)

A team of researchers affiliated with the IDDRC at Children's Hospital of Philadelphia identified two new genes that contribute to CdLS, a multisystem genetic disease affecting an estimated one in 10,000 children. Classically, CdLS includes IDD, impaired growth, heart defects, feeding problems, deformed upper limbs, and distinctive facial features. In this current study, mutations in two genes of interest caused IDD, but resulted in less-pronounced facial features and no limb defects, such as missing hands or fingers, that are hallmarks of classic CdLS (Deardorff et al, 2007). In contrast to mutations in the *NIPBL* gene, which cause roughly one-half of all known CdLS cases, mutations in the new genes, *SMC3* and *SMC1A*, cause only about 5 percent of CdLS cases. All three genes (*NIPBL*, *SMC3*, and *SMC1A)* encode cohesin proteins, which are known to play an important role in controlling the integrity of chromosome pairs during cell division and early development. Mutations seem to have a particular effect on brain development. Researchers hope that by studying mutations that give rise to a rare genetic disease, they will be able to identify biological pathways that may play broader roles during human development, and potentially identify genetic causes of more common forms of intellectual impairment and ASDs.

Genetics of Myelin Production

Peripheral neuropathies, disorders affecting the nerves outside the brain and spinal cord, are often characterized by numbness, weakness, pain, and impaired movement. One of the most common genetically inherited disorders, Charcot-Marie-Tooth disease, is a peripheral neuropathy characterized by defects in production of myelin, a fatty coating made by Schwann cells that covers nerve cells and increases the speed and reliability of their electrical signals. Investigators affiliated with the University of Wisconsin IDDRC discovered that the *Early Growth Response 2* (*EGR2)* gene produces a protein that serves as a master regulatory gene by activating several other genes necessary for myelin production (LeBlanc, Ward & Svaren, 2007). Defects in the *EGR2* gene affect the normal copy of the gene as well as the functioning of the other genes encoding critical myelin proteins, such as peripheral myelin protein 22 (PMP22) and myelin protein zero (MPZ). Not only is MPZ the most abundant myelin protein in the peripheral nervous system, but the overproduction or underproduction of MPZ and PMP22 accounts for the majority of inherited peripheral neuropathies. This discovery enhances understanding of myelin production within Schwann cells and may facilitate the development of new therapies for peripheral neuropathies.

PROGRAM ON FRAGILE X SYNDROME (FXS) AND ASSOCIATED DISORDERS

FXS, estimated to occur in 1 in 2,500 births, is the most common inherited form of IDD. FXS results from a mutation in the *FMR1* gene, on the long arm of the X chromosome, that is associated with an unstable expansion of a CGG trinucleotide repeat within the gene. The length of the trinucleotide repeat determines the severity of the condition, ranging from:

- Normal (fewer than 55 repeats), to
- Premutation (between 55 and 200 repeats), to
- Affected or full mutation (more than 200 repeats).

Because males carry only a single copy of the X chromosome, they tend to be more severely affected than females, who have a normal X chromosome to partially compensate. Although the full mutation can affect both males and females, premutation and full-mutation females may exhibit marked variability of characteristics depending in part on the extent of X-chromosome inactivation. Individuals with FXS can exhibit a range of cognitive impairment, with particular deficits in visual-spatial perception, speech and language, attention, self-regulation, and short-term memory. Many individuals with FXS also exhibit symptoms of ASDs, and some have seizures.

In the past several years, researchers have gained a greater understanding of the medical consequences of carrying a premutation, such as risks for a Parkinson-like condition characterized by tremor and ataxia in older males, called Fragile X-associated Tremor/Ataxia Syndrome (FXTAS), and risks for premature ovarian insufficiency, in this case known as Fragile X-associated Primary Ovarian Insufficiency (FXPOI), in women of reproductive age.

FXS RESEARCH CENTERS (FXSRCS): THE CENTERS-WITHIN-CENTERS MODEL

The FXSRC Program, associated with the existing Eunice Kennedy Shriver IDDRC Program, supports research that will improve the diagnosis and treatment of FXS and its related conditions. The Branch's three FXSRCs were initially funded in fiscal year 2003 in response to the *Children's Health Act of 2000* (P.L. 106-310), which provided for the establishment of at least three centers to conduct and support basic and biomedical research into the detection and treatment of FXS. The FXSRCs stimulate the formation of multidisciplinary, multi-institutional teams with the common goal of facilitating the translation of basic research findings from bench to bedside to community. The Centers were refunded after a successful recompetition in early fiscal year 2008.

Each FXSRC includes research programs in both basic and clinical science. Several projects focus on newborn screening and include studies that assess methods of testing immediate and extended family members and the impact of newborn screening on the family. A description of the Centers and their affiliates appears below. For a map of the Center locations and their affiliate sites, see Figure 10.

FXSRC at Baylor College of Medicine, Texas

(IN COLLABORATION WITH EMORY UNIVERSITY, GEORGIA, AND UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN, ILLINOIS)

Research at the Baylor FXSRC revolves around a common theme of determining the full phenotypic spectrum of humans and mice with genetic alterations in the *FMR1* gene and the underlying pathological causes, with an aim of discovering and testing effective treatments. The four research projects focus on:

- Using mouse models to understand the developmental timing requirements for *Fmr1*;
- Measuring behavioral and electrophysiological responses to genetic alterations in the *Fmr1* knockout mouse model;

- Drug treatments in fly models and mouse neurons; and
- The human male premutation phenotype, which involves late-onset tremor and cognitive decline.

An additional strength of this FXSRC is the Neuronal Imaging Core, which offers expertise in neuroimaging at the molecular and cellular levels to support the development of better mouse-model phenotypic definitions and methods to assess treatment outcomes. These projects provide improved understanding of the function of the *FMR1* gene and its protein product and have the potential to inform treatment development that will improve quality-of-life for affected individuals.

FXSRC at UNC, Chapel Hill

(In Collaboration with University of Kansas; University of Wisconsin; RTI International, North Carolina; and the University of California, Davis/ Medical Investigation of Neurodevelopmental Disorders [MIND] Institute)

This FXSRC focuses on family adaptations to FXS. Currently, 13 investigators from 11 disciplines (including anthropology, developmental psychology, educational psychology, clinical psychology, forensic medicine, social work, law, medical genetics, special education, speech and hearing sciences, and psychiatry) collaborate on an integrated and longitudinal set of studies, including: Determining Maternal Responsivity and Development of Children with FXS, Adaptations of Families of Adolescents and Adults with FXS, and Family Adaptation to Newborn Screening for FXS. The projects have direct relevance to public health because they identify the specific challenges faced by parents of children with FXS. Findings from these projects provide information that facilitates development of support and services to maximize family well-being and provide important information about the ramifications of newborn screening for families.

FXSRC at University of Washington

(In Collaboration with University of California, Davis/MIND Institute; Rush University Medical Center, Illinois; University of Illinois at Urbana-Champaign, Illinois; and Fred Hutchinson Cancer Research Center, Washington)

The University of Washington FXSRC brings together clinical and laboratory researchers to address research projects, such as a multi-institutional effort on newborn screening for the FXS full mutation and premutation. The goal of the project is to clarify the developmental consequences of the full spectrum of the FXS mutation in infants and to understand FXS-related disorders in families. In addition, the researchers are exploring the functional and structural roles of the antisense transcript of the *FMR1* gene, including possible molecular and clinical correlations with FXTAS. Another collaboration addresses the phenotypic consequences of restoring partial function to the Fragile X protein in conditional mouse mutants, which vary by regional and temporal levels of *Fmr1* expression. Finally, investigators are using NIH-approved lines of human embryonic stem cells to help understand early developmental processes that lead to the variable epigenetic inactivation of *FMR1*.

THE NIH FRAGILE X RESEARCH COORDINATING GROUP (FXRCG) AND THE NIH RESEARCH PLAN ON FXS AND ASSOCIATED DISORDERS

In January 2007, the Director of the NICHD established the FXRCG to encourage coordinated FXS research efforts and facilitate collaboration across NIH and with other federal agencies and advocacy groups. Led by the IDD Branch, the Group is composed of NIH extramural staff and intramural researchers at Institutes that support and conduct research projects related to FXS and its associated disorders, FXTAS and FXPOI. In addition to the NICHD, participating Institutes include the NIMH, the NINDS, the National Institute on Aging (NIA), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of General Medical Sciences, the National Cancer Institute (NCI), and the National Institute on Deafness and Other Communication Disorders (NIDCD). During the past several years, research programs with support from across NIH have made significant advances in understanding FXS and associated disorders. This Group will help to ensure continued coordination of efforts and resources.

The Senate Committee on Appropriations, in its report for the fiscal year 2008 budget for the U.S. Department of Health and Human Services (DHHS), requested that "*the NIH, through the NICHD and other participating Institutes, convene a scientific session in 2008 to develop pathways to new opportunities for collaborative, directed research across Institutes, and to produce a blueprint of coordinated research strategies and public-private partnership opportunities for Fragile X*." In response, the IDD Branch, via the FXRCG, brought together representatives from the research, advocacy, and clinical communities along with other relevant federal agencies and affected individuals and their families. The Group convened three working groups in March 2008 to develop comprehensive recommendations for specific high-priority research objectives for each of the primary disorders associated with the *FMR1* gene: FXS, FXTAS, and FXPOI. The recommendations were designed to be used by the NIH and the FXS, FXTAS, and FXPOI research and advocacy communities and to be shared with other federal agencies to facilitate coordinated research activities in pursuit of timely detection, diagnosis, treatment, and prevention of the targeted disorders.

The FXRCG completed the *NIH Research Plan on FXS and Associated Disorders* in September 2008. The final version of the research plan was published on July 20, 2009, and is available through the NICHD Web site at http://www.nichd.nih.gov/publications/pubs_details.cfm?from=&pubs_id=5729.

COLLABORATIVE EFFORTS ON FXS

The Branch continues to collaborate with other NIH Institutes and Centers and to cultivate public-private partnerships in its efforts related to FXS and associated disorders. Among these activities is the annual FXS conference held at Cold Spring Harbor Laboratory's Banbury Conference Center. This cutting-edge meeting has enjoyed continuous primary support from the NIMH and joint funding from the NICHD and FRAXA since 2001.

In addition, multiple research efforts currently aim to develop treatments and novel interventions for FXS. One such effort seeks to develop metabotropic glutamate receptor (mGluR) antagonists as therapeutics for FXS and for ASDs. The project has, as its basis, an ongoing cooperative agreement led by the NIMH in partnership with the NICHD, including the Obstetric and Pediatric Pharmacology Branch (OPPB) and its congressionally mandated activities as described in the Best Pharmaceuticals for Children Act (BPCA), as well as NINDS, FRAXA, and Autism Speaks.

In May 2008, the IDD Branch, in collaboration with the NICHD OPPB and its activities being performed under the BPCA, the NIH Office of Rare Diseases Research (ORDR), NINDS, NIMH, FRAXA, the National Fragile X Foundation (NFXF), and representatives of the Fragile X Clinics Consortium (a body established by the NFXF that includes clinics throughout the United States and Canada that treat individuals with FXS), held a two-day scientific meeting to discuss challenges related to selecting outcome measures for use in clinical trials involving children with FXS. Participants included members of constituency groups, representatives from the Food and Drug Administration (FDA), clinicians who treat children with FXS, and researchers experienced in clinical trials of pharmaceuticals involving children with FXS. Additional participants included researchers with expertise in successful clinical trial design, in development of psychometric assessments, and in conduct of behavioral and cognitive studies of children with FXS. A second outcomes measures workshop is planned for November 5-6, 2009.

The Branch's efforts to understand the relationships between FXS and ASDs also continued through the Program Announcement (PA) soliciting research to study the *Shared Neurobiology of FXS and Autism* (PA 06-429/430). This PA, originally issued in 2005 and reissued in 2007, represents a public-private partnership led by the NIMH in collaboration with NINDS and NICHD that also includes the Canadian Institutes of Health (Institute of Neurosciences, Mental Health, and Addiction and the Institute of Genetics), the Health Research Board of Ireland, FRAXA, Autism Speaks, and the National Alliance for Autism Research (which is now part of Autism Speaks). This mechanism has supported 12 grants (seven with primary NICHD funding) since its inception that encompass a broad spectrum of research, ranging from studies of language in children with FXS to studies of FXS mouse models that explore the structural abnormalities observed in neurons.

FXS RESEARCH PROGRAM SCIENCE ADVANCES

The mGluR Theory

The mGluR theory of FXS (Bear et al, 2004) posits that long-term depression of glutamate receptors in the hippocampus leads to the neurological, cognitive, and behavioral problems in FXS. The work presented in the Bear paper, funded in part by NICHD, presented a novel theory to explain many of the deficits in FXS. Loss of FMRP, the defect responsible for FXS in humans, increases long-term depression in mouse hippocampus. The research presented a theory to account for diverse neurological and psychiatric aspects of FXS based on the assumption that many of the protein synthesis-dependent functions of metabotropic receptors are exaggerated in FXS. The theory suggests new directions for basic research as well as novel therapeutic

approaches for individuals with FXS. The field has moved rapidly to preclinical and phase I clinical trials using mGluR antagonists as treatments for FXS as a result of this research.

Mouse Models of FXS

The *Fmr1* gene has two paralogs in humans and mice, and researchers hypothesize that one of these, *Fxr2* (encoding FXR2P), partially compensates for the loss of FMRP in FXS. In one Branch-supported study, investigators examined long-lasting synaptic plasticity in *Fmr1* knockout, *Fxr2* knockout, and *Fmr1/Fxr2* double knockout mice (Zhang et al, 2009). Findings indicated that the long-term depression of mGluR in the hippocampus was affected in all knockout mice at young ages (4 to 6 weeks old). In addition, *Fmr1/Fxr2* double knockout mice showed significant deficiencies in baseline synaptic transmission and short-term presynaptic plasticity, suggesting that the gene products may cooperate to regulate presynaptic plasticity. These findings indicate that both FMRP and FXR2P function in synaptic plasticity, and that they likely operate in related, but independent, pathways.

Rapid Polymerase Chain Reaction (PCR) Assay for FXS

Current testing for FXS, which employs a combination of Southern blot and PCR techniques, is laborious, expensive, and has limited utility for identifying not only female carriers, but also those with intermediate repeat sizes. As a result of the absence of an effective screening tool for expanded *FMR1* alleles in large populations, there are no unbiased estimates of the number of full-mutation *FMR1* alleles in the general population. Branch-supported researchers have described a rapid PCR-based screening tool for expanded *FMR1* alleles that would have applicability for testing both males and females, and for determining allele sizes throughout the premutation and full-mutation ranges (Tassone et al, 2008). The methodology has potential for screening large populations of newborns or those at high risk for expanded *FMR1* alleles using a small sample of blood from a single dried blood spot. Additional efforts could use this low-cost method to identify the frequency of premutation alleles on a large scale, and to enhance the understanding of family adaptation to newborn screening.

RARE DISEASES COOPERATIVE RESEARCH CONSORTIA (RDCRC)

The *Rare Diseases Act of 2002* (P.L. 107-280) directed the NIH ORDR to establish a Rare Diseases Clinical Research Network—a collaborative, cooperative network of investigators and patient groups in partnership with technology leaders that focuses on studying rare diseases to enhance communication and resource sharing via a multidisciplinary approach. The resulting RDCRC program conducts the following activities:

- Collects clinical information to develop biomarkers and new approaches to diagnosis, prevention, and treatment;
- Provides content for an Internet-based resource site about rare diseases;
- Trains new clinical investigators in rare diseases research; and

- Supports a comprehensive and integrated approach to data collection, storage, and management and integrates clinical data with other unique data, including genetic, imaging, pathologic, and laboratory data through the Data and Technology Coordinating Center.

The first competition for the RDCRC in 2003 established eight funded consortia using the U54 mechanism, and the program subsequently expanded to 10 centers. During the past six years, the IDD Branch provided scientific management for two Consortia (listed below) and their affiliate sites that have made significant progress and research contributions within the field of rare diseases research. Recompetition of the entire program, including the Data and Technology Coordinating Center, occurred in 2009; both of the IDD Branch-supported Consortia will continue for another five years.

UREA CYCLE DISORDERS RARE DISEASE CONSORTIUM

Primary Site: Children's National Medical Center (Washington, D.C.)

AFFILIATED U.S. SITES: CHILDREN'S HOSPITAL, BOSTON; CHILDREN'S HOSPITAL OF PHILADELPHIA; YALE UNIVERSITY; GEORGETOWN UNIVERSITY; BAYLOR COLLEGE OF MEDICINE; UNIVERSITY HOSPITALS OF CLEVELAND/RAINBOW BABIES AND CHILDREN'S HOSPITAL; UCLA; VANDERBILT UNIVERSITY; MOUNT SINAI SCHOOL OF MEDICINE; CHILDREN'S HOSPITAL, DENVER; OREGON HEALTH AND SCIENCE UNIVERSITY; AND SEATTLE CHILDREN'S HOSPITAL

AFFILIATED INTERNATIONAL SITES: THE HOSPITAL FOR SICK CHILDREN (TORONTO, CANADA) AND THE UNIVERSITY CHILDREN'S HOSPITAL (ZURICH, SWITZERLAND)

This RDCRC is a highly integrated network of investigators with a long history of cooperative interactions (see Figure 11 for site locations). With a focus on urea cycle disorders, the Consortium's investigators have established a registry to estimate incidence and prevalence of the eight urea cycle disorders they study. In general, this RDCRC conducts the following activities:

- Performs longitudinal natural history studies of urea cycle disorders to understand morbidity, mortality, and treatment efficacy;
- Surveys and promotes newborn screening for urea cycle disorders to aid in identification and treatment;
- Tests new approaches to therapy for these disorders to help bring new drugs to market in collaboration with pharmaceutical companies;
- Develops novel non-invasive methods for assessing changes in urea synthesis, both over time and under varying treatment conditions;
- Performs neuropsychological and neuroimaging studies on affected individuals identified at various sites to better understand the effects of hyperammonemia on neurocognitive function;
- Maintains a Web site, in collaboration with the Data Management Coordinating Center (formerly called the Data and Technology Coordinating Center) and the National Urea Cycle Disorders Foundation, to provide clinical and research information on urea cycle disorders to the public, health care providers, and affected families; and

- Promotes the entrance of M.D. and Ph.D. investigators into the study of urea cycle disorders through a postdoctoral fellowship training program.

Additional information about the activities of this Consortium is included in the *Urea Cycle Disorders* Section of this report.

CONSORTIUM FOR RARE EPIGENETIC DISORDERS

Primary Site: Baylor College of Medicine (Houston, Texas)/University of Alabama, Birmingham

AFFILIATED SITES: UNIVERSITY OF FLORIDA; CHILDREN'S HOSPITAL, BOSTON; GREENWOOD GENETIC CENTER (SOUTH CAROLINA); VANDERBILT UNIVERSITY MEDICAL CENTER; CHILDREN'S MERCY HOSPITAL (KANSAS)/UNIVERSITY OF KANSAS MEDICAL CENTER; CHILDREN'S HOSPITAL, SAN DIEGO; AND UNIVERSITY OF CALIFORNIA, IRVINE, MEDICAL CENTER

This RDCRC, which had its primary site at the Baylor College of Medicine until August 1, 2009, at which time it switched to the University of Alabama, Birmingham, studies a collection of rare epigenetic disorders, including Angelman syndrome (AS), Rett syndrome, and Prader-Willi syndrome (PWS) (see Figure 12 for site locations). Among its activities, the Consortium focuses on new diagnostics and new therapies and seeks to:

- Establish natural history protocols for the three disorders;
- Develop new therapeutics for AS;
- Use microarray comparative genomic hybridization (array-CGH) to search for deletions in patients with PWS-like features, or in those with early morbid obesity;
- Develop new methodologies for detecting large chromosomal deletions in individuals with Rett syndrome;
- Provide prenatal diagnosis of deletion cases of PWS and AS using chromosome microarray analysis; and
- Distinguish between different-sized deletions for PWS and AS with two unique research microarrays.

Additional information about the activities of this Consortium is included in the *Epigenetic Disorders* Section of this report.

SENATOR PAUL D. WELLSTONE MUSCULAR DYSTROPHY COOPERATIVE RESEARCH CENTERS

The *Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001*, also called the MD-CARE Act (P.L. 107-84), authorized the establishment of the Muscular Dystrophy Coordinating Committee (MDCC) to develop a federal plan across NIH and other federal agencies and programs on research and education in the various forms of muscular dystrophy and authorized NIH to establish centers of excellence for muscular dystrophy research. In response to the Act, the *MDCC Action Plan for the Muscular Dystrophies* was approved in December 2005, and the NIH established the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers (referred to hereafter as the Wellstone Centers). The NIH currently funds six Wellstone Centers through a U54 Cooperative Agreement mechanism, permitting significant Institute staff involvement in design and execution of the research program.

The NICHD, NINDS, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) each fund two Wellstone Centers. The NICHD-funded centers are: Children's National Medical Center and the Boston Biomedical Research Institute (BBRI) in Watertown, Massachusetts. The NICHD also funded a third Wellstone Center at the University of Washington in Seattle through 2008 (see Figure 13 for Wellstone Center locations).

Each Wellstone Center brings together expertise, infrastructure, and resources focused on major questions in muscular dystrophy and provides resources used by national muscle biology and neuromuscular research communities. The Wellstone Centers also serve as focal points for research collaborations in the muscular dystrophy field and provide training and advice about muscle diseases for basic and clinical researchers. To further enhance activities at the Wellstone Centers, the NIH funds administrative supplements to promote collaborations and to maximize opportunities for career development among junior investigators affiliated with the Centers. The NICHD funded one such fellowship at the Children's National Medical Center.

Specifically, the NICHD-supported Wellstone Centers address the following topics:

- The Wellstone Center at the Children's National Medical Center, in Washington, D.C., analyzes genetic and cellular factors that contribute to the progression of a severe form of muscle disease, Duchenne muscular dystrophy (DMD), and the response of patients to treatments. DMD, found predominantly in males, affects one in every 3,500 males. Females can be carriers of the DMD gene, but usually do not show symptoms of the disease.
- A new Wellstone Center, funded in fiscal year 2008 at the BBRI, investigates facioscapulohumeral muscular dystrophy, also called FSHD, a common form of muscular dystrophy affecting one in 20,000 individuals and causing progressive weakness of skeletal muscles of the face and shoulder region. Although atrophy typically progresses slowly, there may be periods of rapid decline and eventual involvement of the pelvic girdle and inability to ambulate. The BBRI Wellstone Center identifies biomarkers to evaluate outcomes of clinical trials through four research projects and three support cores.

- The third Wellstone Center at the University of Washington, which was funded by NICHD until 2008, focused on gene therapy and muscle stem cells as potential therapies for DMD, approaches that may also have applications for other forms of muscular dystrophy.

The NICHD is currently leading the latest round of competition for the Wellstone Centers, to be funded in fiscal year 2010. IDD Branch staff anticipate that several current and past Centers will compete for the two slots available.

WELLSTONE CENTERS SCIENCE ADVANCES

The research team at the Wellstone Center at the Children's National Medical Center recently reported an exciting finding. They found that injecting a cocktail of antisense oligonucleotides into the bloodstream of dogs with a genetic form of DMD reduced skeletal muscle deterioration (Yokota et al, 2009). Using a novel genetic technology, known as "exon skipping," researchers developed a successful treatment for the canine version of DMD, which occurs naturally in dogs and affects the same gene affected in the human form of the disease. Using this "exon skipping" technology, portions of DNA-like molecules, known as morpholinos, act as "molecular patches" to cover mutant DNA sequences of the Dystrophin gene, responsible for DMD. Injecting the morpholinos into the dogs' bloodstream allowed the dogs to make an imperfect—but functional—version of the needed protein, significantly slowed their muscle deterioration, and improved their muscle functioning. This finding may lay the foundation for human testing of gene therapy for this devastating disease.

The NICHD co-funded two highly successful workshops focused on specific topics in muscular dystrophy research through administrative supplements to the Wellstone Centers. The first workshop aimed to develop standard operating procedures (SOPs) for clinical trial endpoints in the *mdx* mouse, a mouse model for DMD. A follow-up meeting, sponsored by Treat-NMD, a European-based advocacy organization focused on neuromuscular diseases, approved the SOPs for clinical trial endpoints in humans (visit http://www.treat-nmd.eu/research/preclinical/SOPs/). Adopting these procedures enables standardized toxicity and efficacy studies of investigational new drugs, a prerequisite for FDA licensing. Another workshop, *Translational Research in Muscular Dystrophy*, included keynote talks, a case study in therapy development for a rare neuromuscular disorder, working group summaries of topics for which consensus was reached prior to the meeting, individual talks by selected experts, and feedback by a panel of distinguished industry scientists and regulators who work outside of the muscular dystrophy community. The number of companies at the Workshop with active muscular dystrophy programs and the innovative partnerships that have already formed between academia, corporations, advocacy groups, and funding agencies serve as evidence of the potential for new therapeutics for muscular dystrophies.

