

Down Syndrome Directions

**The National Institutes of Health
Research Plan on Down Syndrome**



National Institutes of Health
Turning Discovery Into Health

Down Syndrome Directions

**National Institutes of Health Research
Plan on Down Syndrome**

U.S. Department of Health and Human Services

National Institutes of Health

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

Significant progress has been made in research on Down syndrome since the first *National Institutes of Health (NIH) Research Plan on Down Syndrome* was published in October 2007. This 2014 revision takes into account extensive input from the Down syndrome community, including researchers, constituency organizations, and individuals with Down syndrome and their families. This input and how it has been incorporated into the final plan are summarized in [Appendix B](#). Once again, the Plan is organized into five major research goals:

- Pathophysiology of Down Syndrome and Disease Progression
- Down Syndrome-Related Conditions: Screening, Diagnosis, and Functional Measures
- Treatment and Management
- Down Syndrome and Aging
- Research Infrastructure

Included within each of these goals are more specific objectives designed to move forward these areas of research. Notably, because more people with Down syndrome are living longer lives, new research questions are emerging, warranting a new goal, *Down Syndrome and Aging*, which, in conjunction with *Treatment and Management*, replaces the original category *Living with Down Syndrome* from the 2007 plan.

The 2014 revised Plan also provides an extensive bibliography ([Appendix A](#)) of NIH-supported publications since 2007 to provide concrete evidence of research advances made since the original plan was published. These research articles are grouped according to each of the research goals in the revised Plan to track progress in those areas. Summaries of the major conferences and workshops held since 2007 are included in the [Appendix C](#), along with links to [helpful NIH websites](#) and [congressional report language](#) that demonstrates the deep interest of Congress in Down syndrome research.

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) expanded a major contract to develop, characterize, and produce mouse models for cytogenetic disorders, such as Down syndrome (including the Ts65Dn mouse), and renewed 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 specifically on research registries, databases, and biological repositories (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 and international 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 the Consortium website (<http://downsyndrome.nih.gov>); 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 Consortium, as well as the broader 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, researchers, health care providers, and industry 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 the draft 2014 Research Plan. In March 2014, a draft Plan was posted for public comment; the

responsive feedback from the Down syndrome community—families, clinicians, and researchers—also has been incorporated into this final version, *Down Syndrome Directions: The NIH Research Plan on Down Syndrome*.

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 *NIH Research Plan on Down Syndrome* so that NIH ICs could start working toward common Down syndrome research goals (http://www.nichd.nih.gov/publications/pubs/Documents/NIH_Downsyntaxe_plan.pdf).

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 C](#)), 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 font**. The status of an objective is noted in parentheses 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 as [Appendix A](#). These citations are organized by primary goal and listed alphabetically by the first NIH-funded investigator's 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 full 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; include testing on mice at different stages of development and decline. (*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, microtubule-associated protein 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. Study the biochemistry and cell biology of lysosomal and autophagy pathways in animal models and humans with Down syndrome. (*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 and signaling pathways for growth factors** in humans with Down syndrome and in animal models (including mechanisms of trafficking and amyloid-beta [Abeta] production, degradation, and clearance); study the biochemistry of tau proteins, the development of tau pathology, and the biochemical evolution of tau-containing neurons in animal models and humans with Down syndrome compared to those seen in humans with Alzheimer's disease. (*Status: In progress.*)

Longer Term Objectives

7. Using standardized techniques and measurements and advanced mapping and network analysis techniques, undertake a systematic **analysis of the development of key brain structures and brain circuits** 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 (e.g., differences in telomeric length for mothers, maternal and paternal age, and health disparities across the lifespan), cognitive function or decline, 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 with Down syndrome. *Expand research on Down syndrome in the prenatal period, including the impact of prenatal maternal supplementation, and 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 **genetic and molecular factors** (at the single-cell level and the entire genome) that appear to protect individuals with Down syndrome from some types of cancers and heart disease, and which may be protective in the subset of individuals with Down syndrome who do not develop Alzheimer's disease-related dementia.* (*Status: In progress.*)
11. *Support the development of **induced pluripotent stem cells (iPSCs)** from individuals with Down syndrome to explore the potential phenotypic variability that arises from differential expression of genes in the Down syndrome critical region or in the rest of the genome. Consider establishing an integrated database for existing Down syndrome iPSCs that includes methods of development, characteristics, and properties; such a database may be utilized to study molecular and cellular processes, and for translational studies to develop and test pharmaceuticals.* (*Status: In progress.*)
12. *Explore whether **nanotechnology and other small molecule approaches** can be used to ascertain developing neuropathologies in Down syndrome.* (*Status: Yet to begin.*)

B: DOWN SYNDROME-RELATED CONDITIONS: SCREENING, DIAGNOSIS, AND FUNCTIONAL MEASURES

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 for medical, cognitive, and behavioral conditions related to Down syndrome.

