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National Institutes of Health Research Plan on Down Syndrome

2014 Draft

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Developed by the *Eunice Kennedy Shriver* National Institute of Child Health and Human
Development and the NIH Down Syndrome Working Group

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EXECUTIVE SUMMARY

[Content to be added at a later date.]

INTRODUCTION

Despite the challenges of tight fiscal times, progress has been made on many aspects of Down syndrome research since the first NIH Research Plan on Down Syndrome was published in 2007. The NIH Down Syndrome Working Group (DSWG), which developed the original plan, has led the plan's implementation for the NIH, coordinating research efforts and sponsoring both scientific conferences and funding opportunity announcements.

For example, in addition to funding new research projects (including several short-term projects funded through the American Reinvestment and Recovery Act), the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) renewed a major contract to develop, characterize, and produce mouse models for cytogenetic disorders such as Down syndrome (including the Ts65Dn mouse), and expanded another contract for the human brain and tissue repository at the University of Maryland. Scientific meetings held since 2007 included a jointly sponsored public-private conference in 2010 to discuss the research resource needs of the Down syndrome community, focusing on registries, databases, and biological sample banks (called biobanks). In 2013, the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Aging (NIA), NICHD, and several Down syndrome organizations co-sponsored a workshop, *Advancing Treatment for Alzheimer's Disease in Individuals with Down Syndrome*, to discuss how best to integrate current research activities, research resources, and future opportunities to inform development of therapies.

The 2007 Research Plan also called for increased outreach and collaboration with the Down syndrome community. In 2011, the public-private Down Syndrome Consortium was established. This Consortium includes the NIH DSWG, more than a dozen national organizations whose missions focus on Down syndrome, and individuals with Down syndrome and family members. The Consortium serves to foster exchange of information on biomedical, behavioral, and biobehavioral research on Down syndrome; to provide an avenue for outreach and information dissemination to the Down syndrome community, including through a new Consortium website; and to offer a forum for discussing the update of the NIH Research Plan on Down Syndrome, among other collaborative activities.

The NICHD also consulted regularly with the Down syndrome research and family communities as it prepared to establish *DS-Connect™: The Down Syndrome Registry* (<https://dsconnect.nih.gov>), which was launched in September 2013. This national registry serves as a health resource for people with Down syndrome and their families, for researchers, and for health care providers and facilitates participation of people with Down syndrome in clinical trials aimed at improving knowledge about the condition and potential treatments.

In August 2012, the NICHD published a Request for Information (RFI) inviting Down syndrome researchers, health care providers, and patient advocates to comment on progress made since the 2007 Research Plan, to note research gaps, and to provide input on research priorities for NIH. The response to the RFI was excellent; the majority of the comments were incorporated into this draft 2014 Research Plan.

**HIGHLIGHTS OF ONGOING RESEARCH ON
DOWN SYNDROME AT THE NIH**

The following summarizes ongoing research supported by the NIH primarily through these NIH Institutes.

[Content to be added at a later date.]

RESEARCH GOALS AND OBJECTIVES

Initially formed in 2005, the NIH DSWG first met to discuss research activities related to Down syndrome, and how the NIH Institutes and Centers (ICs) supporting and conducting research on aspects of this condition could better coordinate their efforts and share expertise. In 2007, the NIH DSWG published the first Down Syndrome Research Plan so that NIH ICs could start working toward common Down syndrome research goals. More recently, the NICHD and the DSWG, augmented by input from the Down Syndrome Consortium and the research community and considering the information presented at a series of facilitated, targeted meetings (see [Appendix D](#)), developed the following list of research goals and objectives to complement investigator-initiated research and to guide the NIH's future efforts regarding Down syndrome.

The following sections list the research areas as five primary goals (A to E). Because of the uncertainty of public funding, objectives are grouped under each goal by the approximate timeframe for accomplishing them, specifically “shorter term” and “longer term.” Non-italicized text represents objectives and language from the 2007 plan; new objectives or new language within an existing objective appear in italics. Key terms and concepts for each objective appear in bold. The status of an objective is noted in parentheses and italics at the end of each objective.

In addition, a bibliography of NIH-funded research articles published since 2007 and related to each goal is included in [Appendix A](#). These citations are organized by primary goal and listed alphabetically by NIH-funded investigator last name; no article is listed more than once.

A: Pathophysiology of Down Syndrome and Disease Progression

In 1973, investigators mapped the first two of several hundred genes on human chromosome 21. By 2000, a cadre of investigators published the DNA sequence of chromosome 21, making it possible to identify the effects of having an extra copy of individual genes or clusters of genes. Today, researchers use model systems, including fully or partially trisomic mice, which have features of the human condition, to study these effects.

Shorter Term Objectives

1. Continue **cognitive testing and analysis of synaptic function** in a Down syndrome mouse model, focusing specifically on relevant genes also located on human chromosome 21. (*Status: In progress.*)
2. **Develop mouse models to study synaptic and vesicular trafficking** specifically for Down syndrome, including metabotropic and ionotropic glutamate receptors and other neurotransmitter receptors. Allow studies of other disorders associated with intellectual and developmental disabilities (IDD) (e.g., Fragile X and Rett syndromes) to guide and inform directions for such studies. (*Status: In progress.*)
3. **Expand and improve proteomic, metabolomic, transcriptomic, and phenomic approaches** for studies in Down syndrome cells and tissues, including:
 - Sample preparation techniques to create suitable proteomic samples from mouse brains;

- Fractionation techniques to visualize many of the proteins that exist in cells;
- Additional proteomic analysis methods beyond two-dimensional gels;
- Rigorous statistical techniques to determine whether a statistically significant change in protein levels has biologic relevance;
- Methods to relate findings in the mouse to the health of humans;
- Emerging techniques to move research beyond proteins and proteomics toward metabolites and metabolomics and to begin examining what generates alterations in learning and memory; and
- Methods to link data from the transcriptome to the proteome, metabolome, and phenome.

(Status: In progress.)