CHROMOSOME ABNORMALITIES, GENETIC/GENOMIC SYNDROMES, AND EPIGENETIC DISORDERS

Cytogenetic abnormalities, such as trisomy, mosaicism, or chromosome rearrangements, cause a significant proportion of cognitive impairment and morbidity and mortality, especially among infants and children. Recent advances in high-resolution cytogenetic analysis and the development of the molecular cytogenetics field, mainly through the application of fluorescence *in situ* hybridization and array-CGH, provide opportunities to identify subtle chromosomal rearrangements, such as cryptic deletions or duplications, in individuals with IDD or genetic syndromes. Other genetic syndromes may be caused by mutations in single genes or by other, as yet unknown, genetic or epigenetic (resulting from changes in the regulation of gene activity and expression not dependent on gene sequence) mechanisms. Studies of genetics, epigenetics, and genomics are a core portion of the IDD Branch portfolio and represent exciting new areas of research for the NICHD and the NIH, through the Roadmap initiative (http://nihroadmap.nih.gov/epigenomics/). The following section highlights some findings from Branch-supported research on chromosome abnormalities, genetic syndromes, and epigenetic disorders.

DOWN SYNDROME

Down syndrome is a significant genetic cause of IDD in human populations, occurring in approximately one in 800 newborns, an incidence that has remained relatively constant for the past century in virtually every ethnic group in the world. More than 95 percent of individuals with Down syndrome possess an extra copy of the smallest human chromosome, chromosome 21, a situation known as trisomy 21 (Ts21). Of the remaining individuals with Down syndrome, 2 percent to 4 percent have an extra copy of the majority of chromosome 21, derived from a balanced translocation of chromosome 21 to another chromosome inherited from one of the parents (called a Robertsonian translocation); 1 percent to 2 percent of those with Down syndrome are mosaic, meaning they have both normal cells and Ts21 cells in their bodies.

Individuals born with Down syndrome today enjoy a greatly increased life expectancy compared with their counterparts from 25 years ago. Approximately 45 percent of individuals with Down syndrome survive past the age of 60 years, and about 15 percent live almost to the age of 70 years. Among Caucasians with Down syndrome, life expectancy is approximately 70 years of age, triple the expectancy of several decades ago. The life expectancy of non-Caucasians with Down syndrome has risen during the same time frame, from younger than five years of age to nearly 35 years of age in Western cultures, but this expectancy is still significantly lower than in the Caucasian population. Many older adults with Down syndrome develop Alzheimer-like dementia, but they do so at younger ages than the general population.

Science Advances in Down Syndrome Research

In the past decade, one of the goals of the IDD Branch has been to encourage multiple Institutes to work together to create and implement a matrix for research issues related to Down syndrome. A congressional directive in 2005 led to the establishment of the Trans-NIH Taskforce on Down

Syndrome to coordinate NIH efforts on Down syndrome research. IDD Branch staff chair the Taskforce, which includes representatives from NIA, NINDS, the National Eye Institute, NIDCD, NIAMS, the National Human Genome Research Institute (NHGRI), NCI, the National Heart, Lung, and Blood Institute, and the National Institute of Allergy and Infectious Disease, among others. The Trans-NIH Taskforce met three times, once with members of the Taskforce on Down Syndrome organized by the National Down Syndrome Society. Three additional meetings resulted:

- Gatlinburg Conference, March 2007, *Down Syndrome: Genes, Brain and Behavior*
- Trans-NIH Taskforce Meeting, July 2007, *Down Syndrome and Cognition* (funded by the NICHD Office of the Director)
- R13 conference, September 2007, *The Biology of Chromosome 21 Genes: Toward Genotype/Phenotype Correlations in Down Syndrome*

This effort resulted in the issuance of the *NIH Research Plan on Down Syndrome* in October 2007. Table 2 lists the matrix of research objectives from the Plan; the full Plan is available at http://www.nichd.nih.gov/publications/pubs/upload/NIH_Downsyndrome_plan.pdf. This research agenda will address, within the next five to ten years, topics such as:

- Aging and family dynamics
- Measures of cognitive function in Down syndrome throughout the lifespan
- Issues involving medications and clinical trial participation
- Use of Alzheimer disease research to inform potential therapeutics
- Transitions to independent or assisted living for adults
- Comorbid psychiatric and medical conditions throughout the lifespan
- Improving and expanding availability and studies in animal models
- Health disparities in survival and access to care

In 2009, NICHD issued an RFA, *Factors Affecting Cognitive Function in Adults with Down Syndrome* (RFA HD 09-028). Applications in response to that RFA were reviewed in August 2009; two R01 grants have been awarded, with co-funding provided by NIA.

Other advances in the realm of Down syndrome research include:

- An assessment of gastrointestinal anomalies by sex, race, and ethnicity;
- Identification of modifier genes located on other chromosomes that impact variability in Down syndrome features;
- Evidence from animal models of specific genes involved in craniofacial and brain development and in reduced solid-tumor formation; and
- Identification of specific genes that are candidates for the constant features of Down syndrome.

There continues to be compelling evidence for the benefit of early intervention programs for children with Down syndrome as well as other forms of IDD (Guralnick, 2005). Other ongoing

activities include efforts to develop clinical trials, in humans and animal models, for agents that ameliorate or improve intellectual development and cognitive performance and to identify biomarkers that predict likelihood of progression to Alzheimer-like dementia in older individuals with Down syndrome. In particular, partnerships with the NIA have been fruitful for the latter initiative.

In addition, advances in Down syndrome research have been a direct result of the Branch's establishment and support of the Repository for Mouse Models for Cytogenetic Disorders. Initiated in the 1970s, the Repository generates and distributes mice that recapitulate, at least in part, human cytogenetic disorders, with a special focus on Down syndrome. Please visit the *Research Resources* section for a more detailed description of this resource.

WILLIAMS SYNDROME

Williams syndrome, which has a prevalence of between one in 10,000 and one in 20,000, arises from deletions in a group of genes, including the Elastin locus, on the long arm of chromosome 7 at 7q11. Congenital heart defects, as well as distinctive facial features, abnormal calcium metabolism, failure to thrive during infancy, unique personality with increased friendliness, and moderate levels of intellectual impairment characterize many individuals with Williams syndrome.

One focus of IDD Branch-sponsored research in Williams syndrome is the dissection of the unique cognitive and behavioral phenotypes of this condition. Investigators found that concrete and relational vocabulary at five to seven years of age is highly predictive of future concrete and relational vocabulary, and that relational vocabulary at these ages correlates closely with later visuospatial construction ability (Mervis and John, 2008).

Characterization of the comorbid psychiatric disorders found in Williams syndrome children at different ages is also an area of emphasis, as is research on the role of altered neuroanatomical pathways identified through specific imaging techniques during social engagement and during social and affective language tasks. Additional studies aim to characterize specific phenotypes related to the extent of deletion of specific genes in the critical region of chromosome 7, and to understand the effects of both inversion and duplication of that region on phenotypic characteristics.

SMITH-MAGENIS SYNDROME (SMS)

SMS, a contiguous gene-deletion syndrome associated with missing genetic material on the short arm of chromosome 17, has a prevalence of one in 25,000. Individuals with SMS typically demonstrate: moderate IDD; speech and motor delays; behavioral abnormalities, including self-injurious behavior; insensitivity to pain; sleep disturbance; short stature and short fingers; and distinctive craniofacial features. Many with SMS are also obese. The minimal critical region of chromosome 17 associated with SMS is about 950 kilobases, a region that contains approximately 25 genes.

Some individuals with SMS have no obvious large-scale deletions, but they do have novel deletions in the *retinoic acid induced-1* (*RAI1*) gene on chromosome 17p that result in shortened RAI1, a protein normally localized in the nucleus. RAI1 resembles transcriptional co-activator TCF20 and might stimulate transcription by interacting with DNA-binding proteins. Ongoing Branch-sponsored research in this field suggests that *RAI1* haploinsufficiency correlates significantly with many features of SMS. In addition, mice with a single copy of *Rai1* vary in their craniofacial phenotype depending on differences in their genetic strain of origin, suggesting a role for modifier genes.

Genome-wide expression studies have characterized a variety of metabolic and genetic pathways affected in SMS. Ongoing studies seek to understand the highly variable and complex duplications and deletions on chromosome 17p that produce distinctive phenotypes in individuals with atypical SMS and in a separate syndrome characterized by a duplication of this same region—called a reciprocal disorder—or Potocki-Lupski syndrome.

DISORDERS WITH A SHARED PATHWAY

The IDD Branch also supports research to clarify a role for common pathways in the pathogenesis of IDD conditions, such as CdLS. Among the efforts the Branch supports are a number of grants that aim to understand the cohesin complex, a protein complex essential for the proper mitotic segregation of chromosomes that plays an essential role in gene expression during development and is disrupted in CdLS. Common signaling pathways are also the subject of research in the FXS portfolio, particularly studies involving mGluR.

The Branch also supports research to understand disorders, including Costello syndrome, Noonan syndrome, Cardiofaciocutaneous syndrome, and Neurofibromatosis 1, that result from genetic defects in the molecules that participate in the Ras and mitogen-activated protein kinase (MAPK) pathways. The Ras/MAPK pathway is an area of great interest to the Branch because the shared clinical features of many of these disorders could facilitate understanding of the underlying etiology and provide opportunities to identify potential targets for interventions.

EPIGENETIC DISORDERS

Within the IDD community, increased emphasis on research into the roles of methylation, histone modification, imprinting, and other epigenetic factors in the pathogenesis of IDD has also led to enhanced support of such research within the Branch's portfolio. For example, Branch staff initiated and led an Epigenetics and Systems Biology Working Group for the NICHD during 2008. The Group hosted six seminars featuring area scientists and participated in NIH-wide seminars related to these research interests. The Branch is also sponsoring a *Workshop on the Epigenetic Basis of IDD,* which will be held in 2010.

A number of Branch-supported grants funded during the past four years focus on three specific epigenetic disorders—AS, PWS, and Rett syndrome. All three disorders are characterized by

variable degrees of IDD, but the manifestations are quite disparate. Children with AS have significant cognitive and speech impairments, often exhibit seizures and an ataxic gait, and have a tendency toward inappropriate laughter. Deletions of the maternal copy of a portion of chromosome 15q, paternal uniparental disomy for this region, or point mutations in the *UBE3A* gene have been implicated as causative. In contrast, deletions of the paternal copy of chromosome 15q or imprinting defects of this region cause PWS, characterized by failure to thrive and poor feeding in infancy that evolves into insatiable appetite, preoccupation with food, and risk of morbid obesity if not treated aggressively. Other compulsive behaviors, such as skin-picking, can also evolve in PWS. Rett syndrome, as described earlier, is associated with loss of purposeful hand movements and speech in affected girls in early childhood, problems with balance and coordination, and seizures, hang wringing, and other features of ASDs. Most cases of Rett syndrome are caused by mutations in the *MECP2* gene on the X chromosome.

Among the research topics addressed by Branch-supported projects are the following: mouse models of imprinting defects on chromosome 15 in PWS and AS; a mouse model of AS based on an *Ube3a* point mutation; *MECP2* gene regulation in Rett syndrome; and the role of MECP2 in chromatin methylation. The Branch also supported an R13 conference proposal establishing a multisite clinical network for international studies on Rett syndrome.

As described earlier in this report, the Consortium for Rare Epigenetic Disorders, whose primary site was at Baylor College of Medicine but is now at the University of Alabama, Birmingham, focuses on AS, PWS, and Rett syndrome and includes longitudinal natural history studies and drug treatment interventions aimed at altering aberrant methylation patterns in these disorders.

Science Advances in AS, PWS, and Rett Syndrome

Discoveries in AS, PWS, and Rett syndrome include the following:

- Mice that lack *Ube3a*, a gene implicated in AS, have altered numbers, length, and spine morphology in cerebellar Purkinje cells and in hippocampal and cortical pyramidal cells (Dindot et al, 2008).
- Researchers identified four genes (*NIPA1, NIPA2, CYFIP1,* and *GCP5*) in the 15q critical region that are implicated in the ASD phenotype observed in many children with AS.
- Branch funding supported the creation of new mouse models of AS that affect the imprinting center shared with PWS.
- Studies demonstrated shared features between several epigenetic disorders, including the discovery that altered *MECP2* expression often occurs in AS as well as in PWS and Rett syndrome (Nagarajan et al, 2006); similarly, researchers found significant deficits of *Ube3a* expression in mouse models of Rett syndrome and in the brains of individuals with Rett syndrome and ASD (Swanberg et al, 2009).
- Mouse models of PWS have been hampered by embryonic lethality in the past, but by placing a deletion of the chromosome 15 imprinting center on a different genetic strain, investigators created mouse pups that survive to birth, providing a valuable new tool for research and demonstrating the presence of modifier genes (Chamberlain et al, 2004).
- To address the problem of excessive food consumption in PWS, investigators developed a hyperphagia questionnaire (Dykens et al, 2007). These investigators also detected neural

differences in visual responses to food stimuli based on the food's composition and suitability for consumption in different forms of PWS.

- The *First International Conference on Hyperphagia* explored similarities and differences in five syndromes associated with hyperphagia: PWS, Bardet-Biedl syndrome, WAGR syndrome (characterized by Wilms tumor, aniridia, genitourinary anomalies, and IDD), Alström syndrome, and in a subset of individuals with FXS.
- Researchers examined the relative abnormalities of the perisylvian region of the brain with respect to speech and language problems in PWS. Other studies provided an analysis of visuospatial processing involved in solving jigsaw puzzles.
- Branch-funded clinical studies revealed that maladaptive and behavioral problems decreased in PWS as age and intelligence quotient (IQ) increased.
- The Branch supported studies to evaluate clinically available interventions for PWS, including those that examine the incidence of sleep apnea after growth hormone treatment. These studies also found that treatment with topiramate had a positive effect on reduced skin picking, but had no effect on overeating behaviors.
- Branch-sponsored research on Rett syndrome included support of the creation of InterRett and RettBASE—international databases for Rett syndrome that include mutations and clinical features for affected girls with this condition (Bebbington et al, 2008).
- Researchers also developed an understanding of the correlation between clinical severity and various mutations in the *MECP2* gene, although the impact of X-chromosome inactivation on this correlation is now providing an additional challenge.
- Researchers identified histone modifications and methylation patterns that associate with specific *MECP2* mutations.
- Ongoing research on Rett syndrome also includes:
    - Studies to demonstrate a correlation between expression of *Mecp2* in specific neuronal populations, in astrocytes, and in feeding behavior, aggression, and stress responses in animal models of Rett syndrome (Maezawa et al, 2009)
    - Efforts to correlate *MECP2* expression with ASD features
    - Studies of a unique syndrome identified in males who have duplications of *MECP2*; these males have neurological delays and increased susceptibility to respiratory infections (Velinov et al, 2009)

BIOCHEMICAL AND METABOLIC RESEARCH

Because biochemical pathways are fundamental to normal body and brain function, changes in those pathways can disrupt the processes and functions that rely on the pathway's products and byproducts. The IDD Branch funds research on biochemical processes and metabolism as these topics relate to brain functioning, brain injury, and long-term consequences to the brain. A few of the Branch's efforts are described below.

HYPOXIA/ISCHEMIA

Fetal hypoxia (low oxygen levels) can lead to severe hypoxic ischemic encephalopathy (HIE), a major problem worldwide with significant morbidity and mortality. HIE occurs in three to nine of every 1,000 term infants; about one-half of these infants die or suffer severe lifelong problems, such as IDD or cerebral palsy. Knowing the mechanisms of hypoxic injury could enable health care providers to prevent or even reverse the injury, possibly improving neurodevelopmental outcomes for affected infants.

During the last four years, Branch research shifted from an emphasis on very basic animal and *in vitro* studies to more clinical and translational studies, as summarized below:

- The IDD Branch, in partnership with the NICHD Pregnancy and Perinatology Branch (PPB), supports translational research on HIE. The PPB currently funds a study of head cooling in newborns, the only intervention for hypoxia/ischemia currently in clinical trials. Although efforts to reduce the effects of HIE by hypothermia (cooling) have been hampered by the lack of a reliable non-invasive method for monitoring infant brain temperature during the treatment, the IDD Branch funded a Small Business Technology Transfer Phase I study that demonstrated use of Passive Microwave Radiometry for monitoring intracranial temperature in neonates. The Branch is also funding a Phase II study to develop an affordable system for reliable and continuous monitoring of intracranial temperature in neonates.
- Preterm infants are at risk for reduced blood flow and hemorrhage to the periventricular areas that surround the fluid-filled spaces of the brain (ventricles). Such lesions can lead to unilateral or multi-focal white-matter damage, known as periventricular leukomalacia (PVL). Children with PVL are more likely to have cerebral palsy and neurodevelopmental disabilities. The goal of one Branch-sponsored study is to relate the degree and patterns of white-matter damage from PVL to linguistic and cognitive outcomes. Diffusion-Tensor Imaging (DTI) provides detailed voxel-based quantitative information on the integrity of white-matter microstructure, and functional Magnetic Resonance Imaging (fMRI) characterizes the patterns of neural activity that underlie cognitive skills. The combination of these methods allows linkages between brain structure, brain functioning, and behavioral outcomes.
- The Branch funds several research studies on outcomes of HIE in rodent models, including the following:
    - One study is following juveniles to adulthood to determine long-term behavioral outcomes of HIE in sensory processing and learning, with a focus on electrophysiology and neuroanatomy.
    - Another study builds upon a ten-year history of rodent model research resulting in the discovery that the delta opioid receptor (DOR) protects cortical neurons from hypoxic injury. This study is testing the hypothesis that electro-acupuncture-induced up-regulation of DORs is a therapeutic strategy that may protect against hypoxic injury and damage to the cortex.
    - Another study aims to capitalize on a decade-long research effort using piglets to test the therapeutic benefit of neuronal nitric oxide synthase (nNOS) inhibition in hypoxia. The hypothesis for this effort derives from the discovery that the highly selective nNOS-catalyzed nitrous oxide mediates neuronal injury in this model.

- The Branch funded a new R01 grant to support researchers using erythropoietin and cooling to treat HIE in non-human primates. Given the importance of testing therapies in closely related species before moving into studies with humans, Branch funding for this project was a natural progression from earlier Branch-supported studies in rodents with HIE.
- In addition, the Branch supports annual meetings of the Society for Inherited Metabolic Disorders through an R13 conference grant mechanism.

MITOCHONDRIAL DISORDERS

Mitochondria represent the primary energy-producing organelles in the cell. Approximately one in 4,000 children has a mitochondrial cytopathy; although the symptoms can vary in severity and distribution, organs with high energy demands, such as central nervous system, kidneys, skeletal muscle, heart, liver, eyes, ears, and pancreas, are particularly susceptible. Mitochondrial disorders can result from defects of the mitochondrial DNA (mtDNA), which encodes the mitochondrial transfer RNAs and ribosomal RNAs comprising the mitochondrial protein assembly machinery, and some of the electron transport chain (ETC) subunits that generate energy as adenosine triphosphate, or from defects in genes encoded by nuclear DNA (nDNA).

One of the Branch's long-standing program project grants focuses on the natural history of a large cohort of individuals with MELAS (Mitochondrial Encephalopathy, Lactic Acidosis, and Stroke-like Episodes) syndrome. MELAS syndrome is caused by a point mutation in mtDNA (A3243G) and is estimated to occur in one out of every 750 individuals; many of those with the mutation are asymptomatic.

Researchers looking for ways to improve quality-of-life for individuals with and reduce symptoms of MELAS syndrome found early promise in dichloroacetate (DCA), a compound to improve mitochondrial function; unfortunately, a clinical trial of DCA determined that long-term treatment was associated with neurotoxicity in the form of peripheral neuropathy. Another Branch-supported project is screening for therapeutic compounds that enhance respiratory chain function in cultured primary human cortical neurons. The group found that two superoxide compounds produced protective effects and reduced reactive oxygen species; one of these compounds is currently in a Phase I clinical trial. A third project aims to build an *in vitro* model of the blood-brain barrier to test the ability of compounds, including potential therapeutics, to enter the brain parenchyma to treat MELAS symptoms. The final project in this group is evaluating gene expression, including expression of genes that encode respiratory chain enzymes and tight junction proteins, in the ependymal cells from patients with different mtDNA disorders, including MELAS syndrome.

Many mitochondrial disorders occur because of defects in nDNA genes, which encode proteins important in mitochondrial biogenesis. Two studies of these types of disorders involve Leigh's disease, a progressive neurometabolic disorder that is usually fatal by age six or seven years. The first project studies the French-Canadian variant of Leigh's disease arising from mutations in the *LRPPRC* gene that seem to cause aberrant regulation of mitochondrial transcription and resultant cytochrome c oxidase deficiency. In the second study, investigators created a mouse

model for classic Leigh's disease by knockout of *Ndufs4*, an accessory subunit of complex I of the ETC, with resultant reduced complex I activity.

The diversity of Branch-supported grants examining mitochondrial function has also expanded during the past four years to include topics beyond classic mitochondrial disorders associated with mitochondrial dysfunction. For example, mitochondrial dysfunction in Down syndrome arises, in part, from overexpression of the *ETS-2* gene, which is triplicated in most individuals with Down syndrome. By releasing apoptosis-inducing factor from the mitochondrion, *ETS-2* promotes an apoptotic pathway, which might explain why mitochondria from individuals with Down syndrome exhibit persistent energy-production deficits and increased cellular oxidative stress. This mitochondrial dysfunction in both neurons and astrocytes of those with Down syndrome could cause aberrant amyloid precursor protein metabolism, providing potential clues to the dementia seen in older persons with Down syndrome.

UREA CYCLE DISORDERS

In addition to the general goals of the Urea Cycle Disorders Rare Disease Consortium, which has its primary site at the Children's National Medical Center and focuses on this group of conditions (described earlier in this report), the Branch also supports a wide range of ongoing studies on these disorders through individual research grants. Branch-supported efforts, including those conducted through the Urea Cycle Disorders Rare Disease Consortium, include the following:

- Studies to:
  - Compare intellectual, adaptive, and behavioral functioning in children with urea cycle disorders;
  - Determine biomarkers of brain injury in ornithine transcarbamylase deficiency (OTCD) using anatomic imaging, fMRI, DTI, and magnetic resonance spectroscopy;
  - Create new animal models that more closely resemble the characteristics of specific urea cycle disorders; and
  - Examine the pathophysiology of astrocytes in urea cycle disorders.
- In addition to cross-sectional multicenter studies of patients with urea cycle disorders, clinical research efforts are also underway to determine the:
  - Role of specific amino acids in the clinical variability of individuals treated with sodium phenylbutyrate;
  - Effect of treatment of individuals with urea cycle disorders with N-carbamylglutamate; and
  - Medical management and nutritional interventions for difficult-to-treat urea cycle disorder patients.
- Gene therapy approaches to urea cycle disorders include creation of new mouse models that more faithfully represent the typical clinical presentation of specific urea cycle disorders, such as OTCD, and creation of conditional knockout mice to permit a better understanding of critical developmental time points and cell populations to target with therapeutic interventions.

CHOLESTEROL METABOLIC PATHWAY DISORDERS

The Branch also supported efforts to understand cholesterol metabolic pathway disorders during the reporting period. For example, Branch staff organized a symposium titled *Smith-Lemli-Opitz Syndrome (SLOS) and Inborn Errors of Cholesterol Synthesis*, held June 27-29, 2007, in Portland, Oregon. This symposium, which was co-organized by staff from the NICHD Division of Intramural Research, sought to promote interactions among scientists who have expertise in SLOS, cholesterol homeostasis, brain cholesterol metabolism, embryonic development, and oxysterol and neurosteroid biology with clinician-scientists who study and treat patients with inborn errors of cholesterol biosynthesis, such as SLOS.

RESEARCH ON AUTISM SPECTRUM DISORDERS (ASDS)

ASDs are complex neurodevelopmental disorders characterized by social impairments, communication difficulties, and restricted, repetitive, or stereotyped patterns of behavior. The most recent ASD prevalence estimates from the CDC are nine children per 1,000 children, or one child per 110 children (CDC, 2009). During the last decade-and-a-half, the NICHD has supported a considerable number of research projects related to ASDs. The NICHD's past efforts included the Collaborative Programs of Excellence in Autism (CPEA) Network on the Neurobiology and Genetics of Autism, which was co-funded by the NIDCD, and the Studies to Advance Autism Research and Treatment (STAART) Network, with co-funding from the NIMH, NINDS, NIDCD, and the National Institute of Environmental Health Sciences (NIEHS). These projects were highlighted in previous Branch reports to the NACHHD Council.

AUTISM CENTERS OF EXCELLENCE (ACE) PROGRAM

To maximize coordination and cohesion of NIH-sponsored efforts in autism research, the NIH consolidated the CPEA and STAART Networks into the trans-NIH Autism Centers of Excellence (ACE) in 2007 to avoid duplication, allow pooling and most efficient use of resources, and involve a larger number of investigators in autism research. The NICHD is one of the five NIH Institutes (in addition to NIMH, NIDCD, NINDS, and NIEHS) sponsoring the ACE Program, which supports studies on a range of autism topics, including early identification and intervention in infants at risk for ASDs, early brain abnormalities and functioning, potential environmental risk factors and biomarkers, intensive early behavioral intervention, long-term effects of early intervention, multidisciplinary studies of insistence on sameness, and trials of new medication treatments. The ACE Program includes ACE research centers that foster collaboration between teams of specialists who share the same facility to address a particular research problem in depth, and ACE research networks that consist of researchers at many facilities in locations throughout the country, all of whom work together on a single research question. To date, the NIH has funded six ACE research centers (via the P50 mechanism) and five ACE research networks (through the R01 mechanism). The NICHD has primary

responsibility for four centers and one network (see Figure 14 for locations). The NICHD-supported ACE centers and their PIs include:

- UCLA—Original PI: Marian Sigman; current PI: Susan Bookheimer. Researchers at the UCLA ACE center are seeking to determine the causes and treatments for social communication deficits in ASDs.
- University of Washington—original PI: Geraldine Dawson; current PI: Bryan King. Researchers at this ACE center are trying to identify genetic and other factors that could predispose an individual to develop an ASD. These researchers are also examining factors that might be protective against ASDs.
- University of Pittsburgh—PI: Nancy Minshew. Researchers at this ACE center are studying how people with ASDs learn and understand information.
- University of Illinois at Chicago—PI: Edwin Cook. Researchers at this ACE center focus their research on genetic factors, brain chemicals, and brain functions that might account for repetitive behaviors in people with ASDs. These investigators are also testing whether genetic differences influence how individuals respond to certain medications intended to reduce the occurrence of these behaviors.