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 and a core set of standardized tests and measures that can be assessed in clinical research on Down syndrome (e.g., nonverbal 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;
 - *Use Magnetic Resonance Imaging (MRI) and micro Positron-emission tomography (PET) imaging in Down syndrome mouse models to help align human and animal model studies; and*
 - Develop measures and tests that assess the same cognitive processes *at different stages of development* in both mice and humans (such as discriminative taste aversion).

(*Status: In progress.*)
3. *Develop more **advanced phenotyping tools** for all domains of function and organ system involvement in Down syndrome, such as assessment of sleep, cardiopulmonary status, gastrointestinal function, endocrine function, immune and hematological function, skeletal involvement, nonverbal problem solving, language and communication, adaptive function, and executive skills.* (*Status: In progress.*)
4. **Link cognitive phenotype of Down syndrome to validated developmental measures**, including defining speech and language, behavioral, and psychological abnormalities. Use MRI, functional MRI (fMRI), and diffusion-tensor imaging (DTI), among other emerging imaging modalities, in conjunction with specific neuro-cognitive assessment measurements, 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 spectrum disorder.* (*Status: In progress.*)
5. Establish whether and how synaptic dysfunction correlates with abnormal cognition to **determine the best phenotype/genotype functional markers** for therapeutic screening. (*Status: In progress.*)

6. **Identify the clinical, cognitive, genetic, and biochemical biomarkers of Alzheimer's disease in Down syndrome for use in detection and management of disease progression.** (Status: In progress.)
7. **Develop and 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

8. **Develop additional outcome measures** for use in clinical trials to offer supplementary options for assessing change across domains of functioning, *including cognitive neuroscience measures, measures of nonverbal communication, measures to assess other organ system involvement in Down syndrome, and measures of quality of life, including patient-reported outcomes.* (Status: In progress.)
9. **Develop standard clinical protocols using newly established measures;** disseminate them to the Down syndrome clinical research community. (Status: Yet to begin.)
10. 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, frontal and parietal cortical, cerebellar, and cognitive function** in people with Down syndrome to enhance current cognitive batteries at specific stages across the lifespan. (Status: In progress.)
11. *In addition to improved imaging technologies, explore the application of less- or noninvasive 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 later in life, 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, also can provide information that allows researchers to design biobehavioral interventions for improving cognition and daily-life functioning. Ultimately, this research may provide the evidence base for practice guidelines established by the professional medical and behavioral societies.

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 across the lifespan 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 lapsed 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, regression) and their interactions with cognitive function*
- *Pulmonary hypertension*
- *Atypical thyroid levels and thyroid-related diseases*
- *Celiac disease*
- *Gastrointestinal structural and functional defects*
- *Hirschsprung disease*
- *Atlanto-axial instability*
- *Endocrine function and Type 1 diabetes*
- *Immune system dysfunction*
- *Obesity, metabolic dysfunction, and 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. *For example, additional evidence is needed on outcomes of surgical and other treatments for obstructive sleep apnea, use of stimulant and non-stimulant medications in children with Down syndrome and other conditions (attention deficit disorder, autism spectrum disorder), or mental health conditions. 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, antioxidants, and other dietary approaches or nutritional supplements** in individuals with Alzheimer's disease and/or Down syndrome, and evaluate whether the function of brain circuits involved in cognition is enhanced. *Also consider using these approaches for prevention studies in these populations. (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 deposition 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. Explore projects to **understand and improve sensory and motor skills** in individuals with Down syndrome, paying particular attention to whether and how sensory organ structure and function (e.g., vision, smelling, hearing, breathing, swallowing) are altered in persons with Down syndrome. *(Status: In progress.)*

7. Identify **effective interventions and educational strategies**, including the role of learning sign language early in life, to help children with Down syndrome process available linguistic input and enhance their communication skills, 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 (including siblings) may react to having family members 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 the research, *clinician*, and family communities, pending clinical trials, and *funding opportunities*. The site 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 of 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**, such as *Global Positioning Systems (GPS) and mobile 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 and other cellular functions, and develop targeted therapies to improve these functions in Down syndrome. The status assessments may include:

- Endocytosis and endosomal trafficking *in vivo* and *in vitro*;
- *Investigation of lysosomal and autophagosomal pathways; and*
- 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 disease in those with Down syndrome may also benefit those with Alzheimer's disease but without Down syndrome.