4. Study **pathways that affect mitochondrial function** (such as adenosine triphosphate [ATP] production), calcineurin, MAP kinases, and oxidative stress. Link pathways to relevant research on specific gene effects, and explore the effects on modulation of development in various organ systems. *(Status: In progress.)*
5. Sequence the **events leading to abnormal dendritic (neuronal) spine development**, including genetic and cellular aspects (this research could include common developmental themes with other disorders, such as Fragile X and Rett syndromes). *(Status: Yet to begin.)*
6. Study the biochemistry of **amyloid precursor protein (APP) processing** in humans with Down syndrome and in animal models (including mechanisms of trafficking and amyloid-beta [A β] production, degradation, and clearance). *(Status: In progress.)*

Longer Term Objectives

7. Using standardized techniques and measurements, undertake a systematic **analysis of the development of key brain structures** of typically developing individuals and individuals with Down syndrome at various developmental stages. *(Status: In progress.)*
8. Explore **genetic, epigenetic, and environmental determinants** that contribute to variation in birth and health outcomes, including specific birth defects, cognitive function, language, and behavioral profiles in individuals with Down syndrome throughout the lifespan. These efforts may involve longitudinal studies of existing and new cohorts of individuals. *Expand research on Down syndrome in the prenatal period, including the factors that may lead to miscarriage or stillbirth. (Status: In progress.)*
9. Connect **cellular mechanisms and genotype** to synaptic and cognitive phenotypes. *(Status: In progress.)*
10. *Explore the **molecular factors** that appear to protect individuals with Down syndrome from some types of cancers and heart disease. (Status: In progress.)*
11. *Support the development of **induced pluripotent stem cells (iPSC)** from individuals with Down syndrome to explore the potential phenotypic variability among individuals with*

Down syndrome that arises from differential expression of genes in the Down syndrome critical region or in the rest of the genome. (Status: In progress.)

B: Screening, Diagnosis, and Functional Measures of Down Syndrome-Related Conditions

The science of assessment has evolved considerably in recent years. While more diagnostic and screening measures are now available to the research and clinical communities, it is important for researchers to capitalize and expand on these advances. For example, utilization of more specialized measures of functioning across domains could facilitate more refined phenotyping and identification of biomarkers.

In the near term, the scientific community needs to further improve tools, techniques, methods, and measures, moving toward a minimum set of common measures for use across studies, age groups, and developmental and behavioral domains. In addition, the field may benefit from an agreement on common domains that can be assessed in clinical research on Down syndrome (e.g., non-verbal problem-solving ability, language and communication skills, adaptive abilities, executive function) to allow for comparability across studies, while noting that domains appropriate for one stage of life may not be appropriate for others.

Shorter Term Objectives

1. Develop a strategy to **correlate descriptive studies** of development in Down syndrome over the lifespan in both humans and model systems. This strategy will inform the **development of molecular and cognitive phenotypic profiles** for Down syndrome that will support longitudinal studies. *(Status: In progress.)*
2. **Link human and mouse cognitive studies** on Down syndrome to:
 - Better **characterize cognitive deficits** in mice related to psychological functioning;
 - **Develop standardized methods** to test synaptic and cognitive function in Down syndrome mouse models;
 - **Develop tests** that assess the same cognitive processes in both mice and humans (such as discriminative taste aversion).*(Status: In progress.)*
3. **Link cognitive phenotype of Down syndrome to validated developmental measures**, including defining speech and language, behavioral, and psychological abnormalities. Use magnetic resonance imaging (MRI), functional MRI (fMRI), *and diffusion-tensor imaging (DTI), among other imaging modalities*, to examine major pathways and determine how those pathways differ in persons with Down syndrome. *For example, this research could address the correlation of cognitive function/language impairment/behavior issues in individuals with Down syndrome and comorbid autism.* *(Status: In progress.)*

4. Establish whether and how synaptic dysfunction correlates with abnormal cognition to **determine the best phenotype/genotype markers** for therapeutic screening. (*Status: Yet to begin.*)
5. Apply standardized instruments and criteria to **define the clinical profile of Alzheimer's disease in Down syndrome**; these instruments must be sensitive to the baseline functioning of this population. For instance, developing a cognitive battery in mouse models might provide insights into a core set of measures in humans. (*Status: In progress.*)

Longer Term Objectives

6. Consider **developing additional outcome measures** for use in clinical trials to offer supplementary options for assessing change across domains of functioning, *including measures for non-verbal communication and quality of life.* (*Status: In progress.*)
7. Explore developmental perspectives, using standard measures and techniques to **assay specific, vulnerable brain regions**, such as the hippocampus, cerebellum, and prefrontal cortex, in humans and animal models. Develop better **measures of hippocampal and cognitive function** in people with Down syndrome to enhance current cognitive batteries at specific stages across the lifespan. (*Status: In progress.*)
8. *In addition to improved imaging technologies, explore the application of less- or non-invasive brain imaging technologies for assessing health status in Down syndrome, particularly in correlation with cognitive variability.* (*Status: In progress.*)

C: Treatment and Management

For individuals living with Down syndrome and their families, there is an ongoing need to study clinical and behavioral treatments and interventions. At least one-half of all children with Down syndrome also have a comorbid condition. For example, leukemia and congenital heart disease during the early years of life have the potential to significantly affect cognitive function and overall health status and both necessitate extensive medical intervention. Within the context of Down syndrome, an ongoing challenge for researchers is determining the optimal windows for early therapeutics for individuals with the condition, as well as establishing the optimal doses of off-label and new agents. Studies of family and other daily environments, such as those structured to demonstrate specific language interventions for children with Down syndrome, can also provide information that allows researchers to design biobehavioral interventions for improving cognition and daily-life functioning.

Because medical and behavioral interventions may occur simultaneously or on a continuum, objectives for *Treatment and Management* have been combined with those from the *Living with Down Syndrome* section of the 2007 Research Plan.

Shorter Term Objectives

1. **Expand research on cognitive and behavioral outcomes and potential pharmacologic and behavioral therapies for individuals with Down syndrome who have comorbid**

psychiatric and medical conditions that occur throughout the lifespan. Consider a trans-NIH workshop on *building a system of classification and measurement* to encompass the common, combined roles of comorbid medical, behavioral, or mental health conditions that contribute to the complexity of trisomy 21.