The NICHD-supported ACE network is at UNC, Chapel Hill—PI: Joe Piven. This network focuses on increasing understanding of the timing and pattern of brain development in very young children with autism. These investigators compare brain images of very young children who are at risk for developing ASDs to those who are not at risk.

All ACE Program grantees must submit their data to the National Database for Autism Research (NDAR), which is described in more detail below. The first annual meeting of ACE grantees will be held in 2010. Table 3 provides a more detailed listing of all the ACE Program projects, including those for which the NICHD has primary responsibility.

INTERAGENCY AUTISM COORDINATING COMMITTEE (IACC) STRATEGIC PLAN FOR ASD RESEARCH

The *Children's Health Act of 2000* (P.L. 106-310) included language to establish an IACC, to include representatives of federal and public agencies involved in ASD-related issues, members of the public, and an NIH Autism Coordinating Committee (NIHACC). In response to the heightened societal concern about ASDs, congress later passed the *Combating Autism Act* (P.L. 109-416) in 2006. The 2006 Act requires the IACC to develop and annually update a strategic plan for ASD research, including proposed budgetary requirements. In addition to the directors of the NIH Institutes comprising the NIHACC, namely the NICHD, NIDCD, NIEHS, NIMH, and NINDS, members of the IACC include the following: Center for Medicare and Medicaid Services, U.S. Department of Education, Administration for Children and Families, HRSA, Substance Abuse and Mental Health Services Administration, CDC, Autism Society of America, Autism Speaks, Autism Spectrum Consulting, Coalition for Safe Minds, and the Autism Science Foundation, among others.

The IACC Strategic Plan is organized around six critical questions asked by individuals and families living with ASDs:

- When should I be concerned?
- How can I understand what is happening?
- What caused an ASD to happen and can it be prevented?
- Which treatments and interventions will help with ASDs?
- Where can I turn for ASD-related services?
- What does the future hold?

The NICHD, through the IDD Branch, was an active participant in the development of the Strategic Plan. Branch staff were involved in scientific workshops to identify research opportunities, expert workgroup meetings to recommend research objectives and strategies, and programmatic expert meetings to develop and recommend budget estimates. The completed Strategic Plan was first released to the public in March 2009, and the current version is available at http://iacc.hhs.gov/strategic-plan/.

NATIONAL DATABASE FOR AUTISM RESEARCH (NDAR)

As mentioned earlier in this report, the NICHD is one of several NIH Institutes that sponsors NDAR, a bioinformatics system created by the NIH to support ASD research and to accelerate scientific discovery. NDAR has facilitated the formation of a world-wide network of ASD researchers that seamlessly integrates data, research tools, and institutions by providing a common platform for data collection, retrieval, and archiving. This standardized data-sharing system was a key component of the IACC Strategic Plan, which called for wide adoption of this type of system to provide the infrastructure needed to propel ASD research forward during the next decade.

ACE Program award recipients began contributing their common measures data to NDAR in July 2008. More recently, the NIH implemented procedures to allow NDAR to accept and share research data from non-ACE researchers. IDD Branch staff serve as active members of the NDAR Implementation Team and Subcommittee for Policies. Please visit http://ndar.nih.gov for more details on NDAR objectives and capabilities.

OTHER ASD-RELATED RESEARCH ACTIVITIES

Congress tasked the Department of Defense Congressionally Directed Medical Research Program (CDMRP) to manage appropriations specifically targeting ASD research in 2007. An IDD Branch staff member has participated in setting CDMRP's program priorities and making funding decisions since 2007.

The Branch also participates in research funding activities related to vaccines and ASDs. For instance, a member of the IDD Branch staff serves as one of the NIH liaisons to the National

Vaccine Advisory Committee. NICHD also participates in an NIH-wide PA, *Research to Increase Vaccine Safety*.

Outreach to communities affected by ASDs, including advocacy groups and family support organizations, is another key focus of IDD Branch activities in ASDs. In February 2007, IDD Branch staff participated in meetings co-sponsored by the National Association of Broadcasters and the Special Olympics to discuss ways to decrease stereotypes of individuals with IDD. For these meetings, Branch staff provided scientific information about the behavioral heterogeneity and potential work-force productivity of individuals with IDD. The IDD Branch also partners with groups such as Autism Speaks to promote research and education activities with shared goals.

SCIENCE ADVANCES IN ASD RESEARCH

Identifying Early Risk Markers

Rapid progress is being made in the identification of the early behavioral phenotype of autism. Much of this progress has resulted from prospective studies of infant siblings of children with autism. The Baby Sibling Research Consortium, currently sponsored by Autism Speaks, originated at a 2003 meeting co-sponsored by the National Alliance for Autism Research (now Autism Speaks) and the NICHD. Through the IDD Branch, the NICHD funds many members of the Consortium. Research results have helped to identify and characterize the earliest behavioral characteristics and developmental trajectories of children at risk for ASDs. For example, because early intervention is known to improve developmental outcomes for children with ASDs, a crucial research area involves finding the earliest possible age for valid ASD screening. In a prospective longitudinal study co-funded by NICHD, researchers followed the development of social and communication skills in infant siblings, between six months and 36 months of age, of children with ASD and compared them with infants from unaffected families who were considered to be at low risk for ASDs. About one-half of the children with ASD could be diagnosed soon after their first birthdays. However, because others with the disorder may seem to develop normally until one year of age and then regress during their second year, screening would need to be repeated near the second birthday to detect children whose development becomes atypical during this interval (Landa et al, 2007).

A more recent publication from the Baby Siblings Research Consortium summarized the current state of the science regarding the early signs of ASDs and various screening instruments. The researchers also described best practices for the diagnostic assessment of ASDs in children younger than two years of age, including use of the Modified Checklist for Autism in Toddlers (M-CHAT), the development of which was funded by NICHD (Pandey et al, 2008). (Researchers are also planning to use the M-CHAT to screen for ASDs in the National Children's Study, a longitudinal assessment of 100,000 children from diverse backgrounds.) This research provides pediatricians and parents with desperately needed, empirically based guidelines for screening and managing young children suspected to have ASDs (Zwaigenbaum et al, 2009).

Another NICHD-sponsored study sought to understand the stability of an ASD diagnosis at age two years. Although the diagnosis of an ASD is usually thought to be permanent, the study's findings suggested otherwise. A portion of two-year-olds who had a diagnosis of ASD in the study no longer had the diagnosis by age four years. Children with Pervasive Developmental Disorder Not Otherwise Specified were significantly more likely than those with full autistic disorder to move off the spectrum. Motor skills at age two years were the clearest distinguishing factor (Sutera et al, 2007).

Persons with autism have difficulty reading social cues and situations, which leads to inappropriate responses. Researchers measure eye-tracking movements, which emerge within the first few weeks of life, to ascertain the resources devoted to specific environmental cues, such as responses to social situations. Those with autism focus on less-essential or even irrelevant aspects of the social environment, such as mouths or objects, rather than on the eyes or face as a whole. By focusing on such aspects, they miss key information for assessing the situation. Interventions that teach persons with autism to focus on essential aspects of social environments may help alleviate some of the social difficulties related to the disorder (Jones et al, 2008; Klin et al, 2009).

Neuroimaging Studies

Using fMRI, scientists were able to show—for the first time—that instructing children and adolescents with ASDs to focus on a face or on a voice led to increased activity in the areas of the brain that people understand how others feel. These findings could enhance interventions to promote activity in the brain region that processes and integrates multiple sources of what might be considered intangible information, such as the tone of voice and facial expression of another individual.

In another fMRI study supported by the NICHD, in collaboration with the NIDCD, the National Alliance for Autism Research and Cure Autism Now (both now Autism Speaks), and the University of California, Davis, investigators compared how well boys with ASDs and typically developing (TD) boys understood the concept of irony. Compared to the TD group, the ASD group showed less activity in the medial prefrontal cortex and in the right superior temporal gyrus. After explicit instruction to focus on the face or the voice, however, the boys with ASDs showed a significant increase in brain activity in these regions. The TD group showed significant brain activity regardless of instructions. The findings also showed that individuals who were more socially impaired tended to show less brain activity when presented with an ironic scenario (Wang et al, 2007).

Studies to Address Early Brain Overgrowth-Related Issues in ASDs

A consistent finding in individuals with ASD is the increased frequency of macrocephaly and enlargement of cerebral cortical gray and white matter starting at a young age. Studies funded through the NIH CPEA Program examined the developmental trajectory of brain overgrowth and its relation to ASD symptoms. In one unique prospective study of the trajectory of head growth in ASD, head circumference (HC) measures were taken during the first three years of life in infants who were later diagnosed with ASD. The study found a period of accelerated head growth during the first year of life, followed in the second year by slower head growth relative to the excessive early growth. Infants who had a larger HC at age 12 months and greater HC

deceleration between 12 months and 24 months of age were more likely to exhibit ASD symptoms. The authors also described the timing of brain overgrowth relative to the emergence of ASD symptoms (often detected by age eight months to 12 months in rigorous studies of high-risk infants), as well as the phenomenon of regression or slowing of skills acquisition often reported in the second year of life. These findings may be useful in identifying very young children who may benefit from interventions to lessen the functional decline common in ASDs. These findings are also important clues to possible underlying genetic or other neurobiological mechanisms of abnormal brain growth in ASDs (Dawson et al, 2007; Elder et al, 2008).

MRIs of individuals with ASDs show increased volumes of a number of brain structures compared to TD individuals. To learn more about this phenomenon, investigators on one longitudinal study, funded in part by NICHD, found that children with ASDs had an enlarged amygdala at age two years and again at age four years. The enlargement was stable during the two- to four-year-old time interval. The investigators also found that this enlargement was related to "joint attention"—the ability to share information and understand the thoughts and intentions of others—an outcome that extends previous findings from research on brain overgrowth in children with ASDs. Understanding the pattern of early brain changes in ASDs and the relationship of these changes to ASD-related behaviors could lead to improved early diagnosis and interventions for these brain and behavior changes (Mosconi et al, 2009).

Progress in Understanding Motor Impairments in ASDs

Two recent publications from NINDS- and NICHD-supported researchers shed light on the neurobiological basis of deficits in motor abilities often observed in children with ASDs. In one study, investigators sought to determine whether deficits in basic motor function in ASDs could account for dyspraxia, or impaired performance of skilled gestures, such as tool use or communicative signals. They found that children with ASD showed significantly poorer performance on skilled gestures beyond that expected from basic motor deficits. They also found that impaired skilled gesture performance strongly correlated with the social, communicative, and behavioral impairments characteristic of ASD, suggesting that dyspraxia may be a core feature of ASD or a marker of its underlying neurological abnormalities.

In the second study, the same investigators used brain imaging to determine whether motor deficits in ASDs were related to variations in brain anatomy. Increased brain volume, particularly in white matter containing connecting nerve fibers, is the most consistent brain-imaging finding in children with ASDs. This study showed an association between impaired motor performance and increased white matter volume in the primary motor cortex of children with ASDs. The mechanisms and types of anatomical variations that contribute to motor dysfunction may also contribute to other features of ASDs, such as deficits in socialization and communication. Because measures of motor function are more quantifiable and reproducible than measures of complex social behavior, studies of motor function provide an opportunity for increased understanding of ASDs and their causes (Dziuk et al, 2007; Mostofsky et al, 2007).

Study of Psychosocial or Functional Analysis Approaches to ASD Treatment

Joint attention and engaging in symbolic play or "pretending" are key aspects of social interaction—and are often lacking in persons with ASDs. Evidence shows that early interventions can improve language outcomes and social skills in children with ASDs. Among

individuals in one Branch-supported study, children who received intervention, regardless of whether it was a joint attention intervention or a symbolic play intervention, showed greater gains in expressive language than did those who received no intervention. High-functioning children also showed positive outcomes regardless of the type of intervention received. Lower functioning children made greater gains in language if they received the joint attention intervention than if they received the symbolic play intervention or no intervention. This study provides firm evidence that early interventions are an effective way to improve developmental outcomes for those with ASDs (Gulsrud et al, 2007; Kasari et al, 2008).

Progress in Understanding Genetic Contributions to ASDs

Searching for the genetic causes for ASDs represents a major effort in both NICHD- and NIH-funded research. By comparing the DNA of people with ASDs to that of TD individuals, researchers have uncovered an increasing number of variations in specific genes and chromosomal regions (such as 15q and 16p) linked to ASDs and related disorders. Overall, discoveries in the past few years underscore the complexity of the genetics of ASDs. In 2007, researchers made significant advances in identifying specific genetic changes that contribute to a small portion of ASD cases. These findings suggest that changes in many different genes contribute to the development of ASDs. Researchers also proposed two types of genetic changes that may account for the genetic basis of ASDs. One involves rare and spontaneous deletions or duplications of genetic material that typically result in just one affected member in a family; the second involves the combination of multiple common variations in DNA sequence that are transmitted from one or both parents, with the potential to result in more than one affected member in a family.

In two recent studies, partially funded by NICHD, investigators identified both common and rare genetic factors that affect the risk for ASDs. These results pointed to the importance of genes involved in forming and maintaining the connections between brain cells, including neuronal cell-adhesion molecules, such as neurexin and cadherin, and those involved in the ubiquitin degradation pathway related to AS. These results, which validated previous findings demonstrating abnormal cortical connectivity in the brains of those with ASDs and specific gene mutations, represent a successful application of the genome-wide association study (GWAS) approach to identifying common genetic susceptibility alleles. This GWAS approach signifies a major step forward in the larger effort to understand the complex genetic architecture of ASDs (Wang et al, 2009; Glessner et al, 2009).

PLANNED ASD RESEARCH ACTIVITIES: AMERICAN RECOVERY AND REINVESTMENT ACT OF 2009 (ARRA)

On February 17, 2009, President Obama signed the ARRA legislation (also called the Recovery Act or the Stimulus Package) to preserve and create jobs, promote economic recovery, and provide investments to increase economic efficiency by spurring technological advances in science and health. The NIH received and distributed $10.4 billion from this legislation.

The NICHD participated in the NIH-wide ARRA RFAs, *Recovery Act 2009 Limited Competition: Research to Address the Heterogeneity in ASDs*. The RFAs solicited R01,

collaborative R01, R21, R34, and collaborative R34 applications addressing the IACC Strategic Plan in the following topic areas: measurement development, biomarkers/biological signatures, immune and central nervous system interactions, genetics/genomics, model development, treatments and intervention, and services research. The funding plans for these two-year awards have been finalized with a number of NICHD-funded investigators embarking on these additional projects to advance autism research progress.

NEWBORN SCREENING

Newborn screening research initiatives within the NICHD and specifically within the IDD Branch have experienced considerable growth and re-emphasis during the reporting period. Newborn screening enables identification of infants who are at risk for congenital disorders (often biochemical, endocrinologic, and/or genetic) for which early interventions and treatments have the potential to reduce morbidity and mortality. Although routine screening has occurred at the state level since the 1970s, screening tests available have historically varied significantly by state; similarly, few states have evaluated the rationale for or efficacy of the tests systematically. Because these programs screen more than 4 million infants per year, newborn screening represents the most common form of genetic testing performed in the United States.

SECRETARY'S ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN (ACHDNC)

The *Children's Health Act of 2000* (P.L. 106-310) established the Secretary's ACHDNC, currently chaired by an NICHD staff member, to advise on grant programs associated with newborn screening legislation and to provide technical advice on heritable disorders as a means of enhancing and expanding newborn screening. Members of the ACHDNC include medical, scientific, and clinical professionals, members of the public with special expertise, and representatives from many federal agencies. Chartered in February 2003, the ACHDNC advises the Secretary of DHHS about the most appropriate application of universal newborn screening tests, technologies, policies, guidelines, and standards for effectively reducing morbidity and mortality in newborns and children having, or at risk for, heritable disorders. IDD Branch members participate in the meetings as observers to keep abreast of information and recommendations made by the scientific community and vetted by the ACHDNC.

In 2005, the American College of Medical Genetics (ACMG), as commissioned by HRSA, developed a core panel of 29 primary conditions, called the Uniform Screening Panel, and published *Newborn Screening: Toward a Uniform Screening Panel and System*, available at http://mchb.hrsa.gov/screening. After careful review, the ACHDNC approved the Universal Screening Panel and recommended it to the DHHS Secretary. States rapidly adopted the Panel, and now most states have a Panel similar to the recommended version.

The following statistics attest to this remarkable adoption:

- In 2000, 35 percent of states screened for fewer than five conditions, and none screened for more than 30 conditions.
- By 2005, 23 states screened for at least 21 conditions.
- By December 2008, 49 states screened for at least 21 conditions.

The ACHDNC developed a structured, streamlined, and public process for nominating new disorders to the Panel that utilizes an independent, evidence-based review system; final approval is given by the Secretary of DHHS. As of April 2009, several new, potentially screenable conditions have undergone review, with the following outcomes:

- Fabry Disease, SMA, and Niemann-Pick Disease were nominated for inclusion, but were deemed by the Committee as not ready for an evidence review.
- Pompe disease and Severe Combined Immune Deficiency went through formal evidence review, but were not recommended for addition to the Panel at this time. Both disorders were deemed very promising for newborn screening and their reconsideration would require specific additional information.
- Krabbe Disease is currently undergoing formal evidence review; the Committee will discuss the evidence at its meeting in September 2009.

NEWBORN SCREENING SAVES LIVES ACT

In 2008, congress passed the *Newborn Screening Saves Lives Act* (P.L. 110-204) to establish grant programs providing for education and outreach on newborn screening and coordinated follow-up care once newborn screening is conducted. As part of the Act, the Secretary of DHHS must ensure the quality of laboratories involved in newborn screening activities and develop a national contingency plan for newborn screening. The Act also authorized the NIH to carry out research in newborn screening, including identifying new screening technologies and researching disease-management strategies for the conditions that such screening can detect. The latter provision is known as the *Hunter Kelly Newborn Screening Research Program*, named for Hunter Kelly—son of Jim Kelly, former National Football League Hall of Fame quarterback. Hunter died at age eight from Krabbe leukodystrophy, a degenerative neurological disorder. This effort is being led by the IDD Branch and other members of the Center for Developmental Biology and Perinatal Medicine, and some of the advances from this effort are included in the next section. The legislation also expanded the role of the ACHDNC, mandated appropriations to help with the Committee's activities and to fund newborn screening research, and authorized an interagency coordinating committee on newborn screening.

ADVANCES IN NEWBORN SCREENING

Because formal efforts related to newborn screening are still quite new and the infrastructure only being established, the Branch has few science advances to report. However, the Branch has made great progress in laying the foundation for future newborn screening research and in

supporting ongoing research on various aspects of newborn screening. These types of advances are explained below.

Newborn Screening Translational Research Network Coordinating Center (NBSTRN-CC)

The *Hunter Kelly Newborn Screening Research Program* focuses on developing systematic methods to identify additional conditions appropriate for newborn screening; developing and testing innovative interventions and treatments to improve outcomes; educating the provider workforce; developing and implementing appropriate information and communication systems for parents and providers; and sponsoring ongoing programs of research and research training.

One of the challenges to efficient and effective newborn screening is the variability of standards for screening across states and the lack of an infrastructure to connect existing resources. To address these critical needs, the IDD Branch awarded a five-year contract at the end of fiscal year 2008 to create the NBSTRN-CC, designed to establish the necessary infrastructure for research efforts in newborn screening.

The NBSTRN-CC will facilitate development of new screening methods, enable the conduct of clinical trials for new therapeutic interventions, and support longitudinal research on the long-term health of children identified through newborn screening programs. The primary goals of the NBSTRN-CC are to:

- Establish an organized network of state newborn screening programs and clinical centers.
- Develop, implement, and refine a national research informatics system for investigators and policy makers that dovetails with established national clinical networks.
- Establish and administer an efficient and reliable repository of residual dried bloodspots.
- Provide expertise and support related to regulatory requirements associated with informed consent, Institutional Review Boards, and state and local research policies associated with newborn screening.
- Facilitate research on the development of new methods and technologies by maintaining close contact with the scientific and biomedical research community.
- Facilitate research on screened and treated patients to define effectiveness of treatments and long-term outcomes.
- Provide statistical leadership and clinical trial design expertise for the individualized needs of researchers.
- Facilitate the timely dissemination of research findings.

Biomedical Research: Novel Technologies in Newborn Screening

In fiscal year 2006, the Branch issued a Request for Proposals (RFP) titled *Novel Technologies in Newborn Screening*. As a result, the IDD Branch awarded two contracts to develop multiplexed screening assays that could be automated and utilized in a high throughput environment for newborn screening. The intended goal of these projects is to develop a screening technology platform of components based on a range of technologies. One contract, to the University of Washington, is evaluating the expansion of tandem mass spectrometry as an instrument for the enzymatic detection of lysosomal storage disorders, such as Fabry disease, Pompe disease, and

Hurler syndrome, in newborn screening samples. The other contract, to the New York State Department of Health, is developing a Luminex® bead-based microarray assay for newborn screening.

Innovative Therapies and Clinical Studies for Screenable Disorders

Beginning in 2005, the NICHD, NIDCD, and NIDDK issued an ongoing FOA to stimulate translational research on potential therapeutic interventions for conditions currently screened by states, as well as other high-priority genetic conditions for which screening might be possible in the near future. The FOA placed special emphasis on research related to some of the high-priority conditions, defined as those for which the development of an efficacious therapy would make the condition amenable to newborn screening, identified in the 2005 ACMG report. The FOA also supported research designed to elucidate the natural history of these conditions to facilitate identification of potential therapeutic interventions, with the ultimate goal of developing more targeted and effective therapies. The IDD Branch currently funds nine projects under this initiative, targeting the following disorders: Heritable gamma-hydroxybutyric aciduria, hyperammonemia, Gaucher disease, SMA, galactosemia, Krabbe disease, and phenylketonuria.

Other examples of Branch-supported newborn screening projects include the following:

- Digital Microfluidics—The IDD Branch currently funds the development of an automated, inexpensive, multi-analyte and multiplexed screening analyzer to help reduce blood analysis volumes and time-to-result. The project also aims to make the analyzer available at the point-of-delivery (for example, birthing centers). This disposable lab-on-a-chip will use digital microfluidic manipulation of nanoliter-sized droplets of enzymatic reagents and sample for dispensing from on-chip reservoirs, high-speed transport, mixing, splitting and dilution, and absorbance, fluorescence, and luminescence detection of the assays. The project aims to demonstrate the feasibility of performing newborn screening for lysosomal storage disorders, including Fabry, Pompe, and Hurler diseases, from a single dried blood spot obtained from the heelstick of a newborn using this microfluidic technology.
- Quality Control Tool for Newborn Screening Blood Samples—This project aims to develop a simple and economically advantageous imaging-based computer system to evaluate newborn screening blood cards for adequate quality and quantity for testing at the point of care (e.g., birthing center). Use of such a system would allow for the immediate correction of inadequate cards before the card is sent to the lab for testing and while the newborn is still in the birthing center, saving health care dollars and preventing any unnecessary delay in the diagnosis of important metabolic diseases.
- Family Adaptation to Newborn Screening—The numerous ethical, behavioral, and social impacts of newborn screening have yet to be fully explored and understood. These include efforts to investigate the psychological and social impact of false-positive and false-negative results on children and their families—in particular, those newborns whose results are within the abnormal range, but who do not actually have a disease. This ongoing study, led by investigators at the Fragile X Research Center based at UNC, Chapel Hill, evaluates the following in relationship to newborn screening for FXS:
    - Extent to which families from diverse cultural and ethnic groups consent to newborn screening;

- Reasons parents decline or accept screening, and family or sociocultural factors related to screening decisions;
- Extent to which families of identified children believe they were adequately informed about the possible results from screening, are initially satisfied with their decision to participate, and whether and how their views about screening change over time;
- Whether families experience adverse mental health outcomes following a diagnosis, and how adaptation varies as a function of child, family, and support variables;
- Variation in the quality and evolution of parent-child relations following diagnosis; and
- Variation in the ways that parents and extended family members respond to, share, and use information gained from a newborn diagnosis.

Newborn Screening in the Middle East and North Africa (MENA)

In 2006, Dr. Elias Zerhouni, then Director of the NIH, traveled to North Africa with an NIH delegation to discuss plans for collaboration and partnership. During this visit, newborn screening emerged as one of the top health priorities in the region, where such services are limited. Following the initial delegation visit, the Ministry of Health of the Kingdom of Morocco partnered with the NICHD and other organizations to hold a regional conference, *Strengthening Newborn Screening in the MENA Region*, November 13-15, 2006, in Marrakech, Morocco. The meeting brought together representatives from 18 countries in the MENA region and 11 countries in Europe, North America, and Asia/Pacific Islands and received support from 20 international public-private sponsors.

A primary outcome of the meeting was the *Marrakech Declaration*, a document that affirmed newborn screening as a key public health priority for the region and recognized the need for a collaborative, cooperative network to facilitate the development of a newborn screening system for all nations (see *Appendix F* for the full declaration). In addition to the provision that all countries screen for at least one condition, key elements of the declaration stated that participating countries would:

- Develop policies and establish a systematic national newborn screening program.
- Assure that children identified as having screened positive for a genetic disorder have access to care.
- Establish biannual regional meetings to assess progress and increase collaboration.
- Develop training programs.
- Establish national research priorities and stimulate regional research capacity.

