NIH INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) Down Syndrome Research Plan

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Executive Summary

[In Progress]

Introduction

This plan builds upon earlier National Institutes of Health (NIH) research plans on Down syndrome (DS), published in 2007¹ and 2014,² and the 2018 research plan for the INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) Project.³ The previous NIH Down syndrome research plans have been integrated with the INCLUDE Project's goals and with extensive public input from the DS community to create a new *NIH INCLUDE Down Syndrome Research Plan*.

This new plan provides the research, clinical, and DS communities with an overall strategy to support the highest quality, targeted research that will address critical health and quality-of-life needs for individuals with DS and their families. Moreover, this plan represents the evolution of language toward more inclusion of people with DS and their families. For example, the plan refers to "people with DS" rather than "patients," and uses "co-occurring conditions" rather than "comorbidities." In keeping with NIH policy on inclusion in research across the lifespan⁴, this plan aims to demonstrate that research efforts should include people with DS of different ages, socioeconomic levels, and racial and ethnic diversity.

People with DS can have a higher incidence of certain chronic, health- or life-threatening conditions, but are highly protected from other conditions. This health conundrum generated the initial interest of Congress, which directed NIH to develop what became the INCLUDE Project. The breadth of co-occurring conditions covered by INCLUDE garnered involvement of 18 NIH Institutes, Centers, and Offices (ICOs), each contributing its expertise on those conditions. Not only will research into these co-occurring conditions improve the care and health of people with DS, but it could also lead to deeper understanding of these conditions in people who do not have DS, ultimately leading to treatments for the general population.

Research on the co-occurring conditions for people with DS does not happen in a vacuum; it builds on generations of basic research discoveries to develop an understanding of the biological and genetic underpinnings of DS and the wide variation in the conditions experienced by individuals with DS. NIH's goal is to prevent these conditions from reducing the capacity of people with DS to lead healthy and optimal lives.

The Goals and Objectives of the *NIH INCLUDE Down Syndrome Research Plan* are organized in a way that represents a hybrid of the two most recent previous Down syndrome plans. The *Down Syndrome Directions: The NIH Research Plan on Down Syndrome*, published in 2014, was organized into shorter term and longer term objectives under the themes of: Pathophysiology of DS and Disease Progression; DS-Related Conditions: Screening, Diagnosis, and Functional Measures; Treatment and Management; DS and Aging; and Research Infrastructure. The INCLUDE Project Research Plan, published in 2018, was organized into three components: conduct targeted, high risk-high reward, basic science studies on chromosome 21 and DS; assemble a large cohort of individuals with DS across the lifespan; and include individuals with

¹ <u>https://www.nichd.nih.gov/publications/product/331?from=&pubs_id=5695</u>

² <u>https://www.nichd.nih.gov/publications/product/441?pubs_id=5865</u>

³ <u>https://www.nih.gov/include-project/include-project-research-plan</u>

⁴ https://www.nia.nih.gov/Inclusion-Across-Lifespan-2020

DS in existing and future clinical trials. For this research plan, the information is organized around five broad themes:

- Basic Research
- Cohort Development/Epidemiology
- Clinical Research/Co-occurring Conditions
- Living and Aging with DS/Services Research
- Research Infrastructure and Tools

Within each of these themes, there may be subheadings to group related objectives. Each theme also has a Program Portrait to highlight an example of a specific research project that addresses the theme.

Portfolio Analysis

[In Progress]

Goals and Objectives: 2021 NIH INCLUDE Down Syndrome Research Plan

A. Basic Research

Our understanding of DS has significantly expanded since 2000, when investigators published the full DNA sequence of chromosome 21. It is now possible to identify all of the genes present in triplicate in those with DS and, ultimately, to understand the effects of having an extra copy of individual genes or clusters of genes. Today, researchers use model systems, tissues, and new technologies to study these effects.