Other comorbid conditions that could benefit from concerted interdisciplinary efforts include:

- *Leukemias*: Early medical or behavioral interventions can alter the developmental trajectory in children treated for leukemias. In general, children with leukemia have concomitant behavioral and cognitive difficulties. The extent of problems typically depends on the age of the child at treatment, the treatment intensity, and the time lapse since treatment. Children with an underlying trisomic disorder that affects the brain's development who undergo this intensive treatment for leukemia are likely to face problems as they mature. Future research should focus on the mechanisms by which impairments occur in these children.
- *Congenital heart disease*: As survival of children with congenital heart defects improves, clinicians increasingly recognize neurodevelopmental problems in at least one-half of the survivors. The incidence of neurodevelopmental problems appears to increase over time. Typically developing children with congenital heart disease have a somewhat characteristic neurodevelopmental signature; as adolescents, they tend to have difficulty with social cognition. However, neurodevelopmental outcomes vary (often for the worse) among children with Down syndrome, even if they have the same heart defects and receive the same treatments as typically developing children. Possible research opportunities include longitudinal assessments of cognitive and behavioral outcomes in relation to genetic studies, *such as whole exome or whole genome sequencing or targeted sequencing of candidate genes not located on human chromosome 21*.
- *Obstructive sleep apnea*: As with typically developing individuals, this condition may exert an impact on cognition in individuals with Down syndrome.
- *Other comorbid conditions*: Additional investigation on the impact of these conditions in individuals with Down syndrome:
 - *Autism spectrum disorders*
 - *Seizure disorders/epilepsy*
 - *Psychiatric or neurobehavioral problems, (e.g., attention deficit hyperactivity disorder, obsessive compulsive disorder, depression, anxiety, grief) and their interactions with cognitive function*
 - *Pulmonary hypertension*
 - *Celiac disease*
 - *Hirschsprung disease*
 - *Atlanto-axial instability*
 - *Endocrine function*

- *Immune system dysfunction*
- *Hypercholesterolemia*

(Status: In progress.)

2. Encourage studies on therapeutics for individuals with Down syndrome, particularly those targeted toward cognition, to include measurements of **impact of therapeutic use over time**. Because the progression of cognitive decline in different stages of dementia is not linear, such medications may have differential efficacy. *Review the scientific rationale for the use of existing treatments, including alternative medicine, to evaluate their safety and efficacy specifically for people with Down syndrome. Also consider working with the National Center for Advancing Translational Sciences at the NIH on potentially repurposing drugs for use in the Down syndrome population. (Status: In progress.)*
3. Review findings from **clinical trials of vitamin E and antioxidants** in individuals with Alzheimer's disease and/or Down syndrome, and evaluate whether the function of brain circuits involved in cognition is enhanced. *(Status: In progress.)*
4. **Test drugs, such as immunologic agents like anti-amyloids**, already in use for the treatment of Alzheimer's disease, in mouse and other models of Down syndrome to determine their effects on amyloid deposits and cognition. *(Status: In progress.)*
5. Investigate the impact of **early intervention or infant stimulation** on the psychomotor and cognitive development of children with Down syndrome. *(Status: In progress.)*
6. Consider developing Funding Opportunities to support projects on **understanding and improving sensory and motor skills** in individuals with Down syndrome, paying particular attention to whether and how sensory structures (i.e., eyes, nose, mouth) are altered in persons with Down syndrome. *(Status: In progress.)*
7. Identify **effective interventions and educational strategies** to help children with Down syndrome process available linguistic input, with the goal of matching children to therapies best suited to their profiles. *Determine the possible influence of race, ethnicity, and culture on language development in children with Down syndrome. (Status: In progress.)*
8. Explore **new intervention research, including behavioral supports**, for use in family, school, and residential environments to help individuals with Down syndrome enhance *learning*, increase physical fitness and maintain healthy weight, and improve quality of life. Explore ways to disseminate successful interventions to various community settings. *(Status: In progress.)*
9. Examine the **impact of Down syndrome on families and schools**, such as how families react to children with Down syndrome, and on whether integrated schooling has beneficial effects compared to programs that separate children with Down syndrome from typically developing peers. *(Status: In progress.)*
10. Further develop **cross-disciplinary collaborations and public-private partnerships**, as needed, to test and support evidence-based educational, pharmaceutical, and other therapeutic interventions for individuals with Down syndrome, taking appropriate ethical considerations into account. *(Status: In progress.)*

11. **Develop and continue to expand the NIH website with information on Down syndrome** and related research, including user-friendly information relevant to both the research and family communities, pending clinical trials, *and funding opportunities*. The page should also include links to information about up-to-date diagnosis and treatment guidelines adopted by nationally recognized professional societies. *(Status: Completed and ongoing. See <http://downsyndrome.nih.gov>.)*

Longer Term Objectives

12. Encourage **testing orphan drugs** in animal and other model systems to determine potential beneficial effects on cognition in individuals with Down syndrome. *(Status: Yet to begin.)*
13. Develop and/or adapt **assistive devices** to facilitate integration of an individual with Down syndrome into the workplace, residential or home environment, and community. *(Status: In progress.)*
14. Describe more fully the **mitochondrial dysfunction** in Down syndrome and the exact status of mitochondrial function, and develop targeted therapies to improve mitochondrial function in Down syndrome. The status assessments may include:
 - Endocytosis and endosomal trafficking *in vivo* and *in vitro*;
 - Failed signaling and related neurotrophic deficits to help determine the relationship between disease progression and cognitive deficits.*(Status: In progress.)*
15. Determine whether individuals with cognitive impairment, including those with Down syndrome, could be considered as candidates for **organ transplantation**. *(Status: Yet to begin.)*

D: Down Syndrome and Aging (New)

People with Down syndrome are living longer than they were even a few decades ago, and this lengthier lifespan poses many new research questions and opportunities. For example, people with Down syndrome are at higher risk for developing Alzheimer's disease than is the general population; efforts to help discover new treatments for Alzheimer's in those with Down syndrome may also benefit those with Alzheimer's but without Down syndrome.

The emerging needs of people with Down syndrome as they age, and the impact on their families warrant a new section of the 2014 Research Plan.

Shorter Term Objectives

1. Study whether the **impact of aging on physiologic and cognitive processes** is greater for those with Down syndrome than for others. Such research may require a range of longitudinal studies, each with different emphases. For example, such studies could include:

- The population with Down syndrome and dementia. This group is likely to be heterogeneous and may include people in the early stages of unrecognized cognitive impairment or Alzheimer's disease.
- The factors that affect the risk of dementia, and factors associated with not developing dementia. Some people with Down syndrome do not develop dementia by their late 60s. Researchers would also need to improve their understanding of the clinical course of dementia in people with Down syndrome to complete such studies.
- *The differential impact of aging on organ systems in people with Down syndrome, e.g., changes in bone mass and chronic inflammatory conditions.*
- Variations in aging patterns among different subpopulations of individuals with Down syndrome. Much of the scientific literature focuses on early development and on individuals older than age 40, but very little research targets people with Down syndrome during their 20s and 30s.