A Steering Committee was also established to plan for the region's next meeting on newborn screening and to address recommendations of the Marrakech Declaration. The Committee included members from multilateral organizations, ministries of health, universities, and other health care provider groups, as well as international collaborators in the United States, Europe, and Asia/Pacific Islands. The Steering Committee also established a Congenital Hypothyroidism Training Working Group and a Survey Working Group. In response, several countries, including Morocco and Tunisia, have begun developing and expanding their newborn screening programs.

The *2nd Conference of the MENA Newborn Screening Initiative: Partnerships for Sustainable Newborn Screening Infrastructure and Research Opportunities*, held in Cairo, Arab Republic of Egypt, April 12-14, 2008, included more than 30 policy makers, health care providers, health ministry representatives, scientific experts, and family and advocacy representatives from 17 countries in the MENA region, Europe, Asia, and North America. The primary outcome of this effort was the development of National Plans of Action to implement or strengthen screening programs in each of the participating countries. These National Plans detailed program leadership, blood-spot collection and storage, laboratory methods, and linkage to treatment and follow-up. An article summarizing these issues was published in *Genetics in Medicine* (Krotoski, et al, 2009).

Plans for a third conference, to be held in early 2010 in Doha, Qatar, are ongoing. The third meeting will seek to further expand upon these initiatives, build infrastructure, establish collaborations, and initiate newborn screening in MENA countries.

Early Detection of Neuromuscular Diseases

In spring 2009, the NICHD, in conjunction with other NIH Institutes and Centers, including ORDR, NHGRI, and NIAMS, other federal sponsors, including HRSA and CDC, and the Muscular Dystrophy Association, held a 1½ day workshop on March 16-17. Approximately 60 participants, including scientists, health care providers, public health leaders, ethicists, and patient advocacy groups participated in this meeting to discuss early detection and screening for neuromuscular diseases and the steps necessary to consider newborn screening for these disorders. Possible outcomes of this meeting, with the overarching goal of determining the needs of the neuromuscular disease communities, might include funding opportunities, follow-up workshops, and development of networks to support efforts related to the process of newborn screening for these disorders.

RESEARCH RESOURCES

REPOSITORY FOR MOUSE MODELS OF CYTOGENETIC DISORDERS

This project began in the 1970s to generate and distribute mouse models for cytogenetic disorders. With demonstration that a segment of mouse chromosome 16 contained genes closely related to the genes on a large segment of human chromosome 21, the trisomy 16 mouse became a model for studies relevant to Down syndrome. Subsequent genetic dissection of both mouse and human genomes located other genes present on human chromosome 21 that were closely related to genes on mouse chromosomes 10 and 17. In the 1980s, under contract with NICHD, investigators at Jackson Laboratories (JAX) in Bar Harbor, Maine, created mice with partial trisomies for a number of chromosomal segments. One of these partial trisomies, designated Ts65Dn, proved to include approximately 150 genes located in the “Down-syndrome critical region” of human chromosome 21. Subsequently and also under contract, JAX produced and distributed these mice to investigators approved for their receipt by the NICHD.

The creation of a central repository for these mice has ensured maintenance of the appropriate genetic strains and their efficient distribution to investigators. Because Ts65Dn males are usually infertile and females produce fewer litters than normal females, generating large numbers of the trisomic mice is very difficult for any individual researcher. The repository serves the Down syndrome research community by providing mice for a wide variety of studies related to understanding the basic biology of Down syndrome, including neurocognitive dysfunction and Alzheimer-like disease findings that occur with increasing age.

The contract was competitively awarded to JAX in May 1985, for four years and has undergone recompetition or extension since then. The current contract is under extension until mid-fiscal year 2010, by which date a renewal is planned. The Branch intends to revise the contract to ensure that adequate numbers of mice are available in a timely manner to investigators requesting them, so that this important resource can accommodate the increased demand for these valuable murine models.

BRAIN AND TISSUE BANK FOR DEVELOPMENTAL DISORDERS

The NICHD began funding a Brain and Tissue Bank for Developmental Disorders in 1991 to provide a research resource that would increase knowledge of the etiology and pathogenesis of neurodevelopmental disorders. The Bank has served the critical role of collecting, preserving, and distributing human tissues to qualified scientific investigators dedicated to the improved understanding, care, and treatment of individuals with neurodevelopmental disorders, including ASDs.

The Branch released a Request for Information in December 2008 to notify the community that NICHD would publish an RFP for continuation of the Bank and to provide all interested parties with an opportunity to comment on the Bank. The Branch received more than 100 comments, mostly from prior recipients of tissue from the Bank. The comments unanimously affirmed the value and contributions of the Bank and were helpful in formulating the RFP.

In August 2009, the NICHD awarded the contract to the University of Maryland to continue and expand the Brain and Tissue Bank with enhanced tissue processing capabilities and an increased emphasis on the collection and distribution of tissues related to ASDs. This expansion lays the groundwork for establishing an international network of biobanks to collect brain and other tissues. Creation of an international network of autism tissue collection sites is one of the goals of the IACC Strategic Plan on ASD Research.

BRANCH-SUPPORTED TRAINING INITIATIVES

The IDD Branch supports a number of training activities, almost exclusively through investigator-initiated efforts; that is, none resulted from an IDD Branch-initiated RFA

(see Figure 15 and *Appendix E*). The RDCRC and the Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers have separate training components.

The Branch supports training and career development through a number of mechanisms, including F31, F32, K02, K08, K23, and K24. The Branch also supports one K99/R00 award via this relatively new mechanism that aids in career transition from mentored support to independent investigator status.

The Branch also uses T32 grants to support predoctoral and/or postdoctoral trainees at academic institutions with a formal training program. Many of the T32s listed in *Appendix E* support training that has a direct clinical focus on IDD, while others comprise interdisciplinary training experiences in neurodevelopmental disorders with basic science components. In addition, the Branch supports a meeting that brings trainees together annually at the Gatlinburg Conference to make presentations and network through an R13, as previously described.

One of the challenges associated with assessing the success of training programs is the difficulty in tracking the career development of trainees after they complete the program, a logistical dilemma, and one that Branch has not yet fully addressed. In addition, the number and quality of trainees supported in IDD research is relatively high in spite of the limited Branch funds committed to training experiences, but this is an area that the Branch would like to expand. Possible means for enhancing the Branch's efforts in training are included in the *Future Directions for the Branch* section of this report.

FUTURE DIRECTIONS FOR THE BRANCH

On April 30, 2009, in accordance with the NICHD process for improving the transparency of and enhancing public input toward strategic planning, the IDD Branch convened an expert panel to review its activities during the past four years and to suggest possible future directions for IDD-related research. Members of the panel included professionals with expertise in the fields of pediatrics, genetics, neurology, neonatology, developmental pediatrics, psychology, neurobiology, metabolism, and newborn screening; members of the NACHHD Council; and public representatives and stakeholders (see *Appendix C* for a list of panel members).

This group discussed key scientific opportunities, public health issues, and training efforts that the Branch will consider pursuing in the next four years, with a particular focus on prioritizing specific areas of the research agenda. Overall, there was broad consensus among the expert panel members that a major emphasis of the Branch should be efforts to reconceptualize IDD research into broader areas, such as shared pathways or systems approaches, in order to promote development of interventions for a wider population of individuals with IDD. A summary of the panel's discussion is included below and is organized into six main areas of emphasis.

RESEARCH ON THERAPEUTIC INTERVENTIONS FOR IDD

Panel members noted that, in the past, the IDD Branch emphasized basic and clinical studies on the etiology and fundamental mechanisms underlying specific forms of cognitive impairment with great success, but put only limited commitment toward research for developing new drugs and other treatments. The panel recommended a general emphasis on clinical and translational research to identify potential interventions for individuals with IDD. Although individual IDD conditions are somewhat rare, these conditions collectively impact a significant proportion of the population. Therefore, panel members felt that it was critical to fully exploit existing strategies and treatments in this population, particularly given the decrease in available health care resources.

An underlying subtext of this discussion, and an element critical for the success of this approach, was the need to improve outcome measures and to develop biomarkers, both of which depend on accurate phenotyping in the IDD population. Precise definitions of clinical, genetic, epigenetic, and environmental features of various IDD conditions are necessary to understand which subpopulations might benefit from particular therapies. A corollary is the need to promote longitudinal natural history and population-based studies. Recognizing that natural history studies are expensive and not always as competitive in review as traditional, hypothesis-driven research, panel members and Branch staff acknowledged that a broad view and comprehensive approach may be necessary.

The panel also discussed support for empiric studies to assess existing, commonly used behavioral and educational interventions for IDD. In general, there are many interventions available for individuals with IDD, but little or no empiric data support their utility and validity; further, few analyses compare different treatment regimens, doses, or intensities for efficacy. In many cases, parents spend substantial time and energy on unproven interventions for their children, often at great expense to families, schools, care providers, and insurance companies, despite the lack of evidence suggesting that such interventions improve outcomes.

The panel acknowledged that an emphasis on developing therapies for IDD would require a long-term commitment of resources and NICHD program staff, as well as creative collaborative approaches. The expert panel recommended increasing partnerships to build up research resources that might include registries, data-sharing plans, communication and outreach efforts, and public education. The panel reached broad consensus on the need for interventions in the IDD field, recognizing that this represents a far-reaching and ambitious goal.

Within the context of the panel's discussion, the IDD Branch will consider the following research activities during the next four years:

- Explore ways to enhance clinical/translational research efforts in the field, including:
  - Focusing on more common IDD conditions with established patient populations
  - Recognizing contributions from rare but well-defined disorders that may have broader applications to other IDD conditions
  - Supporting tests of drugs that have FDA approval for uses in the IDD population
  - Focusing on pathway disorders/systems biology approaches to develop tools for endpoints

- Support efforts to more precisely define clinical, genetic, epigenetic, and environmental features of various IDD conditions and to adopt these definitions throughout the research community.
- Partner with other Branches, Centers, Institutes, and organizations to promote longitudinal, natural history and population-based studies that include individuals with IDD. Model successful examples of longitudinal efforts, such as the RDCRC, the Newborn Screening Translational Research Network, and the NIH-sponsored Clinical and Translational Science Awards (CTSAs).
- Support research to systematically evaluate commonly used behavioral and educational interventions for IDD to determine whether children who receive these interventions actually benefit from them.
- Encourage and explore partnerships and collaborations to better utilize resources and expertise. Potential partners might include: Groups with multicenter translational research and clinical trials; investigators who use the CTSA infrastructure; other NICHD Branches, Centers, and Programs (such as the National Children's Study and the OPPB); other NIH Institutes and Centers; other federal agencies within DHHS, such as CDC, HRSA, and the Agency for Healthcare Research and Quality; the Institute of Education Sciences, U.S. Department of Education, and other education groups; advocacy groups and other private foundations; and international organizations and consortia.

EARLY IDENTIFICATION AND DIAGNOSIS VIA NEWBORN SCREENING

The expert panel acknowledged the contributions of early identification and diagnosis of IDD to improved treatment and interventions for those with IDD and supported continued expansion of newborn screening programs and development of new technologies. Although newborn screening has significantly improved the ability to diagnose treatable inborn errors of metabolism in a newborn infant, the panel noted a need to develop screening tools for other forms of cognitive impairment not currently identifiable via available methodologies. In addition, the panel expressed interest in developing other modalities for early identification and screening, such as preconceptional testing (testing of parents for carrier status for conditions associated with IDD), prenatal testing (testing *in utero* for IDD), and early childhood screening (testing in the primary care physician's office or educational setting). The panel observed that all of these approaches have associated ethical issues that need to be addressed, but added that they also have implications for public health policy, population surveillance measures, and health care resource allocation, given the need to continue to monitor and follow-up with children identified by screening and their families.

A related topic of interest for the panel was the need to support research on preventable forms of IDD, such as those resulting from maternal drug or alcohol use, malnutrition, preterm birth, low birth weight, hypoxia/ischemia, and other perinatal insults that result in brain injury. Research to identify pregnancies at risk for these sequelae as well as to track infants after exposure to ensure appropriate follow-up could have a profound effect on reducing the incidence of these events leading to IDD and promoting the treatment of exposed infants to optimize outcomes.

Based on the panel's discussion, the IDD Branch will consider pursuing the following research activities:

- Support efforts to develop screening tools for forms of cognitive impairment not detected through currently available means.
- Encourage research to expand modalities for early identification and screening, such as preconceptional testing, prenatal testing, and early childhood screening.
- Partner with allied health care providers to disseminate information related to newborn screening and follow-up.
- Collaborate with health care providers and professional organizations to develop and disseminate counseling guidelines and information for at-risk individuals and families about IDD conditions discovered during routine newborn screening or other modalities.
- Expand research support for preventable forms of IDD to include identification of at-risk pregnancies and follow-up of infants and families; partner with appropriate groups, such as the NICHD PPB, to accomplish this goal.

RESEARCH ON ADOLESCENT BRAIN DEVELOPMENT

The panel noted that adolescent brain development in IDD is an area of relative lack of emphasis in the Branch portfolio. Many experts in the field acknowledge that the adolescent brain is a unique entity with distinct neurobiological and neurochemical properties that may predispose to later development of neuropsychiatric disorders and addictions. The IDD population also has unique challenges in addition to those faced by TD adolescents. As the survival improves for many infants and children with IDD conditions, more members of the IDD community reach adolescence and adulthood. However, the dearth of research on adolescents in the IDD population leaves them vulnerable to poorer outcomes and reduced quality-of-life. Thus, the panel recommended additional research to address the medical, psychosocial, and psychiatric needs of a growing population of adolescents with IDD in the United States.

In light of the panel's discussion, the IDD Branch will consider the following activities:

- Support research to create and expand the existing evidence base related to the adolescent brains of those with IDD and those without IDD to:
  - Better inform future research and treatment interventions
  - Improve quality-of-life for adolescents with IDD and their families
  - Address aspects of adolescent development that are specific to particular IDD conditions and those that are more generalizable
- Explore the characteristics of IDD comorbid conditions, such as obesity, disordered sleep, complications of pubertal or gynecological conditions (such as premenstrual syndrome or other menstrual disorders, fertility, and pregnancy) and support research on their management and intervention.

HEALTH DISPARITIES AND HEALTH PROMOTION RESEARCH RELATED TO IDD

The panel discussed several research topics related to reducing health disparities among IDD populations. Individuals from disadvantaged socioeconomic backgrounds are less likely to receive screening services, diagnostic evaluations, or treatment interventions. These individuals, who already represent a "vulnerable population," have additional factors that increase the likelihood of poor outcomes related to IDD. Panel members noted that little or no research has focused on health disparities that impact life expectancy and quality-of-life for individuals with IDD throughout the lifespan.

In the realm of health promotion, the panel suggested that nutrition, exercise, and obesity were particularly understudied within the IDD population. Obesity is a public health crisis in the United States, and the IDD population is at particularly high risk for a variety of reasons. Although many factors, such as overeating, lack of access to nutritious foods, and inactivity, contribute to this epidemic, the general public shares many of these factors. The panel expressed enthusiasm for development of a research agenda to identify the root causes of obesity and prevention strategies in the IDD population in partnership with other NICHD groups, such as the Obesity Research Strategic Core, that work in childhood obesity research.

In addition, the panel noted a lack of evidence related to transition to adulthood within the IDD population. Adults with IDD often lack services or access to services once they reach age 21, in spite of a developmental IQ that may not match their chronological age. The panel also encouraged the Branch to explore partnerships and public education efforts within the IDD community around these issues.

Within the context of this discussion, the IDD Branch will consider the following activities:

- Support research on the various factors that influence, contribute to, and/or ameliorate health disparities among IDD individuals. This work could include (but would not be limited to) studies on cultural factors, belief systems, educational background, community resources, neighborhood influences, and access to services and their roles in health disparities that impact individuals with IDD and their families.
- Seek out ways to partner with or build upon the work of other entities, such as the NICHD Division of Special Populations, the Arc of the United States, and the American Association on IDD, to address health disparity issues in persons with IDD and their families.
- Support research on medical, emotional, and societal aspects of transition to adulthood in the IDD population and the factors related to positive outcomes and quality-of-life.
- Encourage health care providers who care for adult populations to expand their expertise in the unique medical, psychosocial, and behavioral issues for the IDD population as these individuals transition to adulthood.
- Collaborate with support and advocacy groups to develop health promotion and public education efforts for use within the IDD community to address issues such as obesity, nutrition, diabetes, and other conditions.

TRAINING INITIATIVES IN THE IDD FIELD

All panel participants recognized the need to promote training-related initiatives and to encourage investigators to join the IDD research field. The panel emphasized outreach to advertise opportunities to young people and to promote public awareness about IDD at early ages as critical to exposing young people to the field. Members recognized the need to support continued career development at all stages of training, but in particular, noted the need for early-stage investigators at the postdoctoral and junior faculty levels. Given the paucity of clinician-investigators entering the field and critical shortages of scientists in many pediatric subspecialty areas, the panel recommended that training initiatives be offered not only to medical doctors, but also to allied health professionals and other health care providers from related disciplines. In addition, they noted that the evolution of the IDD field and the complexity of the associated research issues dictate that training programs emphasize multidisciplinary approaches to training. In light of the panel's comments, the Branch might consider the following strategies for enhanced training to promote recruitment and retention of investigators within the IDD field:

- Promote IDD-related fellowships for high school and undergraduate students via summer research programs.
- Support residency programs in IDD-related critical areas, such as child neurology and genetics.
- Partner with international training programs to produce well-rounded investigators and encourage foreign scientists to enter the field.
- Develop well-structured, interdisciplinary programs that support novel career development paths for postdoctoral trainees.
- Recognize that lifestyle considerations (i.e., marriage, family) might compete with the need for intensive training and that flexibility in training opportunities, including NIH career development awards, is essential to encourage promising junior investigators to join the field.
- Explore incentives to induce M.D.s and Ph.D.s to enter the field.
- Partner with advocacy groups and private foundations to promote training initiatives.
- Encourage the IDDRCs to incorporate a mechanism for interdisciplinary training within their Centers.
- Promote research to track the results and outcomes of training initiatives.

TOWARD A NEW CONCEPTUALIZATION OF IDD RESEARCH

Expert panel members and Branch staff also discussed the need for a shift in emphasis for IDD research to integrate the IDD field more broadly, rather than focus on individual, rare disorders. This reconceptualization could apply to basic research, genomic studies, clinical and translational approaches, and provision of services. Essentially, panel members felt that such a paradigm shift could encourage investigators to rethink the IDD field from the perspective of shared etiologic pathways, systems approaches, and interrelated networks, with the goal of developing interventions that may generalize across many conditions. Reconceptualizing many IDD conditions as pathway disorders could also generate new scientific questions and treatment approaches for the Branch to pursue. A systems approach could also stimulate cross-thinking

and would likely increase the impact of publications in the field and make findings more generally applicable and broadly disseminated.

A "pathway" approach would also build power in numbers by bringing together advocacy and family groups impacted by ultra-orphan disorders to focus on similarities in the conditions. Many advocacy organizations are already collaborating in this manner and recognize the value of partnering with related groups and sharing and leveraging existing resources. For example, families affected by a variety of inborn errors of metabolism meet and exchange information at metabolic conferences. This new approach might also encourage advocacy groups to promote research on interrelated conditions and on the field as a whole.

The panel also indicated that workshops provide an excellent venue for shifting the focus to a systems approach and aligning partnerships based on novel criteria. Members suggested that program staff might discover such associations by examining research projects in their portfolios and looking for natural associations. Panel members cited a recent example of such a conference, the *First International Conference on Hyperphagia*. This meeting, sponsored by the Prader-Willi Association, brought together researchers with expertise in PWS, Bardet-Biedl syndrome, WAGR syndrome, Alström syndrome, and FXS, in addition to representatives from the pharmaceutical industry and relevant advocacy groups to discuss shared and unique characteristics of overeating in these disease populations. In another example, the Branch recently supported a conference on disorders involving the Ras/MAPK pathway, bringing together researchers who work on Costello syndrome, Noonan syndrome, cardiofaciocutaneous syndrome, and Neurofibromatosis 1, as well as advocacy groups for the different disorders. Such workshops could also include biotech and pharmaceutical companies developing treatments that target specific molecules involved in the relevant pathway to alleviate symptoms of one or more of these disorders.

Overall, the panel expressed enthusiasm for continued commitment to basic, clinical, and translational research in the IDD field, with an additional emphasis on systems biology and a pathway disorders approach to expand the array of interventions and targeted therapies for individuals with IDD.

In light of this discussion, the Branch might consider the following activities:

- Examine the benefits and limitations, specifically in terms of staffing expertise and cost effectiveness, of reconstructing the Branch portfolio horizontally into content areas, rather than vertically into disease areas.
- Explore ways to integrate the Branch's research portfolio to increase the emphasis on a pathway or systems approach, rather than on specific diseases/conditions.
- Use thematic workshops, rather than disease-specific workshops, as venues for new and exciting research findings and as a way to align people into partnerships and collaborations.

REFERENCES

American Association on Intellectual and Developmental Disabilities. Obtained from the Web site http://www.aamr.org/content_100.cfm?navID=21 on August 11, 2009.

American College of Medical Genetics Newborn Screening Expert Group. (2006). Newborn screening: Toward a Uniform Screening Panel and system. *Genetics in Medicine, 8*(5), 1S-252S.

Bebbington A, Anderson A, Ravine D, Fyfe S, Pineda M, de Klerk N, Ben-Zeev B, Yatawara N, Percy A, Kaufmann WE, & Leonard H. (2008). Investigating genotype-phenotype relationships in Rett syndrome using an international data set. *Neurology, Mar11;70*(111), 868-875.

Bear MF, Huber KM, & Warren ST. (2004). The mGluR theory of fragile X mental retardation. *Trends Neurosci, Jul;27*(7), 370-377.

Boyle CA & Cordero JF. (2005). Birth defects and disabilities: A public health issue for the 21st century. *Am J Public Health, 95*(11), 1884-1886.

Centers for Disease Control and Prevention, DHHS. (2009). Prevalence of autism spectrum disorders—Autism and developmental disabilities monitoring network. *MMWR, Surveillance Summaries, Dec 18;58*(No. SS-10), 1-20.

Chahrour M, Jung SY, Shaw C, Zhou X, Wong ST, Qin J, & Zoghbi HY. (2008). *MECP2*, a key contributor to neurological disease, activates, and represses transcription. *Science, May30; 320*(5880), 1224-1229.

Chamberlain SJ, Johnstone KA, DuBose AJ, Simon TA, Bartolomei MS, Resnick JS, & Brannan CI. (2004). Evidence for genetic modifiers of postnatal lethality in PWS-IC deletion mice. *Hum Mol Genet, Dec1;13*(23), 2971-2977.

Coskun V, Wu H, Blanchi B, Tsao S, Kim K, Zhao J, Biancotti JC, Hutnick L, Krueger RC Jr., Fan G, de Vellis J, & Sun YE. (2008). CD133+ neural stem cells in the ependyma of mammalian postnatal forebrain. *Proc Natl Acad Sci, Jan22;105*(3), 1026-1031.

Dawson G, Munson J, Webb SJ, Nalty T, Abbott R, & Toth K. (2007). Rate of head growth decelerates and symptoms worsen in the second year of life in autism. *Biol Psychiatry, Feb;61*, 458-464.

Deardorff MA, Kaur M, Yaeger D, Rampuria A, Korolev S, Pie J, Gil-Rodríguez C, Arnedo M, Loeys B, Kline AD, Wilson M, Lillquist K, Siu V, Ramos FJ, Musio A, Jackson LS, Dorsett D, & Krantz ID. (2007). Mutations in cohesin complex members *SMC3* and *SMC1A* cause a mild variant of Cornelia de Lange Syndrome with predominant mental retardation. *Am J Hum Genet, Mar;80*(3), 485-494.

Dindot SV, Antalffy BA, Bhattacharjee MB, & Beaudet AL. (2008). The Angelman syndrome ubiquitin ligase localizes to the synapse and nucleus, and maternal deficiency results in abnormal dendritic spine morphology. *Hum Mol Genet, Jan1;17*(1), 111-118.

Dykens EM, Maxwell MA, Pantino E, Kossler R, & Roof E. (2007). Assessment of hyperphagia in Prader-Willi syndrome. *Obesity (Silver Spring), Jul;15*(7), 1816-1826.

Dziuk MA, Gidley Larson JC, Apostu A, Mahone EM, Denckla MB, & Mostofsky SH. (2007). Dyspraxia in autism: Association with motor, social, and communicative deficits. *Dev Med Child Neurol, Oct;49*(10), 734-739.

Ebert AD, Yu J, Rose FF Jr., Mattis VB, Lorson CL, Thomson JA, & Svendsen CN. (2009). Induced pluripotent stem cells from a spinal muscular atrophy patient. *Nature, Jan15;457*(7227), 277-280.

Elder LM, Dawson G, Toth K, Fein D, & Munson J. (2008). Head circumference as an early predictor of autism symptoms in younger siblings of children with autism spectrum disorder. *J Autism Dev Disord, Jul;38*(6), 1104-1111.