Expand Basic Research Approaches

- Conduct mechanistic studies on the links between chromosome 21 and cognition, including identifying the genes involved in neurodevelopment, developmental signaling pathways, and multiple mechanisms of stress. Sequence the events that lead to abnormal dendritic (neuronal) spine development, including genetic and cellular aspects.
- Use available and new technologies to define nervous system development and function in DS, including neuroimaging, electrophysiology, histopathology, metabolomics, induced pluripotent stem cells (iPSCs), and studies of the microbiome.
- Define the impact of sex on dysregulation of genetic and cellular mechanisms.
- Expand genetic and epigenetic profiling beyond chromosome 21 to elucidate complex gene-network effects.
- Study pathways that affect mitochondrial function and use genomics, such as interrogating mitochondrial genes and their possible interactions with genes on chromosome 21, to identify dysregulated pathways, including those related to oxidative stress, that may lead to abnormal organ structures.
- Examine the function, development, and differentiation of both B cells and T cells in individuals with DS.
- Explore the role of interferons and how they drive innate and adaptive immune function and dysfunction. This work may include:
 - Research that could lead to standardized phenotyping of the immune system in individuals with DS, including cell functional assessment, the genetics of immune disorders, and the trajectory of dysregulation and disease, such as what trisomy 21 mechanisms may increase the risk and/or severity of autoimmune conditions in people with DS
 - Genome-Wide Association Studies (GWAS) to determine whether gene variants predispose people with DS to autoimmune conditions, such as thyroid disease
- Study the cellular mechanisms for and role of inflammation in people with DS, including inflammation present in tissues and organs.

- Study the impact of trisomy 21 on diverse human tissues, using iPSCs, differentiated cells and organoids derived from iPSCs, morphogens, and monolayer cultures.
- Use brain tissue samples to help define the genome, epigenome, metabolome, transcriptome, and proteome in DS.
- Obtain microbiome (gut, oral) data from people with DS to help understand the potential associations of the microbiome to commonly co-occurring conditions in DS.
- Explore the role of inherited genomic variation in DS across different age groups to improve cancer screening, diagnosis, and stratification for treatment, particularly for children.
- Determine whether there are genetic variants that modulate the impact of leukemogenic genes on chromosome 21 to help define the risk of developing hematological disorders, such as leukemia.
- Study the genetic and non-genetic risk factors for health conditions related to vision in people with DS, and whether there are predisposing risk factors for these conditions that can be identified during pregnancy.
- Study the mechanisms by which trisomy 21 increases susceptibility to and/or severity of infectious diseases in people with DS, such as whether any specific genes or signaling pathways may be implicated.
- Study the mechanisms by which trisomy 21 increases the risk for different types of diabetes, such as whether any specific genes or signaling pathways may be implicated; obtain lipidomic and other 'omics data to understand risk of diabetes and obesity in people with DS.
- Study the impact of dysregulation of pathways/hormonal circuits that regulate weight, energy metabolism, and appetite control.
- Obtain metabolomics data, both general and tissue-specific, to establish metabolic phenotypes and discover new biomarkers of metabolic disease.
- Define the role of trisomy 21 on metabolic pathways that may modulate the onset and severity of musculoskeletal conditions, such as arthritis.
- Explore molecular and cellular bases for resilience versus the susceptibility of premature aging in DS.
- Combine genomics, proteomics, and metabolomics data to create an integrated dataset that will advance understanding of the fundamental biology of DS.

Expand Basic Research on Down Syndrome-Alzheimer's Disease (DS-AD)

- Study molecular and cellular mechanisms of AD to identify biomarkers for this condition. This activity may include efforts to:
 - Define epigenetic changes and hormonal changes across the lifespan in models of AD in DS to help standardize clinical and genetic phenotyping.
 - Define DS-AD risk alleles and compare them to those for sporadic AD.