The emerging needs of people with Down syndrome as they age, and the impact on their families, warrant this 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. 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, *including consideration of lifestyle factors*, among different *age groups/subpopulations* of individuals with Down syndrome.

(Status: In progress.)

2. Explore the **impact and protective factors for age-related dementia**, including *complementary and alternative medicine products, exercise and diet*, and whether the **use of statins** (including at what stage they are prescribed) 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. Such studies should be aimed at producing sufficient data to show whether post-menopausal HRT reduces the cumulative risk for Alzheimer's disease, and if so, to inform the optimal time and duration for post-menopausal HRT use. (*Status: In progress.*)
4. *Identify factors (medical, intellectual, social, familial) that may be **protective for maximal independence and community inclusion**. Such work may include:*
 - *Participation by individuals with Down syndrome in higher education, employment, volunteer work; and*
 - *Lifestyle factors, such as close relationships.*
(*Status: In progress.*)
5. As the lifespans of individuals with Down syndrome continue to increase, investigate **the impact on families** of caring for them as they age. Such work may include:
 - Identifying the factors that lead to *effective functioning or challenges* 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; and
 - Research on the health (*including onset of Alzheimer's disease*) and lifespans of the parents and siblings, and the *health and educational attainment* of siblings of individuals with Down syndrome, particularly as affected by the intergenerational transmission of caregiving responsibilities, and how best to foster those transitions.
(*Status: In progress.*)

E: RESEARCH INFRASTRUCTURE

Shorter Term Objectives

1. **Establish and continue to develop 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 [Appendix D](#).*)

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. *Use population-based data whenever feasible. (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; and
 - Finding ways to reduce the cost of animal models to NIH-funded investigators.*(Status: Well underway.)*
5. Support **development of, and work in collaboration with the Down syndrome community to expand participation in, 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, [Appendix D](#).)*
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. Ultimately, DS-Connect[®] clinical information should be linked to one or more centralized tissue repositories. Consideration should also be given to linking a Down syndrome repository with the NIH NeuroBioBank and the existing Alzheimer’s Disease Brain Banks so that Down syndrome tissues can be compared to those obtained from individuals with Alzheimer’s disease and other disorders. (Status: In progress.)*
7. *Explore development of a **Down Syndrome Biomarker Initiative**, an integrated research project and shared repository for clinical, imaging, and other biomarkers, including data from recent animal and clinical studies. (Status: In progress.)*

8. Consider ways to **include participants with Down syndrome, including those of racial or ethnic minorities**, in NIH-funded clinical trials. NIH should review existing infrastructure, such as the Clinical and Translational Science Awards, *and* the Alzheimer's Disease Neuroimaging Initiative, 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 *or repurposed* medications on cognitive enhancement, daily function, or behavioral disorders;
 - Appropriate interventions for congenital heart disease, *leukemias*, and obstructive sleep apnea; and
 - 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 nonverbal children.* (Status: *In progress.*)
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 C.](#)) (Status: *Well underway.*)
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, and groups of genes or the entire chromosome 21 equivalent, 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, *integrated* 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. *Develop improved imaging methods for amyloid and diffuse plaque deposition.* (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. See DS-Connect[®], [Appendix D.](#)*)

Conclusion

In the seven years since the first NIH Research Plan on Down Syndrome was published, we have seen increased progress and commitment to this field of research, in large part due to its many stakeholders collaboratively working together in an unprecedented manner. The Down Syndrome Consortium will continue to serve a critical role, including as a source of potential partnerships to leverage all possible resources toward the goals outlined in the revised Plan.