Glessner JT, Wang K, Cai G, Korvatska O, Kim CE, Wood S, Zhang H, Estes A, Brune CW, Bradfield JP, Imielinski M, Frackelton EC, Reichert J, Crawford EL, Munson J, Sleiman PM, Chiavacci R, Annaiah K, Thomas K, Hou C, Glaberson W, Flory J, Otieno F, Garris M, Soorya L, Klei L, Piven J, Meyer KJ, Anagnostou E, Sakurai T, Game RM, Rudd DS, Zurawiecki D, McDougle CJ, Davis LK, Miller J, Posey DJ, Michaels S, Kolevzon A, Silverman JM, Bernier R, Levy SE, Schultz RT, Dawson G, Owley T, McMahon WM, Wassink TH, Sweeney JA, Nurnberger JI, Coon H, Sutcliffe JS, Minshew NJ, Grant SF, Bucan M, Cook EH, Buxbaum JD, Devlin B, Schellenberg GD, & Hakonarson H. (2009). Autism genome-wide copy number variation reveals ubiquitin and neuronal genes. *Nature, May28;459*(7246), 569-573.

Gulsrud AC, Kasari C, Freeman S, & Paparella T. (2007). Children with autism's response to novel stimuli while participating in interventions targeting joint attention or symbolic play skills. *Autism, Nov;11*(6), 535-546.

Guralnick MJ. (2005). Early intervention for children with intellectual disabilities: Current knowledge and future prospects. *Journal of Applied Research in Developmental Disabilities, 18*, 313-324.

Jones W, Carr K, & Klin A. (2008). Absence of preferential looking to the eyes of approaching adults predicts level of social disability in two-year-olds with autism. *Arch Gen Psychiatry, 65*(8), 946-954.

Kasari C, Paparella T, Freeman S, & Jahromi LB. (2008). Language outcome in autism: Randomized comparison of joint attention and play interventions. *Journal of Consulting and Clinical Psychology, Feb;76*(1), 125-137.

Klin A, Lin DJ, Gorrindo P, Ramsay G, & Jones W. (2009). Two-year-olds with autism orient to non-social contingencies rather than biological motion. *Nature, May14;459*(7244), 257-261.

Krotoski D, Namaste S, Raouf, RK, El Nekhely I, Hindi-Alexander M, Engelson G, Hanson JW, & Howell RR on behalf of the Middle East and North Africa Newborn Screening and Steering Committee. (2009). Conference report: Second conference of the Middle East and North Africa newborn screening initiative: Partnerships for sustainable newborn screening infrastructure and research opportunities. *Genet Med, Sep;11*(9), 663-668.

Landa RJ, Holman KC, & Garrett-Mayer E. (2007). Social and communication development in toddlers with early and later diagnosis of autism spectrum disorders. *Arch Gen Psychiatry, Jul;64*(7), 853-864.

LeBlanc SE, Ward RM, & Svaren J. (2007). Neuropathy-associated *Egr2* mutants disrupt cooperative activation of myelin protein zero by *Egr2* and *Sox10*. *Mol Cell Biol, May;27*(9), 3521-3529.

Maezawa I, Swanberg S, Harvey D, LaSalle JM, & Jin LW. (2009). Rett syndrome astrocytes are abnormal and spread MeCP2 deficiency through gap junctions. *J Neurosci, Apr22;29*(16), 5051-5061.

Mervis CB & John AE. (2008). Vocabulary abilities of children with Williams syndrome: Strengths, weaknesses, and relation to visuospatial construction ability. *J Speech Lang Hear Res, Aug;51*(4), 967-982.

Mosconi MW, Cody-Hazlett H, Poe MD, Gerig G, Gimpel-Smith R, & Piven J. (2009). Longitudinal study of amygdala volume and joint attention in two- to four-year-old children with autism. *Archives of General Psychiatry, 66*(5), 509-516.

Mostofsky SH, Burgess MP, & Gidley Larson JC. (2007). Increased motor cortex white matter volume predicts motor impairment in autism. *Brain, Aug;130*(Pt 8), 2117-2122.

Nagarajan RP, Hogart AR, Gwye Y, Martin MR, & LaSalle JM. (2006). Reduced MeCP2 expression is frequent in autism frontal cortex and correlates with aberrant *MECP2* promoter methylation. *Epigenetics, Oct-Dec;1*(4), e1-e11.

Pandey J, Verbalis A, Robins DL, Boorstein H, Klin AM, Babitz T, Chawarska K, Volkmar F, Green J, Barton M, & Fein D. (2008). Screening for autism in older and younger toddlers with the Modified Checklist for Autism in Toddlers. *Autism, Sep;12*(5), 513-535.

Schalock RL, Luckasson RA, Shogren KA, Borthwick-Duffy S, Bradley V, Buntinx WH, Coulter DL, Craig EM, Gomez SC, Lachapelle Y, Reeve A, Snell ME, Spreat S, Tassé MJ, Thompson JR, Verdugo MA, Wehmeyer ML, & Yeager MH. (2007). Perspectives: The renaming of mental retardation: Understanding the change to the term intellectual disability. *Intellectual and Developmental Disabilities, 45*(2), 116-124.

Sutera S, Pandey J, Esser EL, Rosenthal MA, Wilson LB, Barton M, Green J, Hodgson S, Robins DL, Dumont-Mathieu T, & Fein D. (2007). Predictors of optimal outcome in toddlers diagnosed with autism spectrum disorders. *J Autism Dev Disord, Jan;37*(1), 98-107.

Swanberg SE, Nagarajan RP, Peddada S, Yasui DH, & LaSalle JM. (2009). Reciprocal co-regulation of EGR2 and MECP2 is disrupted in Rett syndrome and autism. *Hum Mol Genet, Feb1;18*(3), 525-534.

Tassone F, Pan R, Amiri K, Taylor AK, & Hagerman PJ. (2008). A rapid polymerase chain reaction-based screening method for identification of all expanded alleles of the Fragile X (*FMR1*) gene in newborn and high-risk populations. *J Mol Diagn, Jan;10*(1), 43-49.

Tsai JW, Bremner KH, & Vallee RB. (2007). Dual subcellular roles for LIS and dynein in radial neuronal migration in live brain tissue. *Nature Neuroscience, Aug;10*(8), 970-979.

Velinov M, Novelli A, Gu H, Fenko M, Dolzhanskaya N, Bernardini L, Capalbo A, Dallapiccola B, Jenkins EC, & Brown WT. (2009). *De novo* 2.15 Mb terminal Xq duplication involving *MECP2* but not *L1CAM* gene in a male patient with mental retardation. *Clin Dysmorphol, Jan;18*(1), 9-12.

Wang AT, Lee SS, Sigman M, & Dapretto M. (2007). Reading affect in the face and voice: Neural correlates of interpreting communicative intent in children and adolescents with autism spectrum disorders. *Archives of General Psychiatry, Jun;64*(6), 698-708.

Wang K, Zhang H, Ma D, Bucan M, Glessner JT, Abrahams BS, Salyakina D, Imielinski M, Bradfield JP, Sleiman PM, Kim CE, Hou C, Frackelton E, Chiavacci R, Takahashi N, Sakurai T, Rappaport E, Lajonchere CM, Munson J, Estes A, Korvatska O, Piven J, Sonnenblick LI, Alvarez Retuerto AI, Herman EI, Dong H, Hutman T, Sigman M, Ozonoff S, Klin A, Owley T, Sweeney JA, Brune CW, Cantor RM, Bernier R, Gilbert JR, Cuccaro ML, McMahon WM, Miller J, State MW, Wassink TH, Coon H, Levy SE, Schultz RT, Nurnberger JI, Haines JL, Sutcliffe JS, Cook EH, Minshew NJ, Buxbaum JD, Dawson G, Grant SF, Geschwind DH, Pericak-Vance MA, Schellenberg GD, & Hakonarson H. (2009). Common genetic variants on 5p14.1 associate with autism spectrum disorders. *Nature, May28;459*(7246), 528-533.

Yeargin-Allsopp M, Drews-Botsch C, & Van Naarden Braun K. (2007). "Epidemiology of developmental disabilities." In ML Batshaw, L Pelligrino, & NJ Roizen (Eds.), *Children with Disabilities* (6th edition). Brookes Publishing Co.: Baltimore, MD.

Yokota T, Lu QL, Partridge T, Kobayashi M, Nakamura A, Takeda S, & Hoffman E. (2009). Efficacy of systemic morpholino exon-skipping in Duchenne dystrophy dogs. *Ann Neurol, Mar13;65*(6), 667-676.

Zhang J, Hou L, Klann E, & Nelson DL. (2009). Altered hippocampal synaptic plasticity in the *Fmr1* gene family knockout mouse models. *J Neurophysiol, May;101*(5), 2572-2580.

Zwaigenbaum L, Bryson S, Lord C, Rogers S, Carter A, Carver L, Chawarska K, Constantino J, Dawson G, Dobkins K, Fein D, Iverson J, Klin A, Landa R, Messinger D, Ozonoff S, Sigman M, Stone W, Tager-Flusberg H, & Yirmiya N. (2009). Clinical assessment and management of toddlers with suspected autism spectrum disorder: Insights from studies of high-risk infants. *Pediatrics, May;123*(5), 1383-1391.

FIGURES AND TABLES

Please Note: The numbers and amounts presented in these figures and tables represent unofficial figures prepared by the NICHD Referral and Program Analysis Branch. Some of the amounts may differ from those reported by the NIH Research, Condition, Disease, and Categorization Process, which provides the only official amounts for the NIH. Please visit http://report.nih.gov/rcdc to view official numbers and amounts for specific disease categories. All figures shown are in U.S. dollars unless otherwise indicated.

FIGURE 1: BRANCH FUNDS IN CURRENT AND CONSTANT DOLLARS, FISCAL YEAR 2005 THROUGH FISCAL YEAR 2008

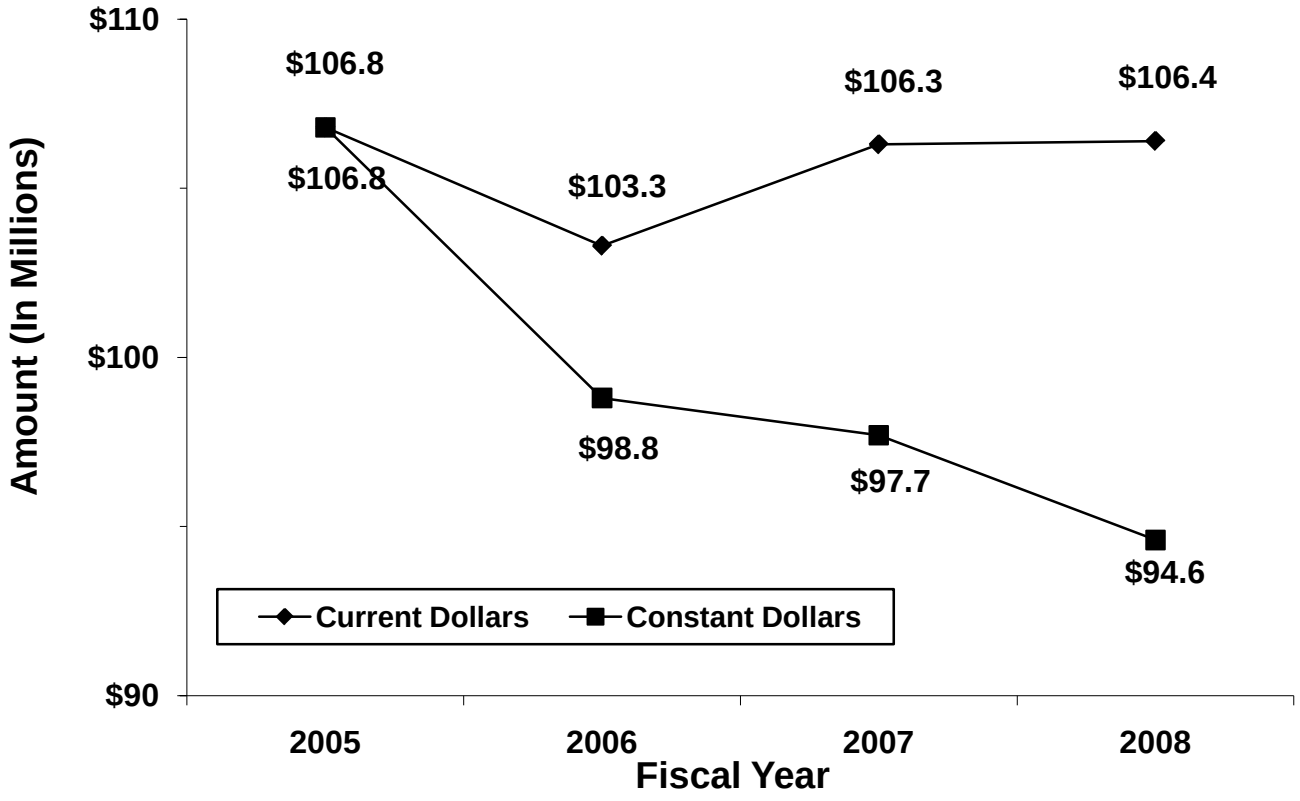
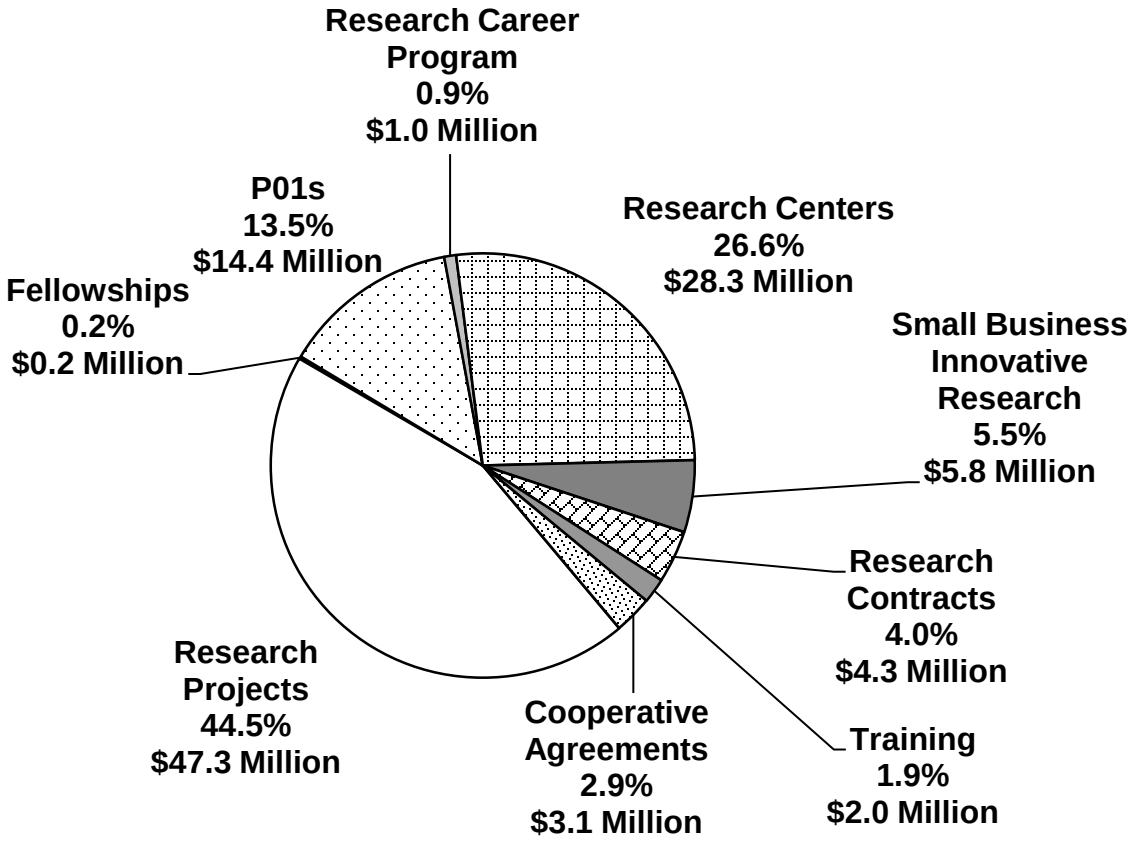