- Develop models of the genetic basis, mechanisms, and significance of dysregulated endosomes, exosomes, autophagosomes, and proteostasis in aging and DS-AD.
- Elucidate conformation and toxic mechanisms of aggregating proteins, such as betaamyloid and tau, from human tissue in DS-AD.
- Create and compare models to assess the impact of other human chromosome 21 genes on aging and DS-AD.
- Define differences and similarities between models of DS-AD versus Late-Onset AD and early onset Familial AD.
- Explore the effects and mechanisms of amyloid angiopathy and breach of the blood-brain barrier in DS-AD.
- Explore the role of the microbiome on AD pathology in DS.

Develop Model Systems for DS-AD Research

- Conduct comprehensive 'omics studies of aging and AD in a wide range of models, including yeast, worm, fly, zebrafish, mouse, rat, non-human primate (NHP), and human cell models.
- Examine telomeric length and regulation in mouse models versus human cell lines.
- Define age-related changes in neurons, glial, and endothelial cells in mouse and human models.
- Define the role of age-related hormonal changes on DS-AD endotypes and phenotypes in mouse models.
- Study the origins and consequences of autoimmune conditions in a mouse model of DS.
- Define in vivo mechanisms in model systems that reflect clinical phenotypes in DS, particularly prenatal developmental studies that cannot be conducted in humans.
- Define and compare genetics, mechanisms, and significance of dysregulated endosomes, exosomes, autophagosomes, and proteostasis in DS animal models.
- Conduct research in a model of inducible silencing of the entire chromosome 21, or of specific genes on chromosome 21.
- Continue to analyze synaptic function in a DS mouse model, focusing specifically on relevant genes also located on human chromosome 21.
- Complete comparative phenotyping, including aging and lifespan of all DS mouse models, to inform the development of phenotypes in people with DS.

Program Portrait 1: Basic Research

Brain Development in DS

Basic biomedical research aims to uncover and understand mechanisms involved in typical development and function and in diseases and conditions such as DS. By examining developmental and other changes associated with DS, researchers hope to identify new ways to improve health and quality of life for people with this condition. Multiple NIH ICOs support basic research on Down syndrome, reflecting its effects on multiple organ systems across the lifespan.

For example, the National Institute of Neurological Disorders and Stroke (NINDS) supports research to understand mechanisms of brain development in DS that lead to intellectual disability, as well as the longer term effects on cognition. In one recent study, researchers used a multidisciplinary approach to show that a defect in the integrated stress response (ISR), a signaling pathway that controls the balance of protein production and destruction inside cells, contributes to cognitive impairment and altered neuronal function in a mouse model of DS. Experimentally suppressing the ISR improved measures of long-term memory in the mice, suggesting that this signaling pathway may be a promising therapeutic target. (PMCID: 7299149; funded by NINDS, the National Human Genome Research Institute, and the National Cancer Institute)

In another study, researchers sought to understand the mechanisms behind the imbalance of inhibitory and excitatory brain activity seen in people with DS, and if and how this imbalance may contribute to intellectual disability. By studying iPSCs from people with DS, they found that increased expression of the *OLIG2* gene leads to excess production of specific types of inhibitory neurons during early brain development. Decreasing the expression of *Olig2* reduced this overproduction and improved behavioral deficits in mice, pointing to another possible strategy for future therapies. (PMCID: 6944064; funded by NINDS, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development [NICHD], the National Institute of General Medical Sciences, the National Institute on Alcohol Abuse and Alcoholism, the National Institute of Environmental Health Sciences, the National Center for Advancing Translational Science, and the National Institute on Drug Abuse)

B. Cohort Development/Epidemiology

To perform studies in people with DS, researchers need groups—called cohorts—with enough people and information to appropriately inform the research. Developing these cohorts of people with DS is essential to following individuals' development over time and performing deep phenotyping and natural history studies. For example, a map that includes comprehensive genomic, epigenomic, transcriptomic, and proteomic information will help scientists understand the predisposing risk and protective factors that underlie the highly penetrant features, those that are very common, in DS. Enrolling a cross-sectional cohort of individuals with DS of different ages, sexes, races, and ethnicities across the lifespan will capture the broadest array of phenotypes and ages of onset for the co-existing conditions, and will identify the critical windows for interventions. Longitudinal studies will improve understanding of these co-occurring conditions in individuals over time. Moreover, many of these co-occurring conditions

also are common in people who do not have DS; therefore, findings from DS research will have implications for the health of the overall population.