Among other advances, improvements in cognition and learning in mouse models of Down syndrome are helping us to gain a better understanding of the potential links between Down syndrome and Alzheimer's disease. NIH recently published a new Funding Opportunity Announcement, Biomarkers of Alzheimer's Disease in Down Syndrome (<http://grants.nih.gov/grants/guide/rfa-files/RFA-AG-15-011.html>), to enable the identification of the longitudinal progression of Alzheimer's disease in adults with Down Syndrome using clinical, cognitive, imaging, genetic, and biochemical biomarkers. Several compounds have been developed which show great promise for attacking the protein that is associated with dementia and cognitive impairment, and which may be ready for human therapeutic clinical trials in the near future. These developments, and the encouraging fact that people with Down syndrome are living longer (estimates show that between 1960 and 2007 life expectancy increased by 456%)¹, warranted an entirely new section of the revised Research Plan, Down Syndrome and Aging.

In addition, the revised Plan calls for more research to better understand and treat comorbid conditions in individuals with Down syndrome, such as congenital heart disease, hearing and vision problems, celiac disease and gastrointestinal problems, thyroid dysfunction, immune disorders, and others. In studying these co-occurring conditions, increased attention to health disparities is necessary.

We also hope that the revised Plan will encourage even more young scientists to enter Down syndrome-related research fields, including working with individuals with Down syndrome and their families to improve our knowledge and potentially develop treatments. No one encouraged young investigators more than Dr. Mary Lou Oster-Granite, who was a major contributor not only to this revised Research Plan, but to the field as a whole; she has retired as chair of the NIH Down Syndrome Working Group and from public service at NIH—we already miss her leadership.

¹ Kucik JE, Shin M, Siffel C, Marengo L, Correa A; Congenital Anomaly Multistate Prevalence and Survival Collaborative. (2013.) Trends in survival among children with Down syndrome in 10 regions of the United States. *Pediatrics*, Jan;131(1): e27-36. PMID: 232482222; and Presson AP, Partyka G, Jensen KM, Devine OJ, Rasmussen SA, McCabe LL, McCabe ER. (2013.) Current estimate of Down syndrome population prevalence in the United States. *J Pediatr*, Oct;163(4): 1163-8. PMID 23885965.

While the recommendations in this second NIH Research Plan on Down Syndrome may seem ambitious, it is healthy to periodically reevaluate what our goals for the next few years should be. We hope to continue to work closely with the Down syndrome community to develop and support projects that lead to significant breakthroughs in the treatment and care of those living with Down syndrome.

—NIH Down Syndrome Working Group

Appendix A: Bibliography of NIH-Supported Publications Since 2007

This bibliography is arranged alphabetically by the last name of the NIH-funded author, which appears in **bold**. These are publications of results from grants classified as Down syndrome grants, not Down syndrome-related (e.g., Alzheimer's disease) grants; or, one of the 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

Highlights of Progress Since the 2007 Plan

- *Identified events that increase the likelihood of developing leukemia*
- *Increased understanding of the roles of specific microRNAs in myeloid differentiation*
- *Better defined the roles specific genes play in relevant phenotypes*
- *Further developed human neural progenitor cells and iPSCs from individuals with Down syndrome*
- *Developed methods to inactivate the extra copy of chromosome 21 in trisomic cell lines*
- *Better defined the profile of lipid metabolism in children at risk of cardiovascular disease*
- *Narrowed the region necessary for heart defects*
- *Identified some of the prenatal molecular signatures in amniotic fluid*
- *Better characterized the phenotypes in some mouse models*
- *Continued to investigate mitochondrial dysfunction*
- *Studied sleep issues in animal models*
- *Better characterized gastrointestinal malformations by race and ethnicity*

(Total of 133 as of December 2013)

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B: DOWN SYNDROME-RELATED CONDITIONS: SCREENING, DIAGNOSIS, AND FUNCTIONAL MEASURES

Highlights of Progress Since the 2007 Plan

- *Improved techniques for cell free nucleic acid detection in amniotic fluid and maternal blood*
- *Identified genotype-phenotype correlations in mouse models of Down syndrome*
- *Characterized the specific language deficits in Down syndrome*
- *Characterized measures of lipid function, body mass, and neurological function in Down syndrome*
- *Identified environmental and genetic modifiers of cardiac defects*
- *Characterized epidemiology of Down syndrome in the U.S.*

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C: TREATMENT AND MANAGEMENT

Highlights of Progress Since 2007 Plan

- *Discovered that some drugs and dietary supplements found to be successful in mouse models were not effective in individuals with Down syndrome*
- *Studied effects of environmental enrichment on neurogenesis*
- *Evaluated interventions to improve physical and emotional health in Down syndrome*
- *Studied how comorbid conditions influence neurodevelopment*
- *Studied effects of glial peptides on mitochondrial function*
- *Studied effects of agents that target specific neurotransmitters*