(Status: In progress.)

2. Explore the **impact of cholesterol on dementia**, and whether the **use of statins** lowers the risk of dementia in people with Down syndrome who have high cholesterol levels.
(Status: In progress.)
3. Explore the specific impact of **post-menopausal hormone replacement therapy (HRT)** use by women with Down syndrome. Women with Down syndrome experience menopause at earlier ages and are at increased risk for dementia compared to typically developing women who are older at the onset of menopause. Such studies should be aimed at producing sufficient data to show whether post-menopausal HRT reduces the cumulative risk for Alzheimer's disease, and to inform the optimal time and duration for post-menopausal HRT use. *(Status: In progress.)*
4. As the lifespans of individuals with Down syndrome continues to increase, investigate **the impact on families** of caring for them as they age. Such work may include:
 - Identifying the factors that lead to positive and negative outcomes in families that include an individual with Down syndrome;
 - The impact on the family, including the individual with Down syndrome, as he or she leaves the school system;
 - Research on the health and lifespans of the parents, sibling educational attainment, and the intergenerational transmission of caregiving responsibilities and how best to foster those transitions.

(Status: In progress.)

E: Research Infrastructure

Shorter Term Objectives

1. **Establish a regular collaboration** among the NIH and the larger Down syndrome community of individuals with Down syndrome, families, advocacy groups, and research organizations. The NIH DSWG should continue to meet periodically with outside groups to share progress on research and hear about concerns of families. These meetings also would help the community to better understand how Down syndrome research is coordinated across the NIH. *(Status: Completed and ongoing; see Down Syndrome Consortium below.)*
2. Develop a more complete **demographic knowledge base, including factors that may contribute to differential survival rates among racial/ethnic groups**, about individuals with Down syndrome. *(Status: In progress.)*
3. Continue to include cohorts of people with Down syndrome in appropriate **longitudinal epidemiologic research and cross-sectional studies**, including those investigating the trajectory and risk factors for psychopathology across the lifespan. *Work toward the development of an adult cohort of people with Down syndrome in different areas of the United States. (Status: In progress.)*
4. **Improve and expand the availability of mouse (such as partial and complete duplication mice) and other rodent models** for research on Down syndrome. A large number of researchers use the Ts65Dn mouse, but cost remains an issue. Researchers not only need the available animal models to be inexpensive, but also for the models to include very early development phases. Possible strategies include:
 - Exploring improvements to the current mouse models and making them available to other researchers;
 - Establishing a “mouse core” to create models for current research needs, and to help predict what mouse strains and reagents researchers are likely to need in the near future;
 - Finding ways to reduce the cost of animal models to NIH-funded investigators.*(Status: Well underway.)*
5. Support **development of a Down syndrome registry and database. Make a minimal dataset available to the Down syndrome research community.** *(Status: Partially completed; see DS-Connect™: The Down Syndrome Registry.)*
6. **Establish a centralized brain, organ, cell, tissue, DNA, and RNA repository** for Down syndrome. Such specimens are necessary to understand the factors that underlie dementia in people with Down syndrome and to offer other insights. Increased banking of organs *and other tissues* from individuals with Down syndrome across the lifespan would help researchers identify the correlates of clinical signs and symptoms. *A centralized repository to augment available services could provide standardized sample collection and processing methodologies, as well as consistent, equitable sample distribution policies. (Status: In progress.)*

7. *Explore development of a **Down Syndrome Biomarker Initiative**, a shared repository for clinical, imaging, and other biomarkers, including data from recent animal studies. (Status: In progress.)*
8. Consider ways to **include participants with Down syndrome** in NIH-funded clinical trials. NIH should review existing infrastructure, such as the Clinical and Translational Science Awards, the Alzheimer's Disease Neuroimaging Initiative, or the National Children's Study, for possible inclusion of participants with Down syndrome. Use Funding Opportunity Announcements to encourage NIH program scientists to consider including, when relevant, individuals with Down syndrome in their studies, such as:
 - The impact of novel medications on cognitive enhancement, daily function, or behavioral disorders;
 - Appropriate interventions for congenital heart disease and obstructive sleep apnea;
 - Therapies used for individuals with Alzheimer's disease.*(Status: In progress.)*
9. Support a scientific meeting to highlight and evaluate the **best assessments** for use at different developmental stages, *including assessments of communication by non-verbal children. (Status: Yet to begin.)*
10. Convene a meeting of the leadership from NIH ICs involved in the NIH DSWG to discuss the best **mechanisms for fostering cross-disciplinary, collaborative, and clinical research** on Down syndrome, in addition to the work already being supported. The Working Group should review ongoing international collaborative research efforts and discuss cost, duplication, infrastructure, and training to decide what specific avenues of inquiry to follow. (For additional detail, see results of recent scientific meetings in [Appendix D](#).) *(Status: Well under way.)*
11. Establish or expand **training programs for clinician/scientists** in research relevant to Down syndrome. *(Status: In progress.)*

Longer Term Objectives

12. Develop **additional new model systems for studying Down syndrome** at the cellular, organ (in addition to brain), and genetic levels. Study the effects of perturbation of individual chromosome 21 genes on the differentiation and maturation of neurons and synapses in organisms such as *C. elegans* and *Drosophila*. *(Status: Yet to begin.)*
13. Develop a coherent program of **genetic modifier analysis** to show how modifiers contribute to the many phenotypes in Down syndrome. Researchers can ask targeted questions using gene models once they identify a region of chromosome 21 for further study and once an appropriate animal model is available. *(Status: In progress.)*
14. Explore whether **magnetic resonance spectroscopy and other neuroimaging methods**, which can show changes much earlier than neurocognitive exams, hold

- promise for studying neurological health in individuals with Down syndrome.
(*Status: In progress.*)
15. Develop **nanotechnology and other small-molecule approaches** to enhance contrast of amyloid imaging reagents for finer resolution studies in younger individuals with Down syndrome. (*Status: In progress.*)
 16. To ensure applicability of research findings to all segments of the population, **expand outreach efforts to recruit** individuals with Down syndrome, including those who are members of racial and ethnic minorities, for clinical trials. Consider using **telemedicine** to screen and enroll participants at distant sites, when appropriate, to enhance enrollment of individuals with Down syndrome in clinical studies. (*Status: In progress.*)

Figure 1: Journal Publications that Resulted from NIH Support, By Goal (to 20131101)

[Content to be added at a later date.]