Develop a Cohort(s) for DS Research

- Develop a cohort of individuals with DS across the lifespan, including older individuals (born 1970-1990), and those from diverse socioeconomic backgrounds and geographic areas, ensuring representation across all age, sex, and racial/ethnic population groups. Define the impact of trisomy 21 on race and ethnicity, specifically addressing whether DS has a disparate impact on particular racial or ethnic populations. Include partial trisomy and mosaic DS cohorts in these studies.
- Include a specific substudy of 5,000 participants with DS in large studies, such as DS-Connect[®]: The DS Registry (see Program Portrait 2) or NIH's *All of Us* research program. Collect GWAS data on this group to provide enough statistical power to develop valid genotypes and phenotypes.
- Conduct research on the health impact of low socioeconomic status in DS.
- Link this cohort to a sufficiently large number of biological samples (e.g., blood, hair, saliva) from people with DS through a federation of coordinated biobanks to allow detailed, longitudinal characterization (phenotyping) of individuals with DS. To achieve this goal, consider linking to existing cohorts, including those maintained internationally.

Conduct Longitudinal/Prevalence Studies of Co-Occurring Conditions in DS

- Expand longitudinal studies of the natural history of aging and AD in DS, beginning early in life. Conduct epidemiological studies of adults with DS to identify the onset and trajectories of co-occurring conditions and mortality related to AD, and ascertain the distribution, demographics, and survival rates of DS-AD, including complications of AD that may contribute to mortality (such as pneumonia). Examine the gender, race, and ethnic differences in DS-AD onset and progression.
- Examine environmental and behavioral factors (e.g., education, work, home settings) and risk factors (e.g., lifestyle, diet, exercise, sleep, substance use) to better understand the impact on cognition and body system function, including cardiovascular health.
- Chart the trajectory of sex differences and co-occurring conditions on the health of people with DS over time.
- Develop diverse cohorts for identifying and validating plasma biomarkers.
- Include assessments of cognitive, functional and motor skills (including executive function), speech/language and hearing, and behaviors (including validated methods to measure adaptive behaviors and successful independence) in conjunction with imaging and genetic biomarkers in longitudinal natural history studies.

- Examine the prevalence of neurological and psychological conditions in people with DS across the lifespan⁵, including identification of variations by race/ethnicity, sex, and/or geography. Collect data on Attention Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD); mental health disorders, such as depression, anxiety, and regression; and sleep/circadian rhythm patterns, including the impact of sleep disturbances on learning and cognition, in longitudinal studies of children with DS.
- Obtain data on the neurodevelopmental trajectories of individuals with DS.
- Conduct longitudinal studies to ascertain the prevalence of cardiovascular conditions in people with DS across the lifespan⁶, and to understand the effects of aging and co-occurring conditions on the cardiovascular system, including evaluation of sex, race, and ethnic differences. Collect epidemiological data to identify potential protective and risk factors for heart disease (such as physical activity) throughout the lifespan, with the goal of informing best practices for treatment.
- Conduct studies to ascertain the prevalence of thyroid disorders in people with DS across the lifespan⁷ and whether there are variations by age, race, ethnicity, sex, or geography.
- Study the prevalence of pulmonary conditions in people with DS across the lifespan⁸, including differences by race/ethnicity, sex, and geography; risk and protective factors; and long-term impact on health and well-being.
- Establish the prevalence of and risk factors for thromboembolic and hemorrhagic stroke in people with DS across the lifespan.
- Determine the prevalence of conditions affecting the eyes and/or vision in people with DS across the lifespan.⁹
- Conduct studies to ascertain the prevalence of ear, nose, and throat conditions in people with DS across the lifespan.¹⁰
- Study oral and dental development, such as the eruption sequence of teeth, speech, language, and auditory development, and risk factors for dental caries and oral inflammation in people with DS.