(Total of 84 as of December 2013)

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D: DOWN SYNDROME AND AGING (FORMERLY, LIVING WITH DOWN SYNDROME)

Highlights of Progress Since 2007 Plan

- *Better characterized the role of amyloid beta precursor protein (APP) in pathogenesis of dementia*
- *Better defined common effects of aging in people with Down syndrome*
- *Better defined relationship of shortened telomeric length and dementia*
- *Began amyloid imaging in adults with Down syndrome*
- *Found that families (including parents and siblings) of individuals with Down syndrome have better quality of life than families with a member who has another developmental disability*

(Total of 55 as of December 2013)

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E: RESEARCH INFRASTRUCTURE

Highlights of Progress Since 2007 Plan

- *Recompeted and reissued contracts for production of mouse models for Down syndrome and the brain and tissue repository*
- *Formed the Down Syndrome Consortium*
- *Launched DS-Connect®: The Down Syndrome Registry*
- *Held scientific meetings focused on needs of the research field*
- *Developed murine models of Down syndrome with greater coverage of syntenic regions on human chromosome 21*
- *Developed and validated a battery of cognitive tests to capture the range of effects of Down syndrome*

(Total of 17 as of December 2013)

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Appendix B: Input into Development of the Revised Plan

REQUEST FOR INFORMATION (RFI): INVITATION TO COMMENT ON THE DOWN SYNDROME RESEARCH PLAN RELEASED IN 2007 (ISSUED IN 2012)

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 Comorbid 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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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 research resources such as *DS-Connect*[®], 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 – *Agreed; revised*
- Using Down syndrome research to inform other intellectual and developmental disabilities, and vice versa – *Agreed; revised*
- Continue proteomic, transcriptomic, phenomic and metabolomics research – *Agreed; revised*

- More research is needed on Down syndrome in the prenatal period, including better estimates of fetal loss – *Agreed; revised*
- More research needs to be conducted on factors that protect those with Down syndrome against certain cancers and heart disease – *Agreed; revised*
- Develop induced pluripotent stem cells for Down syndrome research – *Agreed; revised*

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

- Develop molecular and cognitive phenotypes for Down syndrome – *Agreed; revised*
- Further develop cognitive assessment instruments – *Agreed; revised*
- Better assess the variations in behavioral and cognitive disorders in Down syndrome – *Agreed; revised*
- Encourage researchers to incorporate quality of life measures in clinical trials involving people with Down syndrome – *Agreed; revised*
- Develop and use less invasive technologies for correlation with cognitive ability – *Agreed; revised*

Treatment and Management

- Expand research on comorbid conditions associated with Down syndrome, including autism – *Agreed; revised. 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 – *Agreed; revised*
- Expand research on effective treatments and therapies for various conditions associated with Down syndrome, including behavioral and pharmacologic therapies – *Agreed; revised. Note that several respondents recommended specific therapies to study; these are encompassed in this broader category.*
- Review the scientific rationale for use of existing treatments in people with Down syndrome – *Agreed; revised*
- Test appropriate complementary and alternative medicine treatments in people with Down syndrome – *Agreed; revised*
- Research on improving cognition in people with Down syndrome should be the major focus of the Research Plan – *Agreed in part; it is a major focus, but given the other health issues in the Down syndrome population, it is not the sole focus*

- Explore repurposing drugs currently used by people with Alzheimer’s disease for people with Down syndrome; support clinical trials of these therapies where appropriate – *Agreed; revised*
- Develop additional measures to assess nonverbal communications – *Agreed; revised*
- Expand research on language development and educational strategies to help people with Down syndrome learn, and behavioral supports – *Agreed; revised*
- Support innovative efforts to increase physical fitness for obesity prevention and cognitive improvement – *Agreed; revised*
- NIH should support cross-disciplinary, collaborative research – *Agreed; revised*
- Develop a website to share research-related information about Down syndrome – *Agreed; revised*

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 – *Agreed; revised*
- Support research on the impact of aging on physiologic and cognitive processes in people with Down syndrome, specifically including their organ systems – *Agreed; revised*
- 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 – *Agreed; revised*