CONCLUSION

[Content to be added at a later date.]

APPENDIX A: BIBLIOGRAPHY OF NIH-SUPPORTED PUBLICATIONS SINCE 2007

This bibliography is arranged alphabetically, citing the funded author as well as other authors also funded by NIH since 2007. Authors listed in bold print have grants that are classed as Down syndrome grants, not Down syndrome related (e.g., Alzheimer disease) grants, or one of their cohorts under study is a group of individuals with Down syndrome and/or their families. Each citation is listed only once and only under one category.

A: Pathogenesis and Disease Progression

(Total of 135 as of 20131118)

A Abbeduto L, Warren SF, **Conners FA**. Language development in Down syndrome: from the prelinguistic period to the acquisition of literacy. 2007. *Mental Retard Dev Disabil Res Rev.* 13(3): 247-61. PMID: 17910087.

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APPENDIX B: INPUT INTO DEVELOPMENT OF THE REVISED PLAN

Request for Information: 2012

Request for Information (RFI): Invitation to Comment on the Down Syndrome Research Plan Released in 2007

Notice Number: NOT-HD-12-026

Update: The following update relating to this announcement has been issued:
[October 15, 2012 - See Notice NOT-HD-12-033. Notice of Response Date Extension.](#)

Key Dates

Release Date: August 24, 2012

Response Date: (Extended to November 19, 2012 per [NOT-HD-12-033](#)), Originally October 17, 2012

Issued by

[Eunice Kennedy Shriver National Institute of Child Health and Human Development \(NICHD\)](#)

Purpose

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) recognize that the Down Syndrome Research Plan released in 2007 is now in need of evaluation and updating. As part of this process, NICHD and the Trans-NIH Down Syndrome Working Group welcomes comments from the public concerning the effectiveness of the Plan, its accomplishments, and its remaining gaps, and welcomes suggestions concerning new future research objectives.

Background

The mission of the National Institutes of Health (NIH) is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce the burden of illness of disability.

Part of the mission of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), a component of NIH, is to ensure that all children have the chance to achieve their full potential for healthy and productive lives.

Research on lifelong disorders, such as Down syndrome, has been a fundamental part of the NICHD's mission since the Institute was established almost 50 years ago. Down syndrome usually results from three copies of the entire of human chromosome 21 (Trisomy 21) and occurs in 1:691 live births each year in all races and economic groups in the United States.

To build on this research foundation and coordinate Down syndrome research, the NIH Director at that time, Dr. Elias Zerhouni, asked the NICHD to take the lead in gathering together program scientists from Institutes across the NIH to form a Trans-NIH Down Syndrome Working Group.

The charge to this group was to coordinate ongoing research already supported by the NIH related to Down syndrome and to enhance new, NIH-supported research efforts based on identification of the areas of greatest scientific opportunity, especially as they related to the development of future treatments.

Throughout 2007, the Working Group met with members of the scientific community and representatives from national organizations that focus on Down syndrome to discuss research successes and gaps in knowledge. The Plan was developed by the Working Group, with input from the outside scientific and family communities, at the request of Congress in the Labor-HHS-Education Appropriations legislation for fiscal year 2007, focusing specifically on genetic and neurobiological research relating to the cognitive dysfunction and the progressive late-life dementia associated with Down syndrome. The purpose of the plan was to build upon ongoing NIH-supported research relating to Down syndrome to reflect the changing lives of individuals and families affected, and to take advantage of emerging scientific opportunities. By organizing the research objectives into groupings according to subject area and timeframes, the plan served to inform the Down syndrome community of NIH's goals for moving ahead in this area, fostering collaborations between NIH and other agencies and groups. A draft of the plan was released for public input; comments were incorporated as appropriate into the final plan.

The Research Plan included short-, medium-, and long-term research objectives in five major areas: Pathophysiology of Down Syndrome and Disease Progression; Diagnosis, Screening, and Functional Measures; Treatment and Management; Living with Down Syndrome; and Research Infrastructure. For details of the research plan, see https://www.nichd.nih.gov/publications/pages/pubs_details.aspx?pubs_id=5695.

The broader Down syndrome community acted quickly to advance these research objectives. The NICHD and the National Institute on Aging published a Funding Opportunity Announcement ([RFA-HD-09-028](#) (Factors Affecting Cognitive Function in Adults with Down Syndrome (R01))) in 2009 and funded two longitudinal studies examining and identifying biomarkers predictive of risk for progression to dementia in adults with Down syndrome. In addition, three Program Announcements entitled Understanding Co-Morbid Conditions in Adolescents with Intellectual and Developmental Disabilities were released by the NICHD in 2011 for the R01, R21, and R03 mechanisms, respectively ([PA-11-039](#), [PA-11-040](#); [PA-11-041](#)).

Two meetings were held in 2010 that focused on the immediate need for certain research resources: Down Syndrome Registry Meeting, sponsored by the National Down Syndrome Society in September, 2010; and Down Syndrome: National Conference on Patient Registries, Research Databases, and Biobanks, sponsored jointly by the NICHD and the Global Down Syndrome Foundation in December, 2010. As a result of this latter meeting, two Requests for Information (RFIs) were released to solicit responses from the public at large, the scientific research community, and interested advocacy and self-advocacy communities: [NOT-HD-11-002](#) (Needs For and Impediments to the Development of a Research Database to Facilitate Down Syndrome Research) and [NOT-HD-11-001](#) (Acquisition, Processing, Storage, and Distribution of Human Brain and Other Tissues to Advance Understanding and Treatment of Down Syndrome).

In response to another recommendation that arose from these meetings, the NICHD and the Trans-NIH Down Syndrome Working Group formed the Down Syndrome Consortium, which held its first meeting in September 2011. This group represents a public-private partnership with representation from major Down syndrome researchers, advocacy and medical groups, federal partners, and others to facilitate an exchange of information on research on Down syndrome.