FIGURE 2: BRANCH FUNDS BY SUPPORT MECHANISM, FISCAL YEAR 2008



Total: $106.4 Million

FIGURE 3: BRANCH FUNDING BY RESEARCH AREA, FISCAL YEAR 2005 THROUGH FISCAL YEAR 2008

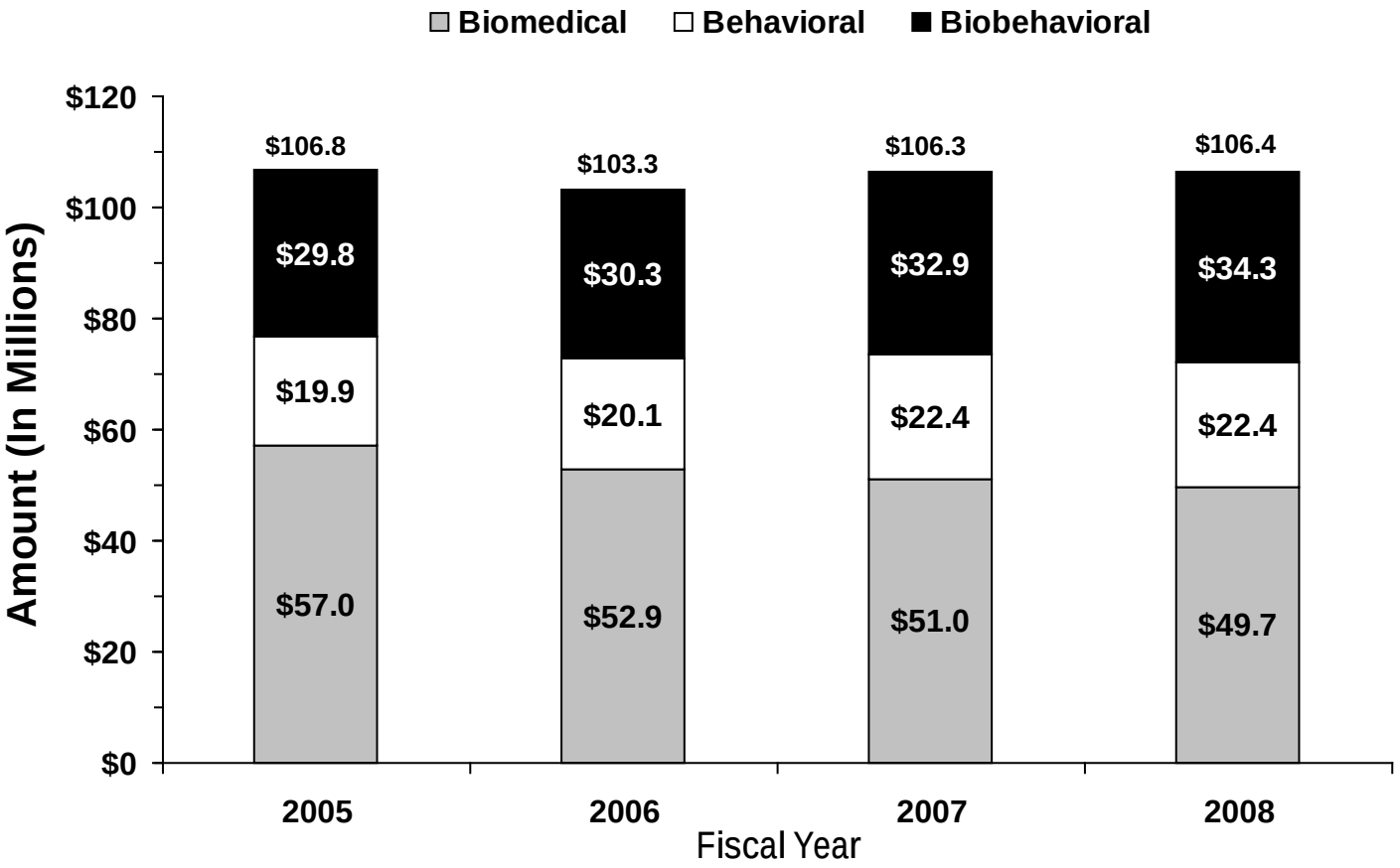


FIGURE 4: BRANCH FUNDING FOR PROJECTS INVOLVING HUMANS BY RESEARCH AREA, FISCAL YEAR 2005 THROUGH FISCAL YEAR 2008

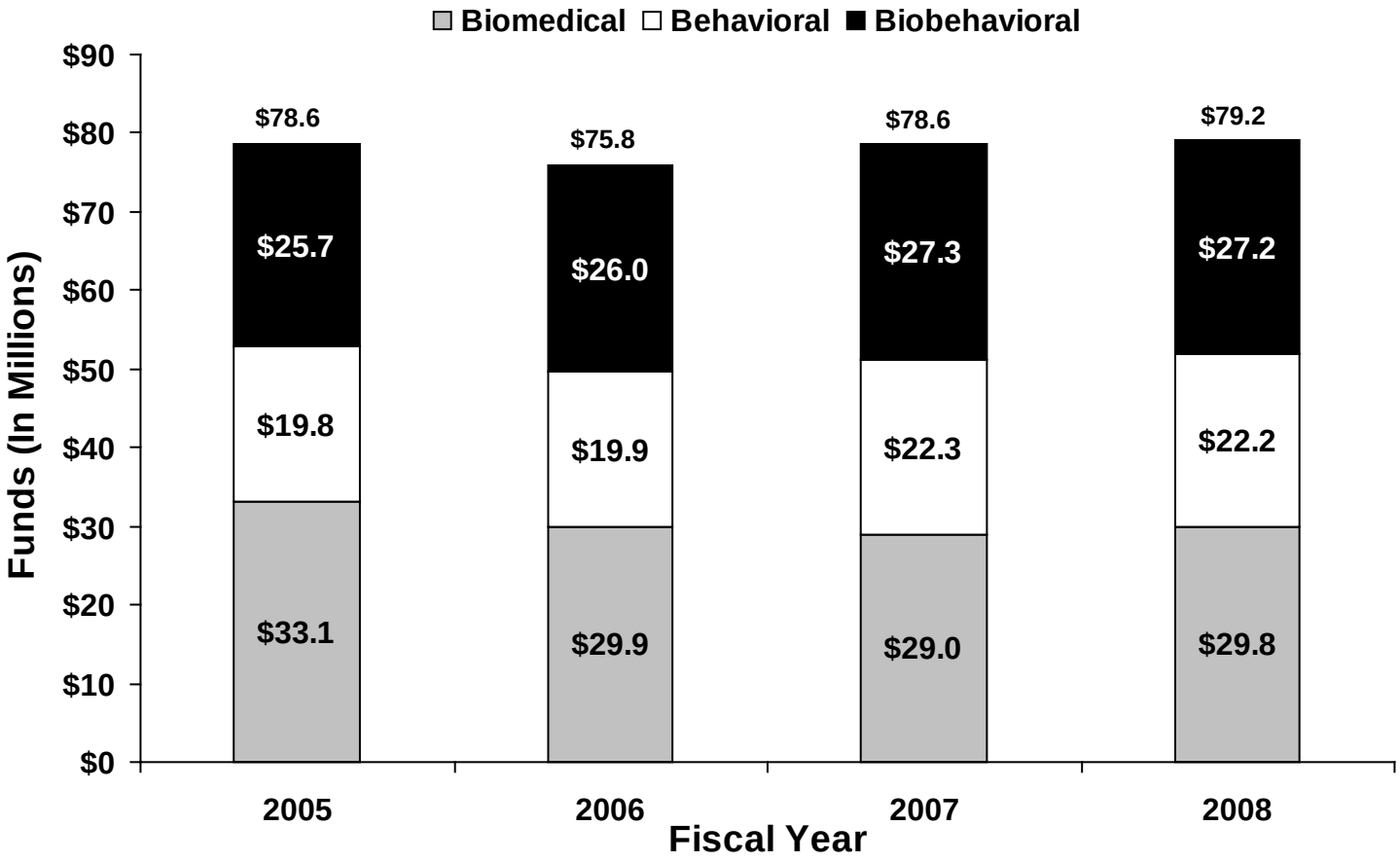


FIGURE 5: BRANCH FUNDING FOR PROJECTS INVOLVING ANIMALS BY RESEARCH AREA, FISCAL YEAR 2005 THROUGH FISCAL YEAR 2008

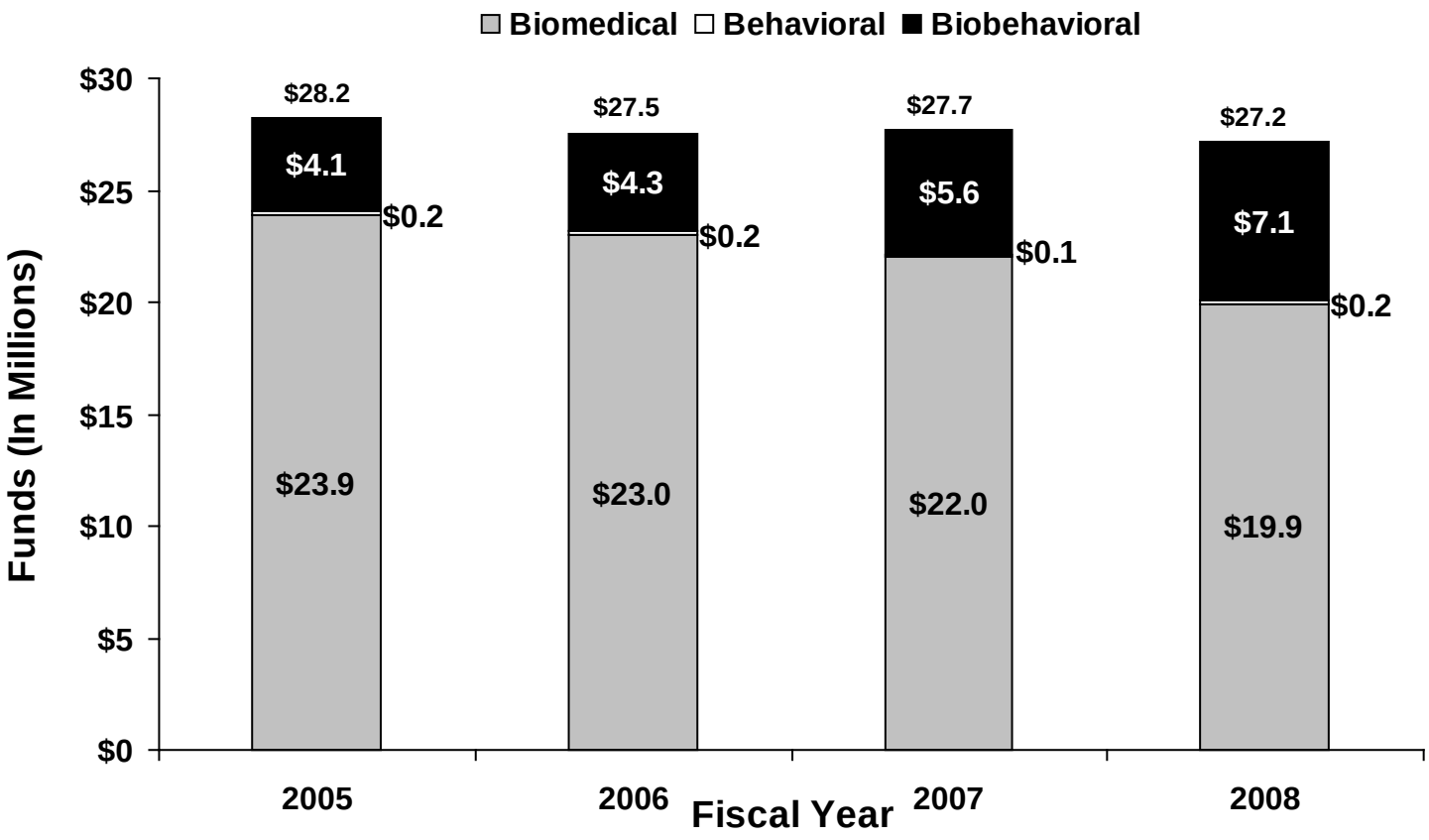


FIGURE 6: BRANCH FUNDING FOR SELECTED DISORDERS, FISCAL YEAR 2005 THROUGH FISCAL YEAR 2008

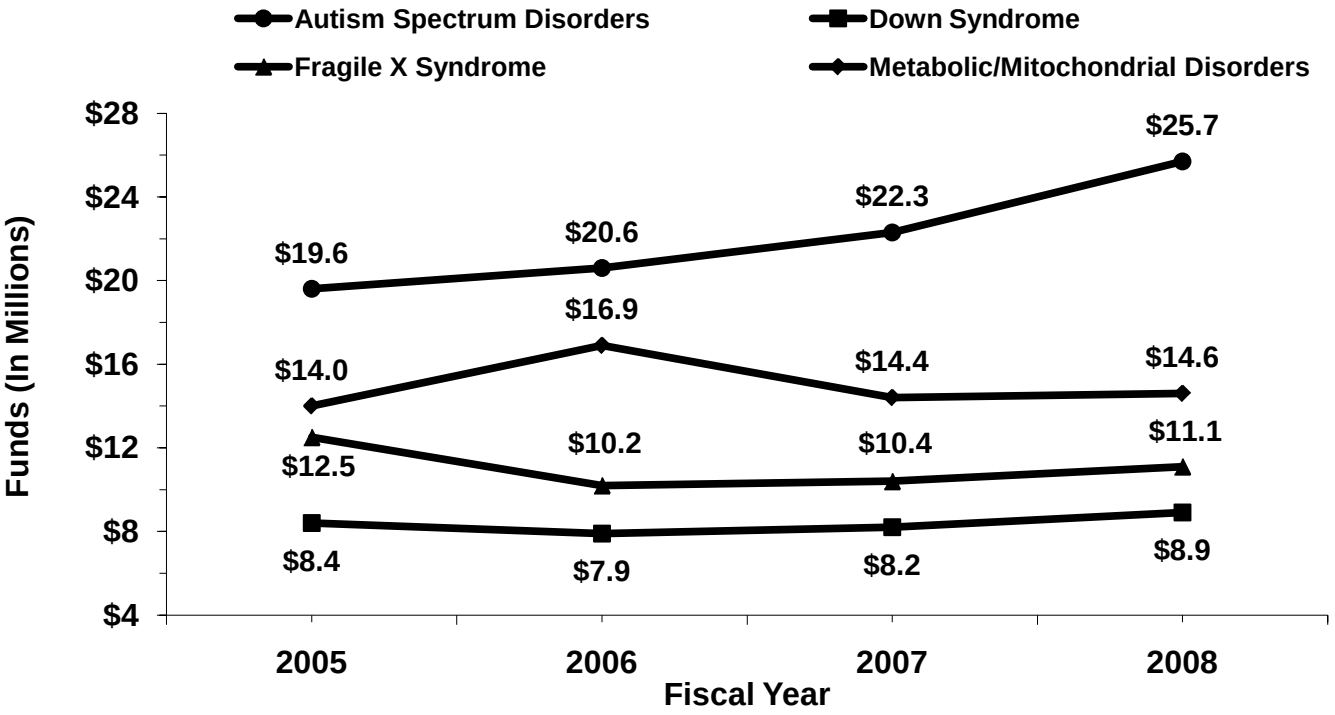


FIGURE 7: BRANCH FUNDING FOR SELECTED DISORDERS OR TOPICS, FISCAL YEAR 2005 THROUGH FISCAL YEAR 2008

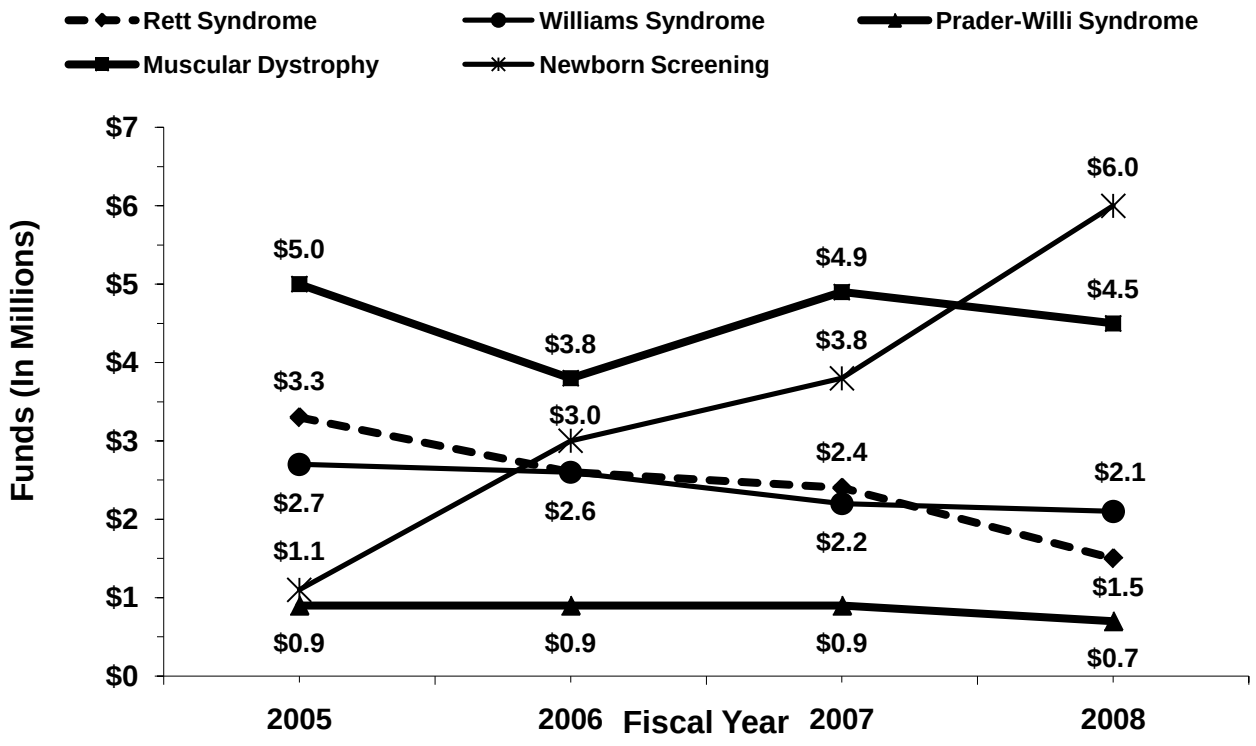


FIGURE 8: EUNICE KENNEDY SHRIVER INTELLECTUAL AND DEVELOPMENTAL DISABILITY RESEARCH CENTERS (IDDRCS), FISCAL YEAR 2008

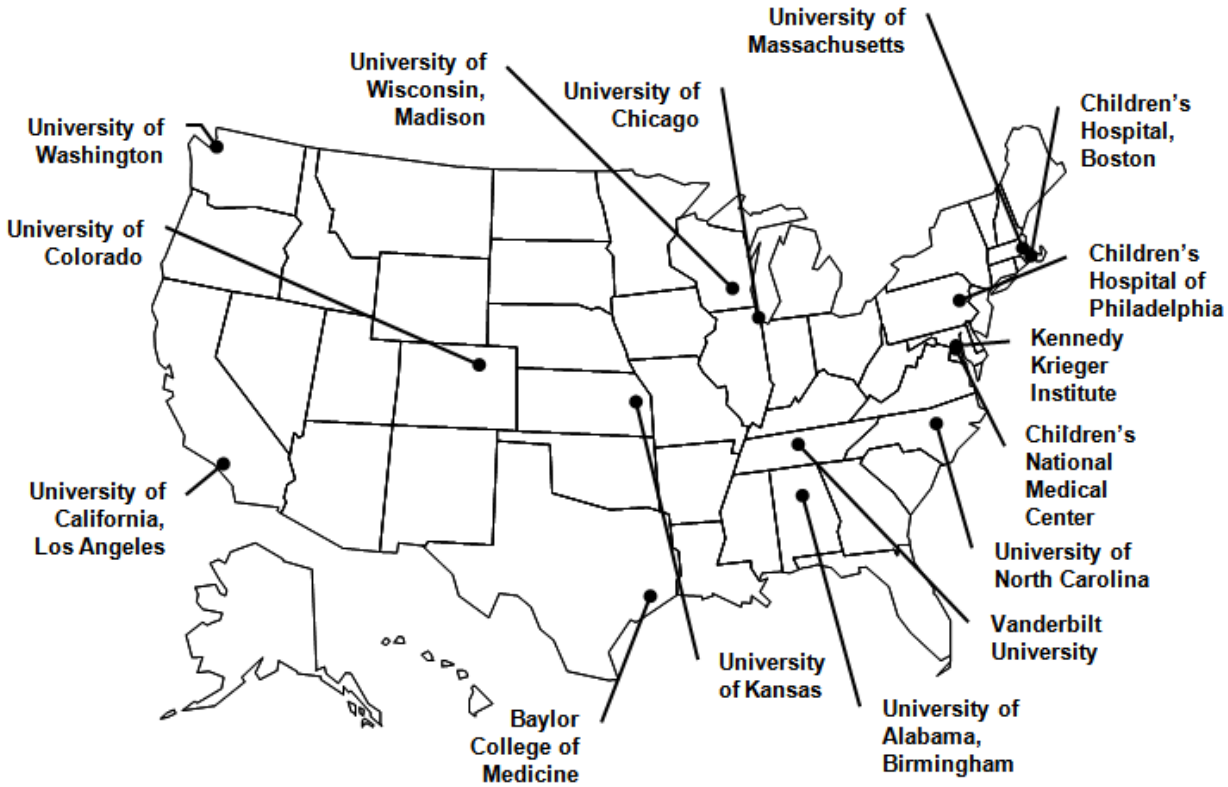


FIGURE 9: NUMBER OF PROJECTS SUPPORTED BY IDDRC CORES, CATEGORIZED BY PRIMARY SOURCE OF FUNDING, FISCAL YEAR 2005 AND FISCAL YEAR 2008

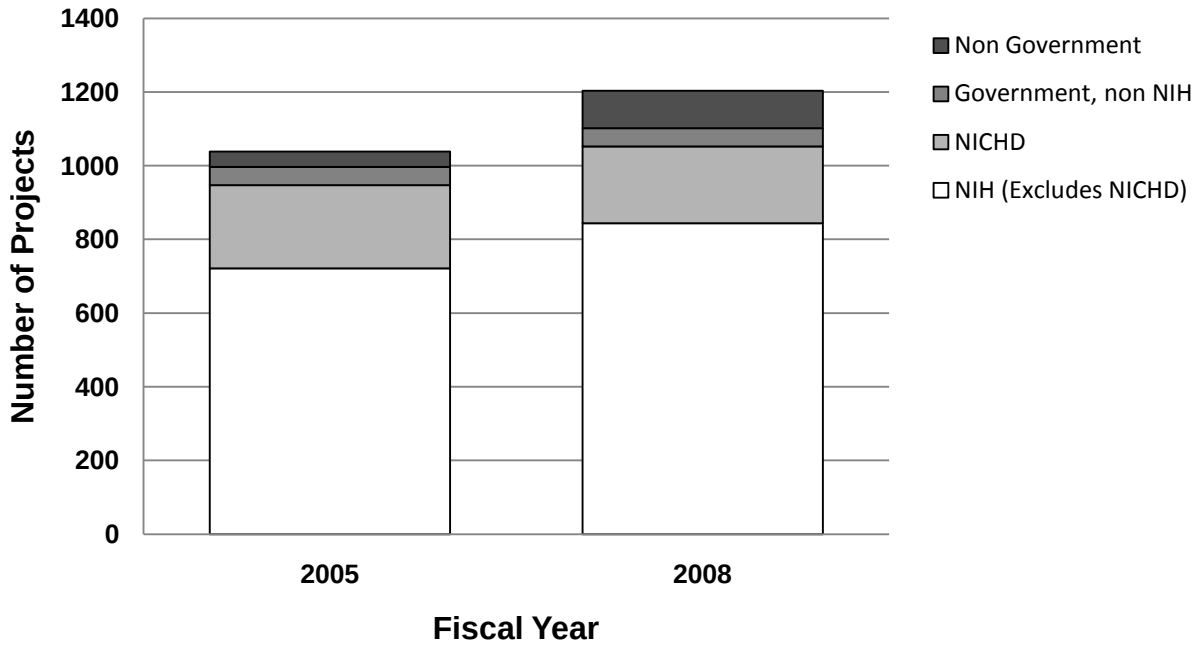


FIGURE 10: FRAGILE X SYNDROME RESEARCH CENTERS (FXSRCS), FISCAL YEAR 2008

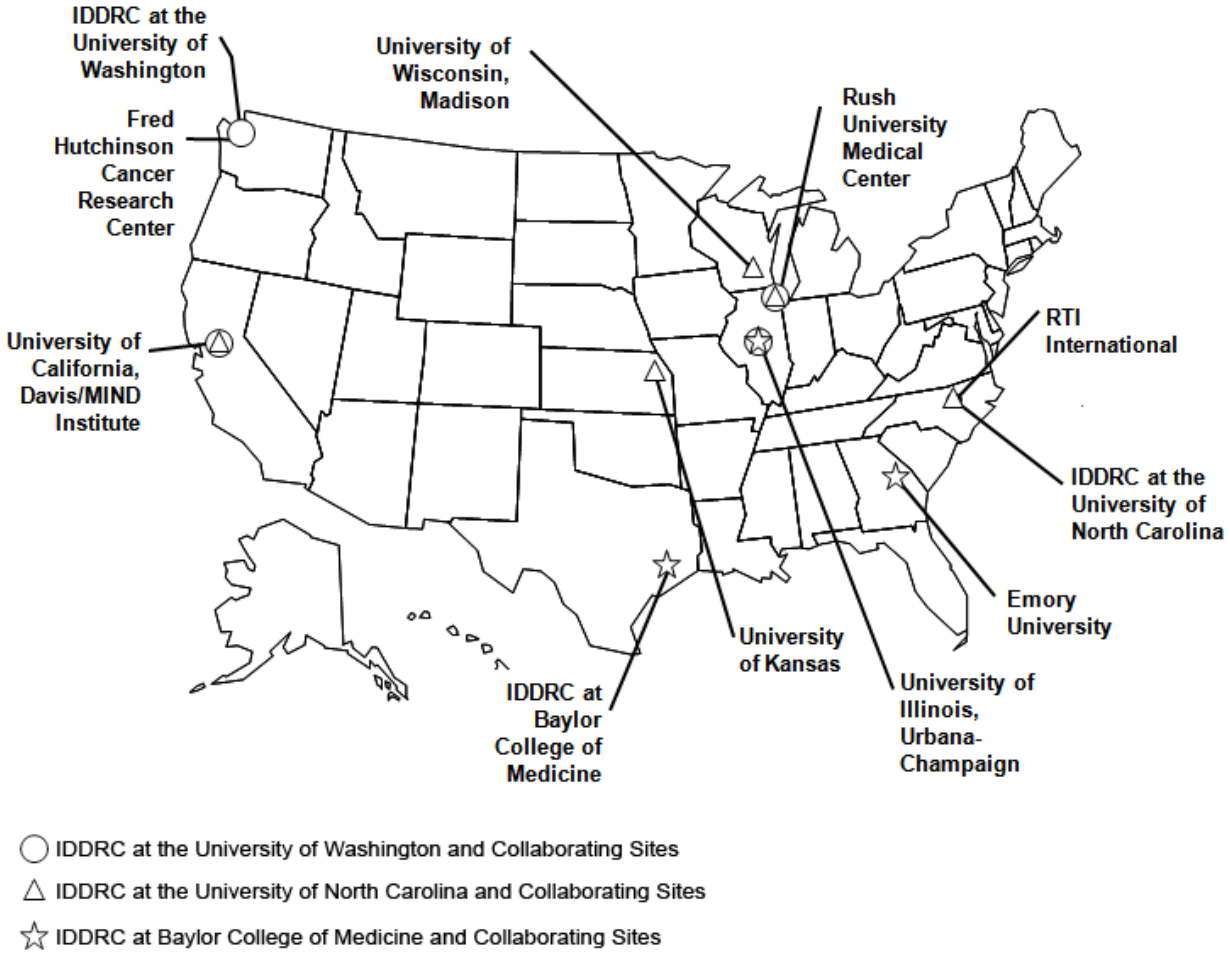
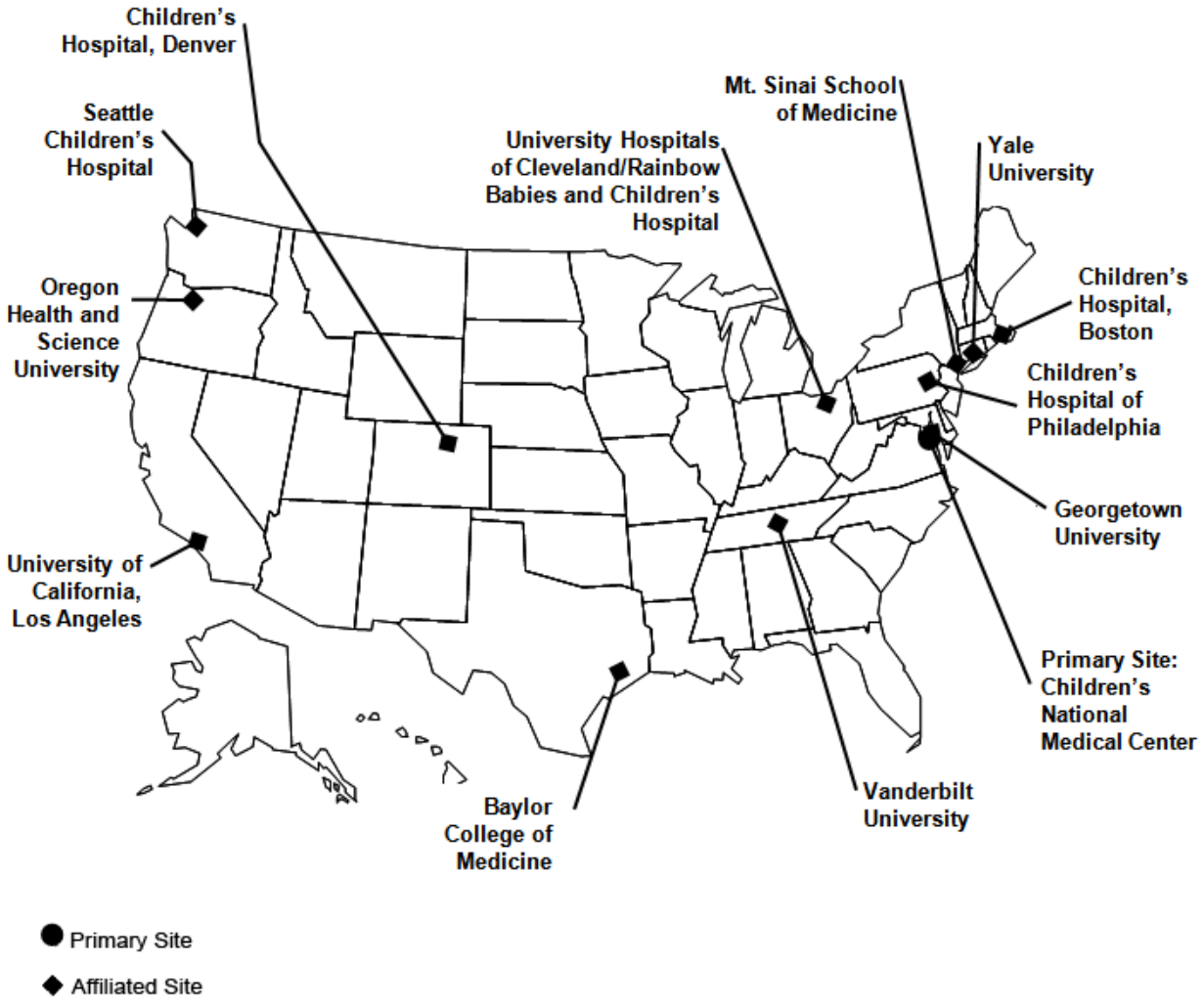


FIGURE 11: RARE DISEASES COOPERATIVE RESEARCH CONSORTIA (RDCRC): UREA CYCLE RARE DISEASE CONSORTIUM, FISCAL YEAR 2008



Affiliated International Sites (not shown): The Hospital for Sick Children (Toronto, Canada), and University Children's Hospital (Zurich, Switzerland)

FIGURE 12: RARE DISEASES COOPERATIVE RESEARCH CONSORTIA (RDCRC): CONSORTIUM FOR RARE EPIGENETIC DISORDERS, FISCAL YEAR 2008