Research Infrastructure

- Increase collaboration with the Down syndrome community – *Agreed; revised*
- Expand the population statistics collected on Down syndrome – *Agreed in part; this is the Centers for Disease Control and Prevention’s (CDC’s) purview*
- Collect data on differential survival rates among sub-populations of people with Down syndrome – *Agreed; revised*
- Support longitudinal research on the risk factors and trajectory of psychopathology in people with Down syndrome – *Agreed; revised*
- Develop a cohort for studies on adults with Down syndrome – *Agreed; revised*
- Expand the availability to researchers of mouse models for Down syndrome – *Agreed; revised*
- Develop and support a Down syndrome registry and database – *Agreed; revised*

- Make a minimal Down syndrome dataset available to the research community – *Agreed; revised*
- Develop and support a brain and tissue bank/biorepository for research on Down syndrome – *Agreed; revised*
- Develop a standardized sample collection and processing methodology – *Agreed; revised*
- Consider the development of a Down syndrome biomarker initiative – *Agreed; revised*
- Include more people with Down syndrome in clinical trials – *Agreed; revised*
- Develop standardized best practices to assess the health of people with Down syndrome – *Agreed; revised*
- Establish a state-by-state research infrastructure – *The NIH is not in a position to support this recommendation at this time, but see Goal E*
- Expand collaboration of NIH Institutes and Centers on Down syndrome research – *Agreed; revised*
- Increase the number of young scientists who choose careers related to Down syndrome research – *Agreed; revised*
- Explore the use of neuroimaging methods for Down syndrome research – *Agreed; revised*

SUMMARY OF RESPONSES TO PUBLIC COMMENTS ON DRAFT PLAN – SEPTEMBER 2014

In addition to the many excellent comments received in response to the initial Request for Information (above), the comments on the draft of the revised research plan were equally thoughtful. These came from across the Down syndrome community, including members of the Down Syndrome Consortium, and families across the country.

Once again, the comments have been grouped according to goal; many were made by more than one respondent. Many of the objectives were edited to be responsive to nearly all of the substantive comments; the specific objectives that have been changed or added are noted after each comment.

Only a handful of comments are beyond NIH's purview, including the need for health care guidelines for people with Down syndrome of all ages, and up-to-date information for expectant couples. However, NIH hopes that the research envisioned within this plan will provide the evidence base that allows professional societies to update their practice guidelines in order to provide the best possible counseling and care.

Pathophysiology of Down Syndrome and Disease Progression

- Since cognitive-related outcomes decline as mice reach middle age, mouse models for Down syndrome should include aging as a parameter – *Agreed; see A.1*
- Study the biochemistry and cell biology of lysosomal and autophagy pathways in animal models and humans with Down syndrome – *Agreed; see A.4*
- Study the biochemistry of tau proteins and development of tau pathways in animal models and humans with Down syndrome – *Agreed; see A.6*
- Study the biochemical evolution of tau-containing neurons (neurofibrillary tangles) in humans with Down syndrome compared to that seen in Alzheimer’s disease – *Agreed; see A.6*
- Study signaling pathways for growth factors – *Agreed; see A.6*
- Undertake a systematic analysis of the development of brain structures during development in individuals with and without Down syndrome – *Agreed in principle; see A.7. NIH’s new Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative may be the best locus for this effort in the future.*
- Increase our understanding of the genetic, epigenetic, and environmental determinants that lead to differing presentations in individuals with Down syndrome, which are highly relevant to counseling and the development of therapeutic interventions – *Agreed; see A.8*
- Study determinants that contribute to birth and health outcomes including telomeric length for mothers, maternal and paternal age, and health disparities across the lifespan – *Agreed; see A.8*
- Include studies on the impact of prenatal maternal supplementation – *Agreed; see A.8*
- Include mothers and siblings without Down syndrome in longitudinal studies – *Agreed, as feasible; see A.8*
- Better understand the impact of Down syndrome throughout the lifespan – *Agreed; see A.8, E.3*
- Explore the genetic and molecular factors that may be protective in the subset of individuals with Down syndrome that do not develop Alzheimer’s disease-related dementia – *Agreed; see A.10; also added cognitive function or decline to A.8 for study of developing Alzheimer’s disease*
- Use induced pluripotent stem cells (iPSCs), with neurobehavioral characterization of individuals, to study molecular and cellular processes and for the basis of translational studies – *Agreed; see A.11*
- Consider establishing an integrated database for existing iPSCs for translational studies to develop and test pharmaceuticals – *Agreed, as feasible; see A.11*
- Explore whether nanotechnology and other small molecule approaches can be used to ascertain developing neuropathology – *Agreed; see A.12, E.15*