Investigator-initiated research proposed since the release of the Research Plan has focused on each of the areas identified in the Research Plan, and a number of investigators new to Down syndrome research are currently engaged in studies the Plan's objectives. For the purpose of updating the Research Plan, the NICHD invites the research, medical, advocacy, self-advocate, and family communities to comment on their perceptions of the progress made in each of these areas over the last five years, and on existing gaps that remain, so that the Trans-NIH Down Syndrome Working Group can identify its research directions for the next five years. Comments addressing specific research objectives and indicating a time frame for new research objectives would also be helpful.

Information Requested

Any input regarding the Research Plan is welcome, especially comments on the following topics:

- General discussion of how well the Research Plan has helped the field.
- The objectives that have been particularly productive or have been successfully achieved.
- Objectives that have a higher or lower priority to expedite research, including possible basic, clinical, or translational focus approaches for these objectives.
- New or persistent gaps in the present Plan.
- New opportunities for research focus not covered in the present Plan.

How to Submit a Response

Responses will be accepted until October, 17, 2012. All responses must be submitted via email to DownSyndrome@mail.nih.gov. **Please include the notice number, NOT-HD-12-026, in the subject line and include your complete contact information with your response.** All submissions will be considered in revising the Research Plan. Submitted information will not be considered confidential.

NICHD will use the information submitted in response to this RFI at its discretion and will not provide comments to any responder's submission. However, responses to the RFI submitted may be reflected in future solicitation(s). NICHD may contact any responder for the sole purpose of enhancing NICHD's understanding of your RFI submission. The information provided will be analyzed and may appear in reports. Respondents are advised that the Government is under no obligation to acknowledge receipt of the information received or provide feedback to respondents with respect to any information submitted. No proprietary, classified, confidential, or sensitive information should be included in your response. The Government reserves the right to use any non-proprietary technical information in any resultant solicitation(s).

Inquiries

Please direct all inquiries to:

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Chair, Trans-NIH Down Syndrome Working Group

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Summary of Responses to RFI

To track more easily how the responses and recommendations for the update to the Research Plan have been incorporated into the Goals and Objectives, the responses have been grouped according to each of the Plan's Goals. Many of the suggestions were made by more than one respondent.

Several submissions commented about the lack of funding for Down syndrome research. One overall goal of the revised and updated NIH Research Plan on Down Syndrome, and the establishment of *DS-Connect*TM, is to provide direction for the field, necessary research resources, thereby increasing the numbers of excellent research grant applications that are funded. Another overarching comment in several responses requested a trans-NIH initiative on Down syndrome; this concept is beginning to be discussed by the Down Syndrome Consortium and in other forums.

Pathophysiology of Down Syndrome and Disease Progression

- Explore more research on the genetic and environmental factors affecting those with Down syndrome, including the role of specific chromosome 21 genes – *Agree, see A.1, A.8 revision*
- Using Down syndrome research to inform other intellectual and developmental disabilities, and vice versa – *Agree, see A.2, A.5*
- Continue proteomic, transcriptomic, phenomic and metabolomics research – *Agree, see A.3*
- More research is needed on Down syndrome in the prenatal period, including better estimates of fetal loss – *Agree, see A.8*
- More research needs to be conducted that protect those with Down syndrome against certain cancers and heart disease – *Agree, see A.10*

- Develop induced pluripotent stem cells for Down syndrome research – *Agree, see A.11*

Screening, Diagnosis, and Functional Measures of Down Syndrome-Related Conditions

- Develop molecular and cognitive phenotypes for Down syndrome – *Agree, see B.1, 3, 4*
- Further develop cognitive assessment instruments – *Agree, see B.2*
- Better assess the variations in behavioral and cognitive disorders in Down syndrome – *Agree, see B.3*
- Encourage researchers to incorporate quality of life measures in clinical trials involving people with Down syndrome – *Agree, see B.6*
- Develop and use less invasive technologies for correlation with cognitive ability – *Agree, see B.8*

Treatment and Management

- Expand research on comorbid conditions associated with Down syndrome, including autism – *Agree, see C.1. Note that updating data on the prevalence of comorbid conditions may fall more within other agencies' purviews.*
- Consider building a system of classification and measurement for the comorbid conditions commonly associated with Down syndrome – *Agree, see C.1*
- Expand research on effective treatments and therapies for various conditions associated with Down syndrome, including behavioral and pharmacologic therapies – *Agree, see C.1,2, 3, 4 and new Section D. Note that several respondents recommended specific therapies to research; these are encompassed in this broader category.*
- Review the scientific rationale for use of existing treatments in people with Down syndrome – *Agree, see C.2*
- Test appropriate complementary and alternative medicine treatments in people with Down syndrome – *Agree, see C.2*
- Research on improving cognition in people with Down syndrome should be the major focus of the Research Plan – *Agree in part, it is a major focus, but given the other health issues in the Down syndrome population, it is not the sole focus, see C.3, 4, 5*
- Explore repurposing drugs currently used by people with Alzheimer's disease for people with Down syndrome; support clinical trials of these therapies where appropriate – *Agree, see C.2, 4, E.8*
- Develop additional measures to assess non-verbal communications – *Agree, see C.6, E.9*
- Expand research on language development and educational strategies to help people with Down syndrome learn, and behavioral supports – *Agree, see C. 7, 8*
- Support innovative efforts to increase physical fitness for obesity prevention and cognitive improvement – *Agree, see C.5, 6, 8*

- NIH should support cross-disciplinary, collaborative research – *Agree, see C.10*
- Develop a website to share research-related information about Down syndrome – *Agree, see C.11*

Down Syndrome and Aging

- Explore the links between Down syndrome and Alzheimer's disease, including why a higher proportion of people with Down syndrome develop dementia – *Agree, see D.1*
- Support research on the impact of aging on physiologic and cognitive processes in people with Down syndrome, specifically including their organ systems – *Agree, see D.1*
- Support research on how families of people with Down syndrome can best manage life transitions, find educational and health services, and care for those individuals as they age – *Agree, see D.4*