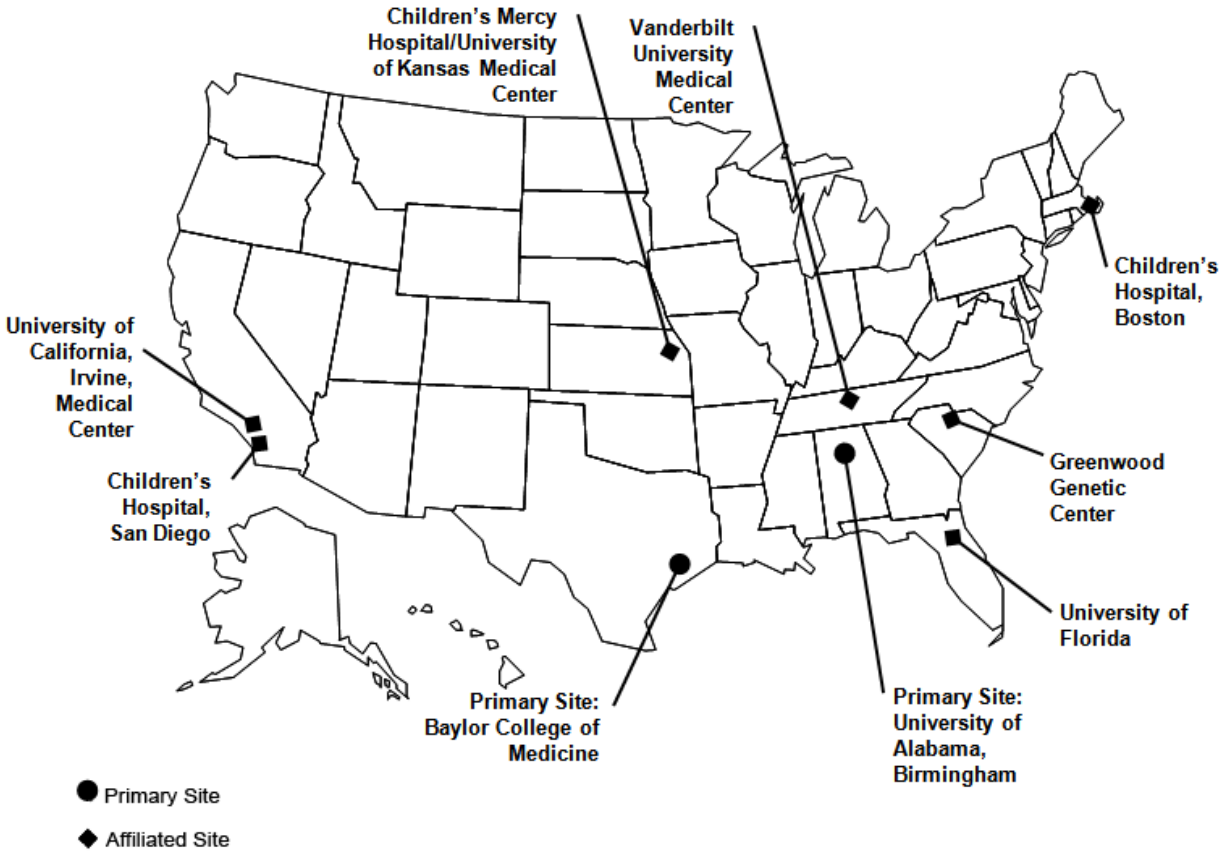
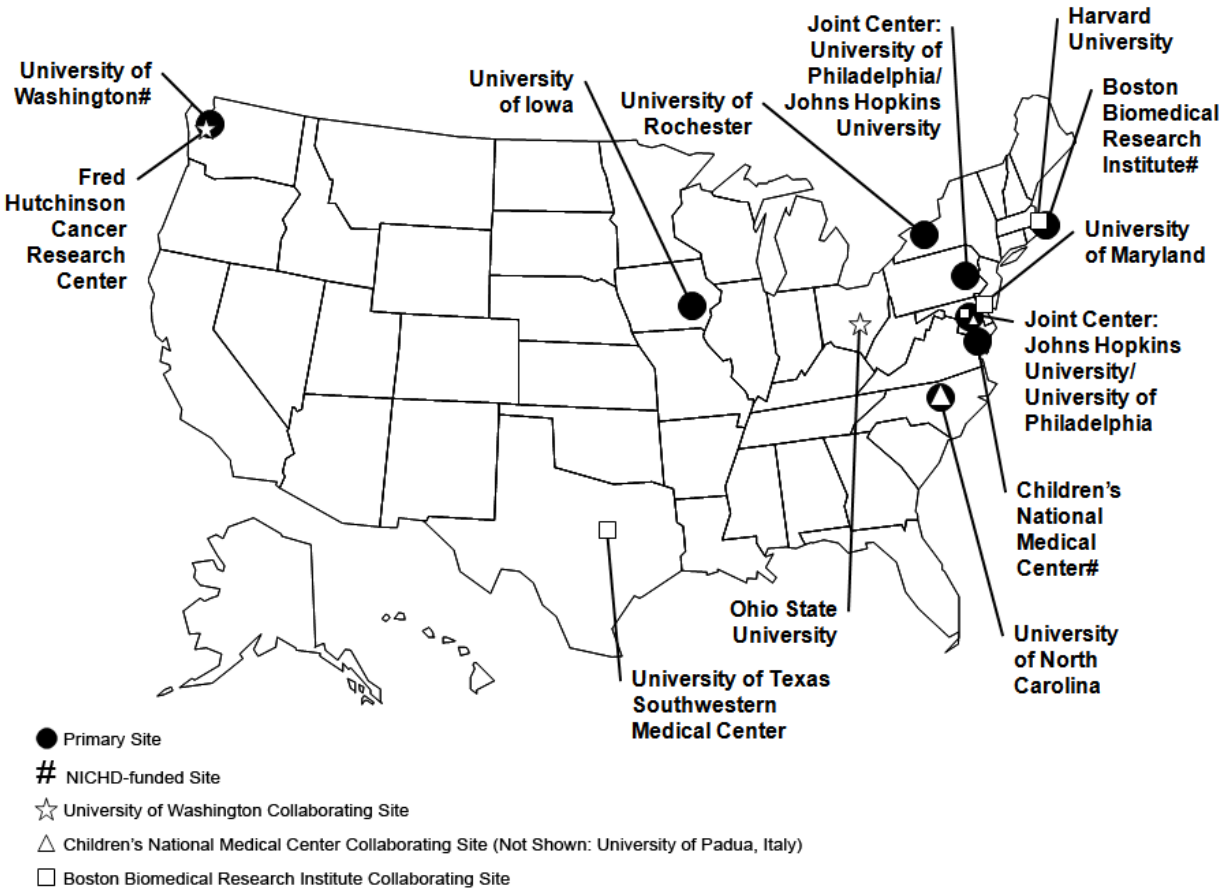
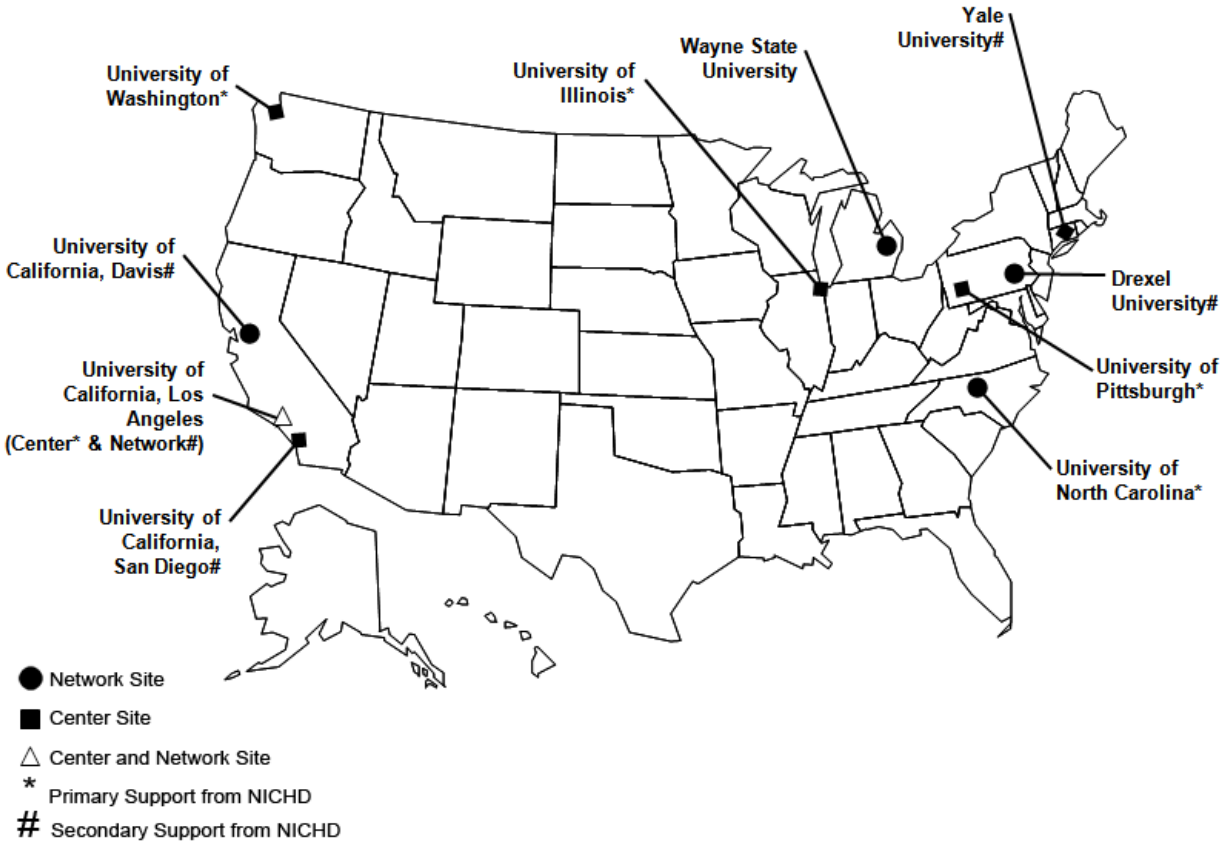


FIGURE 13: SENATOR PAUL D. WELLSTONE MUSCULAR DYSTROPHY COOPERATIVE RESEARCH CENTERS, FISCAL YEAR 2008



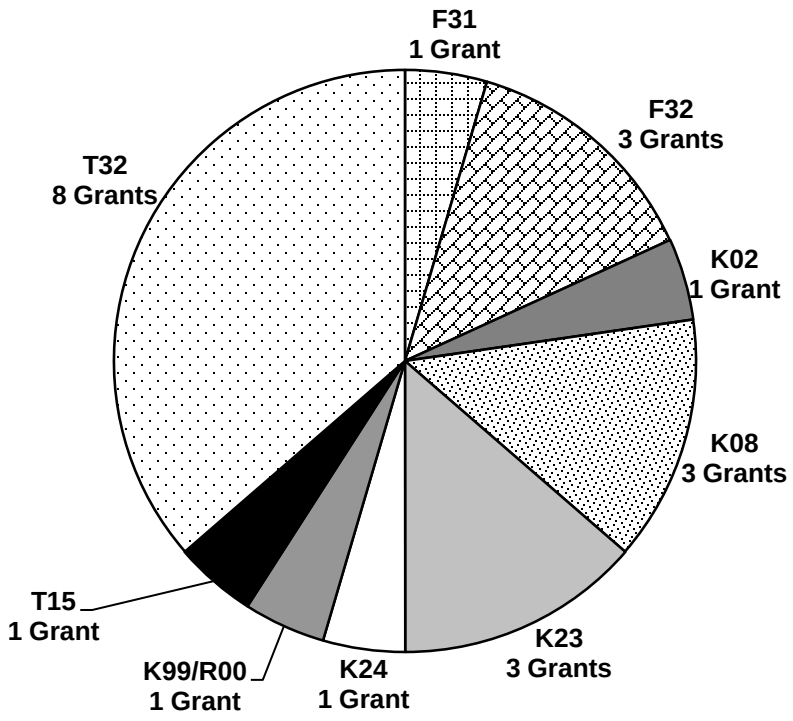
Note: Johns Hopkins University is a joint primary site with University of Pennsylvania and is a collaborating site with both the Children's National Medical Center and the Boston Biomedical Research Institute.

FIGURE 14: AUTISM CENTERS OF EXCELLENCE (ACE) NETWORKS AND CENTERS, FISCAL YEAR 2008



For a description of Center and Network projects, please see Table 3 in this document.

FIGURE 15: IDD BRANCH TRAINING AND CAREER DEVELOPMENT PORTFOLIO BY MECHANISM, FISCAL YEAR 2008



Total = $3.2 Million, 22 Grants

TABLE 1: BRANCH PORTFOLIO BY SUPPORT MECHANISM, FISCAL YEAR 2008

Support Mechanism	Number of Projects	Funds (U.S. $)
Research Projects (R01, R03, R13, R15, R21, R37)	154	47,304,785
Research Program Projects (P01)	13	14,372,226
Research Centers (P30, P50)	21	28,253,411
Small Business Innovative Research (R42, R43, R44)	16	5,832,415
Research Career Program (K02, K08, K23, K24, K99)	9	1,043,359
National Research Service Awards (F31, F32)	4	157,308
Research Contracts (N01)	6	4,323,233
Training Programs (T15, T32)	9	1,968,589
Cooperative Agreements (U01, U13, U54)	4	3,125,275
Totals	**236**	**106,380,601**

TABLE 2: SELECTED RESEARCH OBJECTIVES FROM THE NIH RESEARCH PLAN ON DOWN SYNDROME

Research Area	Short-term Objective (0 to 3 Years)	Medium-term Objective (4 to 6 Years)	Long-term Objective (7 to 10 Years)
Pathophysiology of Down Syndrome and Disease Progression	Continue testing cognitive and synaptic function In Down syndrome model mice.	Study whether the impact of aging on certain processes is greater than on others.	Explore genetic and environmental determinants of cognitive function in Down syndrome throughout the lifespan.
Diagnosis, Screening, and Functional Measures	Identify the cognitive phenotype of Down syndrome in a cohort throughout the lifespan.	Link human and mouse cognitive studies relating to Down syndrome.	Develop better measures of hippocampal and cognitive function.
Treatment and Management	Increase research on comorbid psychiatric and medical conditions throughout the lifespan.	Continue learning from the Alzheimer disease research community regarding the best therapeutics.	Investigate the impact of early intervention on psychomotor and cognitive development.
Living with Down Syndrome	Develop a more complete demographic knowledge base.	Study real-world outcomes for Down syndrome families.	Explore new intervention research, especially during transitional stages.
Research Infrastructure	Improve and expand availability of animal models.	Discuss the best mechanisms to use in fostering cross-disciplinary research.	Include cohorts of people with Down syndrome in longitudinal studies.

Please visit http://www.nichd.nih.gov/publications/pubs_details.cfm?from=&pubs_id=5695 for the full Research Plan.

TABLE 3: NIH ACE PROGRAM RESEARCH PROJECTS
(* Indicates primary support from NICHD)

ACE Center Projects

Site	Project(s) Description
University of California, San Diego	Principal Investigator (PI): Eric Courchesne—Researchers at this ACE Center use brain imaging to track brain development in children believed to be at risk for ASDs. Unlike other ACE projects, which attempt to identify forerunners of ASD in the siblings of children with ASDs, these researchers study infants who were referred by their physicians on the basis of behaviors similar to those of older children with ASDs. The primary goal of this research is to identify brain or other physical differences that might predispose a child to ASDs. The Center is collecting some of the first information ever obtained on how the brains of very young children with ASDs process and respond to information.
University of California, Los Angeles*	PI: Susan Bookheimer—Researchers at this ACE Center seek to understand how ASDs affect the ability to communicate. The researchers are looking for clues to language-related communication problems by examining genes, behavior, and brain structure and function. The researchers are also interested in disorders that affect and ways to stimulate mirror neurons, brain cells that become active either when a person performs an action or watches the action performed by someone else. When many ASD patients are asked to imitate behaviors, neuroimages of their brains show less-active mirror neurons compared to those who don't have ASDs.
University of Illinois*	PI: Edwin H. Cook—This ACE Center focuses on understanding repetitive behavior or "insistence on sameness," a hallmark of ASDs. Examples of this behavior include: wanting to wear the same clothes every day, taking the same route to work or school, or becoming fixated on a certain subject matter, such as buildings or cars. Center researchers focus on genetic factors, brain chemicals, and brain functions that could account for repetitive behaviors, and test whether genetic differences influence how individuals respond to certain medications intended to reduce the occurrence of these behaviors.
University of Pittsburgh*	PI: Nancy Minshew—This ACE Center studies how people with ASDs learn and understand information. Research shows that the ability to organize information into categories is critical to language development. These researchers use brain-imaging techniques to study how infants at risk for ASDs and toddlers diagnosed with ASDs categorize information. Researchers also use brain-imaging techniques to study which parts of the brain are activated in people with and without ASDs when processing information and emotions.
University of Washington*	PI: Bryan King—Researchers at this ACE Center seek to identify genes and other potential factors that may predispose an individual toward an ASD, as well as factors that might protect against ASDs. In addition to genes, the researchers study the risk of developing an ASD by examining communication difficulties, early behaviors, patterns in the sounds babies make, and brain structure and activity patterns. Researchers also aim to determine whether certain types of interactions between the parent and baby can decrease the chances for ASDs.
Yale University	PI: Ami Klin—These researchers study early social interactions and development and disruptions in these processes in children ages 12 months to 24 months with ASDs. The researchers also aim to identify rare genetic variants that may be involved in ASD in this same group of young children. The researchers are using brain-imaging tools to study the structure and functioning of connections in the brains of an additional group of 10-year-old children with ASDs who have been followed since age 24 months in previous research studies. These projects build upon existing research on the behavioral, brain, and molecular aspects of ASDs and may lead to new discoveries on causes and treatments.

ACE Network Projects

Site	Project(s) Description
Drexel University	PI: Craig Newschaffer—This Network, which includes Children's Hospital of Philadelphia, Johns Hopkins University, University of California, Davis, and Kaiser Permanente Division of Research, studies possible risk factors and biological indicators for ASDs that occur during the prenatal, neonatal, and early postnatal periods. Researchers are following 1,200 mothers of children with ASDs at the start of a new pregnancy and will document development of the newborn siblings through age 3 years. This study, Early Autism Risk Longitudinal Investigation (EARLI), will provide a unique opportunity to study possible ASD environmental risk factors and biomarkers during different developmental windows, and to investigate the interplay of genetic susceptibility and environmental exposure. EARLI could investigate environmental exposures ranging from suspected neurotoxins, such as persistent organic pollutants, to medications taken during pregnancy using data and samples collected. The study will also track the natural history and progression of ASDs.
University of California, Davis	PI: Sally Rogers—This Network, under the direction of the University of California, Davis, will compare intensive behavioral intervention to standard community-based treatment in 18-to 24-month-old children with ASDs to address the need for controlled studies of treatments for autism in very young children. This work builds on previous research suggesting that intensive early treatment provided better outcomes than standard community-based treatment. This research is examining factors that can inform efforts to provide the best treatment outcomes for very young children with ASDs.
University of California, Los Angeles	PI: Daniel Geschwind—Researchers in this Network will add to their earlier collaborative effort, which produced the Autism Genetic Resource Exchange (AGRE). The group will recruit 400 additional families with one child affected by an ASD to expand the existing data on the relationship between ASD-related genes and physical traits (phenotype). Of the additional families, 200 will be of African American descent to determine whether African Americans share the same genetic risk factors as those identified in the primarily white, European AGRE sample. The researchers also seek to identify rare genetic variants, mutations, and abnormalities that affect the risk for ASDs. Studying a large population lends greater reliability to the genetic findings, so that the results might be applicable to a wider range of children who have ASDs.
University of North Carolina, Chapel Hill*	PI: Joseph Piven—Researchers in this Network, operating under the direction of the University of North Carolina, will use brain-imaging techniques to compile images of the brains of very young infants to identify brain differences among those who have ASDs. Brain images of children who later develop ASDs will be compared to those from infants who did not develop ASDs. Although previous studies documented enlarged brains in many individuals with ASDs, little is known about the abnormal processes during early brain development in these children. Research findings could offer new insights for earlier diagnosis of ASDs.
Wayne State University	PI: Diane Chugani—Researchers in this Network are studying the effects of using buspirone (Buspar®) to promote more normal growth and development in the brains of children with ASDs. These children tend to have abnormal levels of the neurotransmitter serotonin during important periods of development. Buspirone stimulates serotonin production and, in a pilot study by these researchers, improved social interaction and reduced repetitive behaviors, sensory dysfunction, and anxiety in children with ASDs. Findings from these studies could provide an evidence base for new medication treatments for the symptoms of ASDs.

APPENDIX A: IDD BRANCH PERSONNEL

Gilian Engelson, M.P.H., joined the IDD Branch as a health scientist administrator in December 2004 to assist Dr. Rodney Howell[⊗] with development of the NICHD's Newborn Screening Initiative and to provide programmatic support for IDD Branch grants and contracts related to newborn screening. Ms. Engelson received her bachelor's degree in biology from the University of Michigan, Ann Arbor, and her master's degree in public health, with a focus on public health genetics, from Columbia University. At the Maternal and Child Health Bureau of the Health Resources and Services Administration (HRSA), she served as a program officer within the Genetic Services Branch, where she managed grants for the Sickle Cell Disease and Newborn Screening Programs, and for the Regional Genetics and Newborn Screening Collaboratives, while also providing administrative assistance to the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. Prior to her position at HRSA, Ms. Engelson worked at the American Cancer Society, Planned Parenthood, and the March of Dimes. Since October 2007, Ms. Engelson has worked part-time with the Branch to coordinate the Early Detection of Neuromuscular Diseases Conference and other newborn screening activities.

Alice Kau, Ph.D., joined the IDD Branch as a health scientist administrator in June 2003. Dr. Kau is responsible for activities in the Branch's Biobehavioral Research Program. She also serves as a key member of the autism spectrum disorders (ASDs) and behavioral science research communities on behalf of the Branch and assists in formulating and planning activities of these programs. Dr. Kau received her doctorate degree in developmental psychology from Ohio State University and completed a postdoctoral fellowship in clinical psychology in the Department of Pediatrics at the Johns Hopkins University School of Medicine. Prior to coming to the NICHD, Dr. Kau was an assistant professor/psychologist at the Kennedy Krieger Institute, Johns Hopkins University. Dr. Kau serves as the NICHD representative for the NIH Autism Coordinating Committee and serves as the NICHD liaison to the Interagency Autism Coordinating Committee. She is also the NIH representative on the Department of Defense Autism Funding Committee.

Mary Lou Oster-Granite, Ph.D., joined the IDD Branch as a health scientist administrator in July 1999. A long-time grantee of the NICHD, Dr. Oster-Granite served as a tenured professor of biomedical sciences at the University of California before joining the Branch. As a developmental neuroembryologist, neurovirologist, and neurogeneticist, her research interests include genetic models of IDD and animal models of Down syndrome and urea cycle disorders such as ornithine transcarbamylase deficiency. Her programmatic interests include brain function at the cellular/molecular level, developmental neurobiology, neurochemistry, neurovirology, molecular genetics, and gene therapy. Dr. Oster-Granite serves as the chair of the NIH Down Syndrome Working Group, which drafted the *NIH Research Plan on Down Syndrome* in 2007.

[⊗] Dr. Howell, a former member of the National Advisory Child Health and Human Development Council, now provides expert guidance for the Institute's Newborn Screening Initiative and chairs the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children.

Melissa Parisi, M.D., Ph.D., joined the IDD Branch in October 2008 as chief, after serving as assistant professor in the Department of Pediatrics at the University of Washington and Seattle Children's Hospital, where she was active as a clinical geneticist and as a researcher in the field of congenital malformations of the human hindbrain. She earned her M.D. degree and her Ph.D. in developmental biology from Stanford University, where her research focused on mitochondrial transcription. Dr. Parisi completed a pediatric residency at the University of Washington, followed by fellowship training in medical genetics. In her clinical practice in the states of Washington and Alaska, Dr. Parisi was involved in the evaluation, diagnosis, and management of children and adults with genetic syndromes, the majority of whom had major congenital defects and/or developmental disabilities, including behavioral disorders such as ASDs. In Seattle, she served as the physician leader for the Gender Assessment Team, a multidisciplinary team that provides diagnosis and management for infants, children, and adolescents with disorders of sex development. She is the former chair of the Scientific Advisory Board of the Joubert Syndrome and Related Disorders Foundation.

Tiina Urv, Ph.D., joined the IDD Branch as a health scientist administrator in October 2006. Dr. Urv is a developmental disabilities specialist with a Ph.D. from Columbia University and 25 years of experience working with individuals with IDD in both clinical and research settings. Prior to joining the Branch, she was assistant professor at the University of Massachusetts Medical School's Eunice Kennedy Shriver Center and a research scientist at the New York State Institute for Basic Research in Developmental Disabilities. The focus of her work has been the behavioral aspects of aging and Alzheimer disease in adults with Down syndrome and IDD. Dr. Urv's work in the IDD Branch focuses on behavioral, biobehavioral, and social sciences research with a primary focus on Fragile X syndrome (FXS). Dr. Urv serves as the chair for the NIH FXS Research Coordinating Group, which developed the *Research Plan on FXS and Associated Disorders*. She also serves as coordinator for the research program in newborn screening and manages a diverse portfolio of grants for the IDD Branch related to these efforts.

Ljubisa Vitkovic, Ph.D., joined the Branch as a health scientist administrator in January 2003. Dr. Vitkovic manages the Eunice Kennedy Shriver IDD Research Centers Program and the NICHD-funded Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers. He is responsible for neuroscience research related to neurodevelopmental disorders such as pediatric seizures, hydrocephalus, neurofibromatosis, spinal muscular atrophy, and tuberous sclerosis. Dr. Vitkovic has an M.S. degree in nuclear physics and a doctorate degree in biophysics from Michigan State University. Prior to joining the NICHD, he worked for the National Institute of Mental Health, National Institute of Allergy and Infectious Diseases, and the National Institute of Neurological Disorders and Stroke. He has received numerous awards, including an NIH Director's Individual Award, and was nominated for the U.S. Department of Health and Human Services Secretary's Award for Distinguished Service. He was also a professor for the French Academy of Sciences in Montpellier, France, and has served as a private consultant. Dr. Vitkovic has published more than 50 peer-reviewed scientific articles and edited several books. He serves on the editorial boards of *Molecular Psychiatry* and *IDD Research Reviews*.