Down Syndrome-Related Condition: Screening, Diagnosis, and Functional Measures

- Linking mouse and human models of assessment is important – *Agreed; see B.2*
- Develop cognitive measures to assay neural function at early levels of development – *Agreed; see B.2*
- Add magnetic resonance imaging and micro-PET imaging in Down syndrome mouse models to better align human and animal model studies – *Agreed; see B.2*
- Develop and use more advanced phenotyping tools, particularly for nonverbal problem-solving, language and communication, adaptive function, and executive skills – *Agreed; see B.3 (new)*
- Link cognitive phenotypes of Down syndrome with validated measures, including the use of emerging imaging technologies – *Agreed; see B.4*
- Use imaging modalities in conjunction with specific neuro-cognitive assessment measures to assess cognitive function of individuals with Down syndrome – *Agreed; see B.4*
- Develop cognitive and other measures for the Down syndrome population, especially adults at risk for Alzheimer’s disease – *Agreed; see B.4, B.6 (new)*
- Include cognitive neuroscience measures as potential outcome measures in clinical therapeutic trials – *Agreed; see B.8*
- Develop additional outcome measures regarding nonverbal communication – *Agreed; see B.8*
- Develop standard protocols using established measures, and disseminate these to Down syndrome clinics – *Agreed; see B.9*
- Include frontal, parietal cortical, and cerebellar measures of cognitive function – *Agreed; see B.10*

Treatment and Management

- Support research aimed at developing therapies for cognition, comorbid psychological, neurobehavioral, and medical conditions – *Agreed; see C.1*
- Consider a trans-NIH workshop on building a system of classification and measurement that captures the combined role of comorbid medical, behavioral, and mental health conditions that contribute to the complexity of trisomy 21 – *Agreed; see C.1*
- Explore comorbid medical conditions such as leukemia, epilepsy, and thyroid disease – *Agreed; see C.1*
- Add research on regression to potential topics of research – *Agreed; see C.1*

- Include research on obesity in individuals with Down syndrome – *Agreed; see C.1*
- Include research on the gastrointestinal structure and functional defects, and Type 1 diabetes, in people with Down syndrome – *Agreed; see C.1*
- Study the impact of cholesterol, sleep issues, and epilepsy – *Agreed; see C.1, D.2*
- Further study a range of therapeutic interventions, including critical review of existing treatments – *Agreed; see C.2*
- Investigate communications enhancements – *Agreed; see C.7*
- Include research on the role of learning sign language early in life to improve communication later on for individuals with Down syndrome – *Agreed; see C.7*
- Emphasize intervention research regarding educational strategies and behavioral supports – *Agreed; see C.7, 8*
- Effective interventions and educational strategies should include weight management and exercise – *Agreed; see above*
- Examine the impact on the family of having a family member with Down syndrome – *Agreed; see C.9*
- Investigate lysosomal and autophagosomal pathways – *Agreed; see C.14*

Down Syndrome and Aging

- Explore risk factors for dementia – *Agreed; see D.1*
- Study aging patterns in different subpopulations of people with Down syndrome; these should include lifestyle factors – *Agreed; see D.1*
- Cognitive studies need to be longitudinal, including individuals with Down syndrome in their 20s through 40s – *Agreed, covered by D.1*
- Explore protective factors for age-related dementia, including reduction in cholesterol, low-fat diets, and nutritional supplements – *Agreed; see D.2, C.3*
- Include studies on cholesterol, weight control, and when to begin the use of statins – *Agreed; see D.2*
- Study the impact of quality of life issues, including protective factors (participation) that maximize adult independence – *Agreed; see D.4 (new)*
- Study why families of individuals with Down syndrome may effectively function or struggle – *Agreed; see D.5*
- Study the lifespans of parents of individuals with Down syndrome, considering the development of Alzheimer’s disease in the mothers – *Agreed; see D.5*
- Investigate the role of caretakers of people with Down syndrome – *Agreed; see D.5*