Research Infrastructure

- Increase collaboration with the Down syndrome community – *Agree, see E.1*
- Expand the population statistics collected on Down syndrome – *Agree in part, since this is CDC's purview, but see E.2*
- Collect data on differential survival rates among sub-populations of people with Down syndrome – *Agree, see E.2*
- Support longitudinal research on the risk factors and trajectory of psychopathology in people with Down syndrome – *Agree, see E.3*
- Develop a cohort for studies on adults with Down syndrome – *Agree, see E.3, 5*
- Expand the availability to researchers of mouse models for Down syndrome – *Agree, see E.4*
- Develop and support a Down syndrome registry and database – *Agree, see E.5*
- Make a minimal Down syndrome dataset available to the research community – *Agree, see E.5*
- Develop and support a brain and tissue bank/biorepository for research on Down syndrome – *Agree, see E.6*
- Develop a standardized sample collection and processing methodology – *Agree, see E.6*
- Consider the development of a Down syndrome biomarker initiative – *Agree, see E.7*
- Include more people with Down syndrome in clinical trials – *Agree, see E.8*
- Develop standardized best practices to assess the health of people with Down syndrome – *Agree, see E.9*
- Establish a state-by-state research infrastructure – *The NIH is not in a position to support this at this time, but see E.10*

- Expand collaboration of NIH Institutes and Centers on Down syndrome research – *Agree, see E.10*
- Increase the number of young scientists who choose careers related to Down syndrome research – *Agree, see E.11*
- Explore the use of neuroimaging methods for Down syndrome research – *Agree, see E.14*

Responses to Public Comments on Draft Plan

TBD

APPENDIX C: RESEARCH-RELATED MEETINGS SINCE 2007

Conference

Sponsored by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the Global Down Syndrome Foundation (GDSF)

Down Syndrome: National Conference on Patient Registries, Research Databases, and Biobanks

December 2–3, 2010

<http://www.nichd.nih.gov/about/meetings/2010/Pages/120310.aspx>

Conference

Resulting Publication:

Busciglio, J., Capone, G., O’Bryan, J.P., Gardiner, K.J. 2013. Down Syndrome: Genes, Model Systems, and Progress Toward Pharmacotherapies and Clinical Trials for Cognitive Deficits. *Cytogenet Genome Res* 141(4):260-71. DOI:10.1159/000354306.

<http://www.ncbi.nlm.nih.gov/pubmed/24008277>.

Workshop

Advancing Treatments for Alzheimer’s Disease in Individuals with Down Syndrome

April 16–17, 2013

Bolger Conference Center

Potomac, Maryland

Executive Summary

The workshop “Advancing Treatments for Alzheimer Disease in Individuals with Down Syndrome” was held April 16-17, 2013 in the Washington, D.C. area to bring the Alzheimer’s disease (AD) and Down syndrome (DS) research and advocacy communities together in dialogue to advance the development of treatments for AD in individuals with DS. Sponsored by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Institute of Neurological Disorders and Stroke (NINDS), the National Institute on Aging (NIA), all within the National Institutes of Health (NIH), as well as the Down Syndrome Research and Treatment Foundation (DSRTF) and Research Down Syndrome (RDS), the workshop was convened to integrate current research activities, research resources, and future opportunities to inform development of therapies.

Specific goals included the following:

- Develop a research agenda for advancing treatments for AD in DS.
- Coordinate NIH efforts that will inform updates to the NIH Research Plan on DS (related to aging and dementia in individuals with DS).
- Help inform the Administration for Community Living's implementation of the National Alzheimer's Project Act's (NAPA) Plan specifically with regard to special populations likely to acquire AD (e.g., individuals with DS). (For plan details, see <http://aspe.hhs.gov/daltcp/napa/NatlPlan.shtml>).

Approximately 60 participants and speakers focused on five topic areas: Disease Mechanisms; Model Systems for the Study of Connections between DS and AD; Cognitive Outcome Measures; Biomarkers; and Developing Therapeutics. Each session was preceded by a series of specific questions for each speaker, panel members, and other participants to address in summary discussion sessions. These sessions were augmented by presentations on NIH Resources to Inform Treatment Goals.

At the conclusion of the meeting, the co-chairs for each session topic were asked to summarize the discussion, focusing upon three underlying questions about the research topic area of their session:

- What are the **strengths** and **weaknesses** of strategies currently being undertaken?
- What can be done **right now**?
- What are the **long-term** objectives and **how can we get there**?

The following represents a summary of their conclusions.

Strengths of Current Strategies

Trisomy 21 (Down Syndrome; DS) is a genetic risk for AD with a well-defined, but complex, set of modifier genes and environmental factors that has strong existing genetic models in both human and mouse and new emerging models such as induced pluripotent stem cell (iPSC) and other model organisms, such as rats.

Currently, the DS research community is broadly focused, but small, and has the opportunity to expand into new collaborations with the AD research community and into research avenues to study AD in DS.

The current research community already benefits from cross-sectional and longitudinal studies that include various imaging modalities and targets in clinical trials that benefit from leveraging resources available within Alzheimer's Disease Research Centers (ADC) sites, funded by NIA.

Weaknesses of Current Strategies

There have been few collaborative efforts to recruit the limited number of individuals with DS available at any given site into longitudinal studies that focus on aging. These studies would

allow investigators to make comparisons among adults who are younger and have had a much different life experience from older adults with DS.

There are insufficient research resources from humans and other model systems because of the limited availability of many of the newer mouse and cell models, common substrates, and common reagents. There is a real need to combine virtual and physical biorepositories, including brain banking efforts.

There is a lack of consensus among investigators concerning baseline assessments of clinical measures, outcomes, or testing strategies in model systems and human beings.

The research community lacks measures that are feasible throughout the lifespan, are applicable to a wide population, can be done in a short time frame, are sensitive to a broad range of functional levels, and are sensitive to decline over a short period of time, as seen in DS. Although some test batteries have been developed to assess cognitive function in DS, few of these tools have been validated for adults with DS with cognitive decline. Hence, there is a critical need for longitudinal studies to gather natural history data and to determine the effects of interventions that are based on a minimal dataset with common data elements.

Things To Be Done Right Now

Investigators could inventory current and planned studies that involve cognitive outcome measures in the aging DS population to accelerate research initiatives and to share data among existing and new research groups engaged in longitudinal studies that include a number of subjects of different age ranges, demographic features, and levels of function.

Investigators could use cross-sectional data to understand the trajectory of DS cognition and behavior, particularly among 10 to 40 year olds of both genders and couple this with studies of early neuronal loss and dysfunction in AD via imaging studies.