APPENDIX B: BRANCH FUNDING INITIATIVES, FISCAL YEAR 2005 THROUGH FISCAL YEAR 2008

REQUESTS FOR APPLICATIONS (RFAS)

Title	Activity Code	Announcement No.
Autism Centers of Excellence	R01 P50	RFA-HD-06-004 RFA-HD-06-016
Biomarkers for Neurodegeneration	R21	RFA-NS-07-004
Eunice Kennedy Shriver Intellectual and Developmental Disabilities Research Centers (Formerly Mental Retardation and Developmental Disabilities Research Centers)	P30	RFA-HD-09-012 RFA-HD-08-016 RFA-HD-07-012 RFA-HD-05-030
Facilitating Interdisciplinary Research via Methodological and Technological Innovation in the Behavioral and Social Sciences	R21	RFA-RM-07-004
Factors Affecting Cognitive Function in Adults with Down Syndrome	R01	RFA-HD-09-028
Limited Competition for Fragile X Research Center Revision Applications	P30 Supplements	RFA-HD-07-013
Identifying Autism Susceptibility Genes	R01/ Collaborative R01	RFA MH-05-007
National Research Service Award for Interdisciplinary Individual Postdoctoral Fellows for Training in Neurodegeneration Research	F32	RFA-AG-07-004
Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers	U54	RFA-HD-09-027 RFA-NS-08-002
Rare Diseases Clinical Research Consortia for the Rare Diseases Clinical Research Network; Data Management and Coordinating Center for the Rare Diseases Clinical Research Network	U54	RFA-OD-08-001 RFA-OD-08-002
Recovery Act Limited Competition: Research to Address the Heterogeneity in Autism Spectrum Disorders	R01 Collaborative R01 R21 R34/Collaborative R34	RFA-MH-09-170 RFA-MH-09-171 RFA-MH-09-172 RFA-MH-09-173
Short-Term Interdisciplinary Career Enhancement Awards for Neurodegeneration Research	K18	RFA-DC-07-005
Therapeutics Delivery for Neurodegenerative Diseases	R21	RFA-EY-07-001

PROGRAM ANNOUNCEMENTS (PAS/PARS/PASS)

Title	Activity Code	Announcement No.
Basic and Clinical Research on Rett Syndrome	R03 R21	PA-06-273 PA-06-274
Basic and Clinical Research on Rett Syndrome and *MeCP2*	R01	PAS-07-192
Brain Disorders in the Developing World: Research Across the Lifespan	R01, R21 R21 R01 R01 R21	PAR-05-100 PAR-06-420 PAR-07-268 PAR-08-112 PAR-08-113
Data Ontologies for Biomedical Research	R01	PAR-07-425
Innovative Therapies and Clinical Studies for Screenable Disorders	R21 R01 R03 R03 R21	PAR-06-059 PAR-06-060 PAR-06-061 PAR-06-341 PAR-06-342
Muscular Dystrophy: Pathogenesis and Therapies	R01, R21 R21 R01	PA-05-038 PA-06-508 PA-07-125
Psychosocial/Behavioral Interventions and Services Research in Autism Spectrum Disorders	R34	PA-07-343
Research on Autism and Autism Spectrum Disorders	R01 R03 R21 R01	PA-06-390 PA-06-391 PA-06-392 PA-07-085
Research to Advance Vaccine Safety	R01 R21	PA-08-256 PA-08-257
Shared Neurobiology of Fragile X Syndrome and Autism	R01, R03, R21 R03 R21 R01	PA-05-108 PA-06-429 PA-06-430 PA-07-284
Sharing Data and Tools: Federation using the BIRN and caBIG Infrastructures	R01	PAR-07-426
Exploratory/Developmental Program for Translational Research in Muscular Dystrophy	R21	PAR-06-203
Understanding and Treating Ataxia Telangiectasia	R01 R21 R03	PA-07-272 PA-07-273 PA-07-274

NOTICES (NOT)

Title	Type	Number
Acquisition, Processing, Preservation, and Distribution of Human Tissues to Advance Understanding and Treatment of Developmental Disabilities	Request for Information (RFI)	NOT-HD-09-005
Research Priorities in Fragile X Syndrome, Fragile X Tremor Ataxia Syndrome, Premature Ovarian Failure and Other Relevant Conditions Associated with *FMR1* Gene Function	RFI	NOT-HD-08-003

APPENDIX C: EXPERT PANEL MEMBERS

Don Bailey, Ph.D.
Distinguished Fellow
RTI International, Inc.
Research Triangle Park, North Carolina

Mark L. Batshaw, M.D.
Chief Academic Officer
Children's Research Institute (CRI)
George Washington University
Professor and Chairman, Pediatrics
Associate Dean, Academic Affairs
Children's National Medical Center
Washington, D.C.

Susan A. Berry, M.D.
Professor and Director
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Ian D. Krantz, M.D.
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*COL David S. Louder, III, M.D.
U.S. Air Force
Materiel Command Director, Medical Operations
Air Force Medical Operations Agency
Bolling Air Force Base
Washington, D.C.

Jana Monaco
Parent
Woodbridge, VA

Richard T. Moxley, III, M.D.
Associate Chair for Academic Affairs
Professor of Neurology and Pediatrics
Helen Aresty Fine and Irving Fine Professor of Neurology
Director, Neuromuscular Disease Center
University of Rochester School of Medicine and Dentistry
Rochester, New York

Andy Shih, Ph.D.
Vice President
Scientific Affairs
Autism Speaks
New York, New York

Steven F. Warren, Ph.D.
Vice Provost for Research and Graduate Studies
Professor of Applied Behavioral Science
Office of Research and Graduate Studies
University of Kansas
Lawrence, Kansas

* Denotes NACHHD Council Member

APPENDIX D: BRANCH-SPONSORED CONFERENCES AND WORKSHOPS

2005

Clinical Trials in Rett Syndrome, June 24-28, 2005

The goal of this conference was to form an international alliance that would conduct clinical trials and early interventions in Rett syndrome with sufficient numbers of participating individuals to make the clinical studies valid. The workshop objectives included: an assessment of the current state-of-the-art research in diagnosis, treatment, clinical trials, and early interventions in Rett syndrome; identification of areas of limited knowledge in Rett syndrome; development of recommendations for future clinical research in Rett syndrome; and recruitment of researchers from different disciplines at all levels of training to the field of Rett syndrome research, diagnosis, and treatment.

Expert Panel Work Group on New Tests and Technologies in Newborn Screening, July 28-29, 2005

In 2005, the American College of Medical Genetics issued a report recommending conditions considered scientifically and medically appropriate for inclusion in state newborn screening programs (available at http://mchb.hrsa.gov/screening). This report further highlighted issues surrounding the need to inform the newborn screening community about new technologies emerging from industry and academia that might have applicability to newborn screening, especially with many states lacking significant research capabilities and operating their programs somewhat independently of one another. This work group was formed as a mechanism to respond to this particular issue.

Muscular Dystrophy Coordinating Committee (MDCC) Scientific Working Group, August 16-17, 2005

The Muscular Dystrophy Community Assistance, Research, and Education Amendments of 2001, also called the MD-CARE Act (P.L. 107-84), authorized establishment of the MDCC to develop a plan for research and education on muscular dystrophy. Comprising representatives from Institutes and Centers with research involvement in the muscular dystrophies, other federal agencies and centers, advocacy groups, and public members, the MDCC held a two-stage planning process. The first stage resulted in the *MDCC Research and Education Plan for NIH* (available at http://www.ninds.nih.gov/find_people/groups/mdcc/MD_Plan_submitted.pdf), which provided broad guidelines for the NIH on research priorities for the muscular dystrophies and was submitted to congress in August 2004. Convening the MDCC Working Group, which developed the *Action Plan for Muscular Dystrophies* (available at http://www.ninds.nih.gov/find_people/groups/mdcc/MDCC_Action_Plan.pdf) with specific objectives for coordination of research in muscular dystrophies, was the second stage of this process.

Annual Baby Siblings Research Consortium Meeting, August 24-26, 2005

This collaboration, formed in 2003 between the NICHD and the National Alliance for Autism Research, now part of Autism Speaks, is a consortium comprised of researchers investigating autism spectrum disorders (ASDs) among the infant siblings of those diagnosed with ASDs, a

group considered to be at high risk for developing these conditions. The goal of the consortium is to identify behavioral and biological markers for ASDs that enable clinicians to make more definitive diagnoses in children at younger ages. The initial meeting occurred in August 2004 with the purpose to finalize plans for the initial project focused on head circumference and brain volume in children with ASDs, and this second meeting extended that original purpose to develop additional collaborative projects.

Access to Quality Testing for Rare Diseases, September 26-27, 2005

Although individually rare, rare diseases and conditions collectively affect a significant portion of the population. The majority of the 6,000 to 7,000 rare diseases known today are viewed as genetic conditions, making genetic testing an essential element for the diagnosis and management of the patients and their families. However, the development of tests for rare genetic diseases has not keep pace with the progress of knowledge about the genetic bases of rare diseases. This conference sought to raise national awareness of the growing public need to improve the availability, quality, and accessibility of genetic testing for rare diseases, and to promote development of multiple processes and models to enhance the translation of genetic tests from research to clinical practice.

Workshop on Diet, Nutrition, and Dietary Supplement Use in ASDs: Evaluation of the Evidence, October 6, 2005

Research to document the occurrence of dietary deficiencies or to support the efficacy of dietary intervention in individuals with ASDs has been limited. The purpose of this workshop was to discuss ways of encouraging evaluation of various dietary and non-traditional biomedical supplements to provide the necessary evidence in support of meaningful policies addressing their use. Participants at the workshop included diverse experts in dietary supplement research, evidence-based research, and ASDs.

2006

Mental Retardation and Developmental Disabilities Research Centers (MRDDRC) Program: Planning for the Fiscal Year 2007 Hiatus & Beyond, June 9, 2006

In 2006, the MRDDRC Program (now the Eunice Kennedy Shriver IDD Research Centers Program) funded P30 grants at 14 universities across the country to provide infrastructure for independently funded research to ameliorate IDD. For each of four years of the five year cycle, three to four existing and several new centers compete for P30 grants. In fiscal year 2007, a hiatus in competition allowed the Branch to convene this workshop to discuss potential changes in the Program. Leaders in research on IDD and developmental biology, several of the existing MRDDRC directors, and members of the advocacy community met with NICHD staff to discuss the evolution of the Program and ideas for the future.

Strengthening Newborn Screening in the Middle East and North Africa (MENA), November 15-17, 2006

Health care providers in the MENA region expressed interest in developing newborn screening programs in their areas, particularly because birth defects and genetic diseases have become an increasingly larger public health issue as the infant mortality rate due to infections has declined.

Given the high proportion of consanguineous marriages in many of these countries, there is growing recognition of the value of newborn screening and the role it plays in preventing or ameliorating disabilities resulting from genetic conditions amenable to screening, particularly those with simple and relatively inexpensive treatments available. This conference brought together an international group of experts in the field of newborn screening from countries in the MENA region, Europe, and the United States. The conference summarized the current state of newborn screening in the region and outlined areas for future collaboration and knowledge-sharing in the *Marrakech Declaration* (see *Appendix F*). For additional information about this meeting, visit http://www.nichd.nih.gov/about/meetings/2006/mena.cfm.

2007

Gatlinburg Conference: Down Syndrome: Genes, Brain, and Behavior, March 7-9, 2007

The Gatlinburg Conference represents one of the premier conferences in the United States for behavioral scientists conducting research in IDD. The theme for the 2007 conference was Down syndrome, the leading genetic cause of IDD in the United States. Because research on Down syndrome has achieved a level of "maturity" with regard to the multidisciplinary approaches investigators have developed to study the causal pathways from genes to behavior, it has become a model for planning investigations into less well-understood genetic conditions associated with IDD. The Gatlinburg conference reflected this multidisciplinary approach to understanding Down syndrome with invited speakers from all disciplines relevant to understanding the causes, consequences, life-course trajectories, and environmental circumstances in this condition.

Smith-Lemli-Opitz Syndrome and Inborn Errors of Cholesterol Synthesis, June 27-29, 2007

The goal of this meeting was to promote interactions between scientists with expertise in cholesterol homeostasis, brain cholesterol metabolism, embryonic development, and oxysterol and neurosteroid biology with clinician-scientists studying and treating patients with inborn errors of cholesterol synthesis. It was anticipated that these interactions would lead to collaborative projects that will ultimately improve understanding and treatment of these genetic disorders.

Down Syndrome Expert Meeting: Factors that Affect Cognitive Function in Down Syndrome throughout the Lifespan, July 12-13, 2007

The NIH Working Group on Down Syndrome convened experts in Down syndrome research and related fields, advocacy community members, and members from other federal organizations with relevant research or funding programs (i.e., Centers for Disease Control and Prevention) to focus on the state of the science relative to Down syndrome research. This meeting provided a forum for discussion of future research directions and priorities for Down syndrome research in preparation for the creation of the *NIH Research Plan on Down Syndrome* (available at http://www.nichd.nih.gov/publications/pubs_details.cfm?from=&pubs_id=5695). Broadly identified areas of research focus included: medical issues, behavioral and family issues, clinical trials, and research infrastructure.

Expert Workshop on the Biology of Chromosome 21 Genes, September 28-October 2, 2007

This meeting, an international assembly of experts on Down syndrome convened every two or three years with partial NICHD support, brought together experts to discuss recent progress in understanding the impact of specific genes and metabolic and molecular pathways on the etiology and pathogenesis of Down syndrome. Investigators reflected a collaborative spirit in sharing resources, data, and biological specimens to further understand relevant genes on chromosome 21. Topics of discussion included the integration of pathway approaches to understanding specific developmental defects, the influence of specific genes located on other chromosomes whose expression is impacted by triplication of genes on chromosome 21, the development of new partial trisomic mouse models for Down syndrome, and observations from studies of humans with either complete or partial trisomy 21.

2008

Second Conference of the MENA Newborn Screening Initiative: Partnerships for Sustainable Newborn Screening Infrastructure and Research Opportunities, April 12-14, 2008

More than 30 policy makers, health care providers, health ministry representatives, experts, and family and advocacy representatives from 17 countries in the MENA region, Europe, Asia, and North America attended this second meeting of the MENA Newborn Screening Working Group. The primary outcome of the meeting was the development of National Plans of Action for implementation of newborn screening programs in each of the participating countries. These National Plans detailed newborn screening program leadership, blood spot collection and storage, laboratory methods, and linkage to treatment and follow-up. An article summarizing these issues was published (Krotoski et al, 2009, *Genet Med, Sep;11*(9):663-668). Visit http://www.nichd.nih.gov/about/meetings/2008/mena2.cfm for additional information.

Outcome Measures for Clinical Trials with Children with Fragile X Syndrome (FXS), May 8-9, 2008

This meeting was a collaborative effort between the IDD Branch and the Obstetric and Pediatric Pharmacology Branch within NICHD, in support of Best Pharmaceuticals for Children Act activities to describe outcome measures for safety and efficacy when treating children with FXS; assess validation of those measures for clinical studies; and describe approaches for preclinical toxicology studies to define efficacy and safety. The goal of the meeting was to develop recommendations related to outcome measures for clinical trials in children with FXS. A follow-up meeting to develop a white paper is planned for late 2009.

2009

Early Detection and Screening of Neuromuscular Diseases Conference, March 16-17, 2009

The NICHD, in conjunction with other NIH Institutes and Centers, federal agencies, and advocacy groups, organized this 1½-day workshop with a diverse group of invitees, including experts in the fields of neuromuscular disease research, bioethics, and newborn screening. The goals of the conference were to assess the status of neuromuscular diseases in terms of their

readiness for early detection and screening; share the qualifying parameters for consideration for early detection and screening; and determine the needs of the neuromuscular disease communities and the required opportunities (fiscal and intellectual) needed to support the quest to screen for these conditions. Visit http://www.nichd.nih.gov/about/meetings/2009/031609.cfm for more information.

The First International Conference on Hyperphagia, June 5, 2009

This unique conference crossed boundaries between clinical and research disciplines and syndromes to help participants, including researchers, clinicians, and family and advocacy members, better understand hunger, the drive to overeat, and obesity associated with certain IDD conditions. Speakers included recognized experts in five distinct conditions associated with hyperphagia: Prader-Willi syndrome, Bardet-Biedl syndrome, Alström syndrome, WAGR syndrome (characterized by Wilms' tumor, aniridia, genitourinary anomalies, mental retardation), and a subset of individuals with FXS. Objectives included discussion of the similar and unique clinical features of the hyperphagia disorders, criteria to facilitate more accurate and earlier diagnosis, management issues, and family and quality-o- life issues. The meeting promoted collaboration among participants with diverse professional and personal experiences but with a shared challenging clinical issue.

Third International Conference on Urea Cycle Disorders, August 27-28, 2009, and the Society for Inherited Metabolic Disorders (SIMD) 32nd Annual Meeting, August 29-September 2, 2009

NICHD, in cooperation with the NIH Office of Rare Disorders Research, provided primary support for the 2009 SIMD meeting, which was held in conjunction with the *11th International Congress of Inborn Errors of Metabolism*. The Third International Conference on Urea Cycle Disorders, a jointly sponsored satellite meeting that preceded the SIMD meeting, focused on the theme of understanding urea cycle disorders and catalyzing research collaborations. In part because of new technologies for and expanded programs in newborn screening, a broader clinical and molecular spectrum of inherited metabolic disorders is being elucidated with more affected individuals than previously appreciated. The SIMD's mission is to promote the advancement of research, training, and medical treatment of inherited metabolic disorders. At the annual SIMD meeting, researchers review the current state of metabolic disorders with regard to underlying etiology, diagnostic evaluation, management, and development of new therapies.

APPENDIX E: BRANCH-SUPPORTED TRAINING AND CAREER DEVELOPMENT GRANTS, FISCAL YEAR 2005 THROUGH FISCAL YEAR 2008

PREDOCTORAL INDIVIDUAL NATIONAL RESEARCH SERVICE AWARDS (NRSAS) (F31S)

- Predoctoral Fellowships for Students with Disabilities, University of California, Los Angeles (UCLA), California (2005, 2006)
- Predoctoral Fellowships for Students with Disabilities, Virginia Commonwealth University, Virginia (2005)
- A Longitudinal Study: Adaptations of Families with Children with Developmental Disabilities, Arizona State University, Arizona (2007, 2008)

POSTDOCTORAL INDIVIDUAL NRSAS (F32S)

- Visual Object Representation in Williams Syndrome, Johns Hopkins University, Maryland (2005)
- Mouse Models of Down Syndrome, Johns Hopkins University, Maryland (2005)
- Identifying Down Syndrome Heart Defect Candidate Genes, Emory University, Georgia (2005, 2006)
- Fragile X Repression of Localized mRNA Translation, University of Pennsylvania, Pennsylvania (2005, 2006)
- Analysis of Regional Cortical Development Genes, Beth Israel Deaconess Medical Center, Massachusetts (2005, 2006)
- ERK Regulation of Hippocampal Potassium Channels, Baylor College of Medicine, Texas (2005)
- Analysis of Genomic Imprinting at the *Ube3a* Locus, Baylor College of Medicine, Texas (2005, 2007)
- fMRI of Serotonergic Genetic Variation in Autism, University of Florida, Florida (2005, 2006)
- Migration of Cajal-Retzius Cells, University of California, San Francisco, California (2005, 2006, 2007)
- CK2 Regulation of Fragile X in Circadian Clocks, Northwestern University, Illinois (2006)
- Laminopathy Treatment with Farnesyltransferase Inhibitors, UCLA, California (2006, 2007)
- Hindbrain Dysgenesis in Rett Syndrome and Other Autism Spectrum Disorders, University of California, Davis, California (2007, 2008)
- Retrograde Transport at the Crossroads of Cognitive Decline and Neurodegeneration, Stanford University, California (2007, 2008)
- Neural Substrate for Language and Social Cognition: Autism and Typical Development, Massachusetts Institute of Technology, Massachusetts (2008)

RESEARCH SCIENTIST DEVELOPMENT AWARD (K02)

- Neural Substrates of Socioemotional Development, Georgetown University, Washington, D.C. (2005, 2006, 2007)
- Self-Injury: Pain and Stress Mechanisms, University of Minnesota, Twin Cities, Minnesota (2006, 2007, 2008)

CLINICAL INVESTIGATOR AWARDS (K08S)

- Attention in Children with the 22q11 Deletion Syndrome, Rockefeller University, New York (2005)
- *COX-2* and Injury in the Immature Brain, Children's Hospital of Pittsburgh/University of Pittsburgh Medical Center, Pennsylvania (2005)
- Chromosome Analysis in Single Cells, Mount Sinai School of Medicine of New York University, New York (2005)
- Chromosome Analysis in Single Cells, Columbia University Medical Center, New York (2005, 2006, 2007)
- Effects of Inflammation on Developing Glia, Children's National Medical Center, Washington, D.C. (2005, 2006, 2007)
- *In Vivo* Substrate Utilization in Newborn Rat Brain, University of Minnesota, Twin Cities, Minnesota (2005, 2006)
- Cohesin Complex and Cornelia de Lange Syndrome, Children's Hospital of Philadelphia, Pennsylvania (2007, 2008)
- The Immune Response to Viral Vectors and Transgenes in Fetus, UCLA, California (2007, 2008)
- Mitochondria, Superoxide, and MnSOD in Fetal Cerebral Palsy Model, Evanston Northwestern Healthcare Center, Illinois (2008)

MENTORED PATIENT-ORIENTED RESEARCH CAREER DEVELOPMENT AWARDS (K23S)

- Clinical Phenotype of Imprinted Genes on Chromosome 15, Baylor College of Medicine, Texas (2005)
- Predicting Severe Neonatal Hyperbilirubinemia, Children's Hospital of Philadelphia, Pennsylvania (2005, 2006, 2007)
- Identification of Genes Responsible for X-Linked Mental Retardation, Johns Hopkins University, Maryland (2005, 2006, 2007)

- Attentional Dysfunction in Children with Phenylketonuria, University of Rochester, New York (2005, 2006, 2007, 2008)
- Identification and Management of Developmental Delays, Case Western Reserve University, Ohio (2005, 2006, 2007)
- Elucidation of the Genetic Etiology of Costello Syndrome, University of California, San Francisco, California (2005, 2006, 2007, 2008)
- Identification and Management of Developmental Delays, Boston Medical Center, Massachusetts (2007, 2008)

MIDCAREER INVESTIGATOR AWARD IN PATIENT-ORIENTED RESEARCH (K24)

Genetic Analyses of Cerebellar Malformations, University of Washington, Seattle, Washington (2005, 2006, 2007, 2008)

CAREER TRANSITION AWARD (K99/R00)

Epigenetic Mechanisms of X-Chromosome Inactivation, University of North Carolina, Chapel Hill, North Carolina (2007, 2008)

CONTINUING EDUCATION TRAINING GRANT (T15)

Course in Medical and Experimental Mammalian Genetics, Jackson Laboratories, Maine (2005, 2006, 2007, 2008)

INSTITUTIONAL NRSAS (T32S)

- Mental Retardation and Developmental Disabilities, UCLA, California (2005, 2006, 2007, 2008)
- Mental Retardation and Developmental Disabilities, Mt. Sinai School of Medicine, New York (2005, 2006, 2007)
- Genetics and Genomics of Human Disease, Yale University, Connecticut (2005, 2006, 2007, 2008)
- Behavioral Research Training in Intellectual/Developmental Disabilities, Vanderbilt University, Tennessee (2005, 2006, 2007, 2008)
- Training in Mental Retardation/Developmental Disabilities, University of Miami, Florida (2005, 2006, 2007, 2008)
- Postdoctoral Training in Mental Retardation Research, University of Wisconsin, Madison, Wisconsin (2005, 2006, 2007, 2008)

- Postdoctoral Research in Neurodevelopmental Disorders, University of North Carolina, Chapel Hill, North Carolina (2005, 2006, 2007, 2008)
- Research Training in Mental Retardation, University of Notre Dame, Indiana (2006, 2007, 2008)
- Postdoctoral Training in Developmental Disabilities Research, Children's National Medical Center, Washington, D.C. (2006, 2007, 2008)

APPENDIX F: MARRAKECH DECLARATION

STRENGTHENING NEWBORN SCREENING IN THE MIDDLE EAST AND NORTH AFRICA CONFERENCE

November 15, 2006

The international community has achieved important advances in infant survival and the reduction of neonatal mortality. As a consequence, in view of the United Nation's Convention on the Rights of the Child (1989), governments must now focus increased attention on assuring our children's optimal development and to put in place policies to ensure that tomorrow's adults are as free as possible from disability that will limit achieving their potential. This is facilitated by early screening for congenital genetic disorders that are responsible for major disability; if not treated early, the costs of treatment of preventable disability will be prohibitive for society and the lives of children and their families will be tragically and unnecessarily limited. Systematic newborn screening for these genetic disorders is, thus, a necessity for public health programs based on the resources available.

Participants of the first meeting of *Strengthening Newborn Screening in the Middle East and North Africa* recognize that our children's health is a high priority for our countries. Newborn screening is an important tool in the prevention of disease and disability in our children and thus should be a key part of a comprehensive public health system in all of our countries. Each country should prioritize the panel of genetic disorders and system of care that is appropriate to their situation.

Based on the meeting's deliberations, the following recommendations have received high priority:

- Encourage all countries to develop policies and provide necessary support to establish a systematic national newborn screening program within the context of a global national policy for children's health that will provide access to all newborn infants in these countries and provide follow-up services. Such services should integrate both public and private health care delivery systems.
- All countries in the region should screen for at least one condition and develop a national model program that takes into account all aspects for post-testing care.
- Establish national research priorities around newborn screening, through culturally relevant and ethical strategies.
- Reduce disability and death by assuring that the children identified as having screened positive for a genetic disorder have the opportunity to a good quality of life through access to medical treatment including behavioral, physical therapeutic interventions as well as assistive technology in order to preserve healthy development and improve autonomy and independence.
- Develop population studies to determine the incidence of genetic disorders in the region and consider linking to national databases with standardized measurements. Clearly population

genetic data needs to be accumulated country by country as it is anticipated that each country will have unique disorders related to their own population.

- Begin regionalization and cooperation among countries by sharing of expertise, information, and other resources.
- Develop training programs that focus on role-specific activities that build the interdisciplinary teams needed for newborn screening systems of care.
- Stimulate regional research capacity that addresses the specific conditions of priority to the Middle East and North Africa.

In view of all of the above recommendations, the attendees recognize the need for establishment of collaborative, cooperative networking to facilitate the development of a newborn screening system for all nations.

To develop such a collaborative network it would be of value to:

- Hold annual meetings to assess country advances
- Develop smaller focused meetings on issues of particular importance (e.g., training)
- Establish structures for increased communication across the region including a regional Web site and biennial regional meetings.
- Establish an advisory committee to set up an agenda for addressing the recommendations identified above.
- Establish working groups that can implement identified priorities.