⁵ Conditions for study could include AD, dementia, ASD, anxiety, ADHD, depression, bipolar disorder, posttraumatic stress disorder, schizophrenia, obsessive-compulsive disorder, Parkinson's disease, traumatic brain injury, cerebral palsy, stroke, movement disorder/restless leg syndrome, Moyamoya disease, regression, seizure disorders/infantile spasms/epilepsy, and autoimmune encephalitis.

⁶ Conditions for study could include congenital heart disease, heart arrhythmias, hypertension, cardiomyopathy, high cholesterol, atherosclerosis, atherosclerotic and non-atherosclerotic cardiac ischemia, peripheral artery disease, and myocardial infarction.

⁷ Conditions for study could include hypothyroidism, hyperthyroidism, Grave's disease, and Hashimoto's disease.

⁸ Conditions for study could include asthma, reactive airway disease, pulmonary hypertension, and pneumonia.

⁹ Conditions for study could include amblyopia, astigmatism, cataracts, glaucoma, hyperopia, keratoconus, myopia, nystagmus, strabismus, and blocked nasolacrimal duct.

¹⁰ Conditions for study could include eustachian tube dysfunction, laryngomalacia, chronic rhinitis, hearing loss, deafness, macroglossia, obstructive sleep apnea, sinusitis, and upper respiratory infection.

- Conduct epidemiological research on the prevalence of cancers, including leukemias, in people with DS across the lifespan and particularly in childhood¹¹, and the survivability of these cancers as compared to the general population. Characterize neurocognitive, behavioral, and quality-of-life outcomes related to cancer therapy in people with DS, continuing through survivorship, to identify risk factors for poorer outcomes and targets for interventions.
- Conduct research to establish the prevalence of gut/gastrointestinal/liver/kidney/bladder conditions in people with DS across the lifespan¹², including identification of variations by age, race/ethnicity, sex, or geography. Conduct a longitudinal cohort study of dysphagia in children with DS.
- Conduct epidemiological research to establish the prevalence of skin conditions in people with DS across the lifespan.¹³
- Conduct natural history studies of musculoskeletal conditions in people with DS across the lifespan.¹⁴
- Conduct definitive epidemiological studies to establish the prevalence of diabetes in people with DS across the lifespan¹⁵, including identification of protective and risk factors for these conditions.
- Compile data on the etiology and timing of metabolic/weight status changes in people with DS across the lifespan and the prevalence of secondary conditions associated with obesity.
- Study how the immune system matures in individuals with DS from infancy through adulthood, and how the process might differ from the same maturation process in those without DS. Conduct longitudinal studies to map the immune system, incorporating inflammatory markers, susceptibility to infections, and responses to vaccines.
- Study COronaVIrus Disease 2019 (COVID-19) risk and mitigation strategies for people with DS, including differential effects of SARS-CoV-2 infection on people with DS across the lifespan, in various living settings. Conduct tailored studies of effective dosing and immune response to vaccines to prevent COVID-19 in people with DS.

¹¹ Conditions for study could include acute T-cell lymphoid leukemia, acute B-cell lymphoid leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, Transient Myeloproliferative Disorder, and Transient Abnormal Myelopoiesis.

¹² Conditions for study could include gastroesophageal reflux, chronic constipation, chronic diarrhea, dysphagia, celiac disease, Hirschsprung disease, pyloric stenosis, irritable bowel syndrome, inflammatory bowel disease, peptic ulcers, gallstones, hemorrhoids, diverticulitis, duodenal atresia, stenosis or web, anal stenosis or atresia, esophageal atresia, dysuria, voiding dysfunction, kidney disease, cystic dysplastic kidney, hydronephrosis, hydroureter, posterior or anterior urethral valves, renal agenesis, vesicoureteral reflux, and nonalcoholic fatty liver disease.