Investigators could utilize rat and iPSC models for DS and AD to develop better systems to predict drug responses in humans. They could begin “humanizing” mice by creating transgenic mice with the human versions of critical genes involved in AD pathogenesis such as *β-amyloid precursor protein (APP)*, *tau*, *β-APP-Cleaving Enzyme complex (BACE)*, *γ-secretase*, and *presenilin 1* and *presenilin 2 (PS1 and PS2)*.

Investigators could develop a minimum dataset of co-morbid factors like sleep apnea, gait disturbance, obesity, mother’s age at birth, etc. to study in all subjects with DS. This dataset could be used to develop mouse and human tasks that could measure cognitive and other functional abilities with age.

Longer Term Objectives

The majority of participants agreed that building on existing Alzheimer’s Disease Centers (ADCs) and the Alzheimer’s Disease Neuroimaging Initiative (ADNI) infrastructure, a consortium of NIH, FDA, industry, foundations, and research and advocacy communities could be created to take findings into the clinics. Such a consortium could develop consensus on two or three key measures of basic domains such as memory, learning and delayed recall that could

bring research groups together in longitudinal studies that focus on aging. Such a group would need to develop core functional and adaptive behavior measures through a pilot study to pick key measures and compare them across different groups throughout the lifespan. It would need to agree on a gold standard for what constitutes mild cognitive impairment and AD in DS that includes definitions that are feasible for the average clinician.

Such a consortium could engage the National Alzheimer's Project Act (NAPA) Federal Advisory Committee, leaders in the AD research community, families, and the disability community at large to assist with recruitment and education of special populations in the importance of research involvement and participation. This could include engagement of the research community to pursue prevention and treatment strategies by capitalizing on the unique opportunity presented by DS to understand AD. Primary care physicians with expertise in caring for individuals with DS could also be instrumental in such recruitment strategies.

APPENDIX D: RELEVANT WEBSITES

- **A to Z Topic: Down Syndrome:** *Eunice Kennedy Shriver* National Institute of Child Health and Human Development:
<http://www.nichd.nih.gov/health/topics/down/Pages/default.aspx>
- **The Down Syndrome Consortium:** <http://downsyndrome.nih.gov/Pages/default.aspx>
Note: member organizations' sites are live links
- **DS-Connect™: The Down Syndrome Registry:**
<http://downsyndrome.nih.gov/registry/Pages/default.aspx>
- **National Institutes of Health Research Plan on Down Syndrome (2007):**
http://www.nichd.nih.gov/publications/pubs/Documents/NIH_Downsyndrome_plan.pdf
(Note: The 2007 Research Plan includes a brief history of research on this condition, not repeated in the 2013 Plan)

APPENDIX E: CONGRESSIONAL DIRECTIVES ON DOWN SYNDROME SINCE 2007

Fiscal Year 2014 (Senate Report 113-071)

Down Syndrome – The Committee applauds NIH for the establishment of the Down Syndrome Patient Registry. The Committee urges continued investment and development of the registry to fully realize its potential as a tool to stimulate meaningful clinical trials and research. The Committee recognizes that investing in Down syndrome-focused research has the potential to benefit many other diseases and conditions such as Alzheimer’s disease. Therefore, the Committee urges NIH to seek public-private partnerships aimed at developing preventive therapies for the dementia associated with both Down syndrome and Alzheimer’s disease. The Committee remains troubled by the stagnant number of investigator-driven research awards given in the area of Down syndrome and supports efforts to increase the Federal investment. The Committee requests a status update in the fiscal year 2015 congressional budget justification. The Committee urges the NIH to continue to utilize the Down Syndrome Consortium as it updates and implements the NIH Down Syndrome Research Plan.

Fiscal Year 2013 (Senate Report 112-176)

Down Syndrome – The Committee commends NIH for its ongoing efforts to implement the NIH Down Syndrome Research Plan and for establishing the NIH Down Syndrome Consortium, which is focused on facilitating a dialogue between trans-NIH Institutes and the Down syndrome patient community. Increased Federal funding for translational research is important, and investing in Down syndrome-centered research has the potential for benefiting many other diseases and conditions such as Alzheimer’s disease. The Committee encourages NIH to increase the amount invested in investigator-initiated research grants and plan for the development of the Down syndrome clinical database, research registry, and biobank. NIH is also urged to establish workshops and mentoring programs to encourage young researchers and scientists to successfully pursue NIH grants for Down syndrome research.

Fiscal Year 2012 (Senate Report 112-084)

(Did not include a directive to the NIH regarding Down syndrome.)

Fiscal Year 2011 (Senate Report 111-243)

(Did not include a directive to the NIH regarding Down syndrome.)

Fiscal Year 2010 (Senate Report 111-066)

Down Syndrome - The Committee commends the NIH for creating the NIH Down Syndrome Working Group to develop the NIH Research Plan for Down syndrome. However, the Committee is concerned with the implementation of the plan since its release in January 2008. The Committee requests that the NIH report to the Committees on Appropriations of the House of Representatives and the Senate by September 30, 2010, on the quantity and dollar amount of Down syndrome research grants awarded since the release of the plan, including those awarded

through funds made available by the American Recovery and Reinvestment Act, and how all such grants awarded meet the short- and long-term goals of the plan. In addition, the Committee urges the NIH to pursue public-private partnerships, when available, to help leverage the overall research spent on Down syndrome.

Fiscal Year 2009 (Senate Report 110-410)

(Did not include a directive to the NIH regarding Down syndrome.)

Fiscal Year 2008 (Senate Report 110-107)

Down Syndrome – The Committee is deeply concerned by the significant decrease in funding for Down syndrome research since fiscal year 2003, and it strongly urges the NIH to increase its investment in this area. Due to recent studies and advances, the Committee believes that further research into how to successfully reduce the many adverse health effects of Down syndrome, including eradicating all the ill effects of the extra chromosome 21 of Down syndrome, is an emerging area of study that deserves NIH’s immediate attention. The Committee urges the Director to take note of recent advances in the neurobiology of Down syndrome, especially concerning the structure and function of neural circuits that mediate cognition. These advances point to Down syndrome as a fertile area for research investments that could lead to effective treatments for cognitive difficulties in both adults and children with this disorder. Because the responsibility for researching Down syndrome rests with multiple Institutes, the Committee notes that it is an ideal candidate for a trans-NIH initiative. The Committee requests an update on these efforts in the fiscal year 2009 congressional budget justifications.