Research Infrastructure

- Include the input of self-advocates and families of people with Down syndrome to inform the research agenda – *Agreed; see E.1*
- Consider using population-based data whenever feasible – *Agreed; see E.2*
- Support and link a Down syndrome registry and biorepository – *Agreed; see E.5, E.6*
- Support and expand participation in DS-Connect[®] – *Agreed; see E.5*
- Connect brain and other tissue samples to clinical information – *Agreed; see E.6*
- Compare brain tissues from individuals with Alzheimer’s disease to those of individuals with Down syndrome – *Agreed; see E.6*
- Establish a national network of brain banks to collect tissues – *Agreed in principle; see E.6*
- Separate the Down syndrome contact registry and patient database – *Disagreed; the way DS-Connect[®] is designed, it is collecting medical data from individuals with Down syndrome in a secure database; the Professional Portal will be launched in the fall of 2014.*
- Develop centers of excellence on Down syndrome – *Disagreed; the NIH is not in a position to support centers at this time.*
- Enhance the inclusion of individuals with Down syndrome, including those of racial or ethnic minorities, in clinical trials – *Agreed; see E.8*
- Discuss the best mechanism for fostering cross-disciplinary and collaborative clinical research on Down syndrome – *Agreed; see E.10*
- Investigate imaging techniques for amyloid and diffuse plaque deposition – *Agreed; see E.14*

Other Comments

- Expand funding opportunities for research on Down syndrome – *Agreed in principle, given the current fiscal situation; see Conclusion for other approaches*
- Increase collaboration with other Federal agencies to complement current efforts and provide additional expertise – *Agreed; see Conclusion*
- Mention specific Down syndrome or Alzheimer’s disease professional or advocacy organizations – *Response: The NIH Down Syndrome Research Plan is and should be focused on research goals and objectives; however, the contributions of the members of the Down Syndrome Consortium and other parts of the Down syndrome community are recognized and appreciated; see Conclusion*

- The results of the 2013 Down syndrome/Alzheimer’s disease workshop should be more formally recognized by the National Alzheimer’s Project Act (NAPA) Advisory Council – *Response: While this is not within the purview of the Research Plan, the NIH Down Syndrome Working Group will continue to work with the Alzheimer’s disease community on research-related issues of mutual interest; for a summary of the workshop; see [Appendix C](#)*

Appendix C: Research-Related Meetings Since 2007

DOWN SYNDROME: NATIONAL CONFERENCE ON PATIENT REGISTRIES, RESEARCH DATABASES, AND BIOBANKS

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

December 2–3, 2010

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

Resulting Publication:

Oster-Granite ML, Parisi MA, Abbeduto L, Berline DS, Bodine C, Bynam D, Capone G, Collier E, Hall D, Kaeser L, Kaufmann P, Krischer J, Livingston M, McCabe LL, Pace J, Pefeninger K, Rasmussen SA, Reeves RH, Rubinstein Y, Sherman S, Terry SF, Whitten MS, Williams S, McCabe ER, Maddox WT. (2011.) Down syndrome: National conference on patient registries, research databases, and biobanks. *Mol Genet Metab*, Sept-Oct;104(1-2): 13-22.

WORKSHOP ON COGNITION IN DOWN SYNDROME: MOLECULAR, CELLULAR, AND BEHAVIORAL FEATURES AND THE PROMISE OF PHARMACOTHERAPIES

April 13-15, 2013

Resulting Publication:

Busciglio J, Capone G, O'Bryan JP, Gardiner KJ. (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

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 cells (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 comorbid 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 ADCs and the Alzheimer's Disease Neuroimaging Initiative (ADNI) infrastructure, a consortium of NIH, Food and Drug Administration (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

- *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
A to Z Topic: Down Syndrome:
<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 on this website.)
 - American Academy of Pediatrics
 - American Association on Intellectual and Developmental Disabilities
 - Association of University Centers on Disabilities
 - Down Syndrome Affiliates in Action
 - Down Syndrome Medical Interest Group
 - Global Down Syndrome Foundation
 - International Mosaic Down Syndrome Association
 - Jerome Lejeune Foundation
 - Lumind Foundation
 - National Down Syndrome Congress
 - National Down Syndrome Society
 - Research Down Syndrome
 - Self-Advocate
 - Special Olympics International
 - NIH Down Syndrome Working Group
 - *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
 - National Cancer Institute
 - National Heart, Lung, and Blood Institute
 - National Institute of Mental Health
 - National Institute of Neurological Disorders and Stroke
 - National Institute on Aging
 - National Institute on Minority Health and Health Disparities

- 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 2014 Plan)
- Medline Plus (National Library of Medicine, NIH):
<http://www.nlm.nih.gov/medlineplus/downsyndrome.html>

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.