¹³ Conditions for study could include acne, alopecia areata, atopic dermatitis/eczema, boils/hidradenitis suppurtiva/folliculitis, cellulitis, psoriasis, rosacea, tinea capitis, fungus, vitiligo, and xerosis (dry skin).

¹⁴ Conditions for study could include arthropathy, hypotonia, atlantoaxial instability, fractures, cervical spine degeneration, osteopenia, osteoporosis, osteoarthritis, and scoliosis (curvature).

¹⁵ Conditions for study could include congenital/infant diabetes, insulin resistance, and type 1, type 2, and prediabetes.

Program Portrait 2: Cohort Development

DS-Connect[®]: The Down Syndrome Registry

To augment its research on DS, NICHD launched DS-Connect[®]: The Down Syndrome Registry (<u>https://DSConnect.nih.gov</u>) in 2013. This research registry, supported by the self-advocates, family members, DS organizations and foundations, and NIH ICOs within the DS Consortium (see Appendix A), aims to facilitate information sharing among persons with DS, families, and researchers by collecting demographic and health information about people with DS through a series of online surveys. This confidential, secure, and responsive website was also translated into Spanish in 2019. Since 2013, nearly 5,100 individuals with DS have registered.

The DS-Connect[®] professional portal was launched in 2014 to allow approved investigators, clinicians, and other qualified professionals to access the de-identified data collected through the registry; more than 480 researchers currently hold a professional account. The professional portal offers three levels of access: 1) viewing aggregate, de-identified data or survey content only; 2) performing customized searches or statistical evaluation for analysis, publication, or presentation; and 3) recruiting participants for research or clinical study via communication with the registry coordinator. Researchers have used registry data to develop studies on the etiology, natural history, and treatments for DS and associated conditions; recognize trends in the health characteristics and identify medical needs of those living with DS; and determine feasibility and other features of research studies involving those with DS. The DS-Connect[®] Research Review Committee approves access and use of the registry data for recruitment for studies and surveys by investigators. Researchers have successfully used the registry to recruit participants for over 60 clinical trials and research studies, including 9 funded under the INCLUDE Project.

The registry is facilitating linkages with other research studies, using special codes and identifiers, to allow the INCLUDE Project to build a large virtual DS cohort, helping to achieve the goal of assembling a large study population of individuals with DS. This resource will also help researchers understand factors that may contribute to differential survival and co-occurring condition rates among different racial and ethnic groups.

C. Clinical Research/Co-occurring Conditions

At least one-half of all children with DS also have a co-occurring health condition that can contribute to intellectual and physical problems. For example, leukemia and congenital heart disease during early childhood 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 DS, determining the optimal windows for early therapeutics for individuals with DS presents an ongoing challenge for researchers, as does establishing the optimal doses of off-label and new therapeutic agents for this population. Studies of daily environments, such as those structured to facilitate specific language interventions for children with DS, may also provide information that helps researchers design biobehavioral interventions for improving cognition and daily-life functioning. Ultimately, this research will provide the evidence base for informing

and expanding current clinical care guidelines established by the professional medical and behavioral societies for all age groups of people with DS.

Define DS Phenotypes

- Convene a panel of experts (including both clinicians and researchers) on DS to define DS phenotypes across the lifespan using available clinical and genetic data. Inform the development of updated clinical guidelines to improve care for people with DS by incorporating data on changes related to stages of life (e.g., inflammation and metabolism), and on age ranges when an intervention might be most effective.
- Identify DS phenotypes and genotype-phenotype associations, including behavioral and developmental milestones, to inform: understanding of natural history, beginning prenatally and including puberty and adulthood; the timing of and targets for interventions to improve cognition or intervene in regression; the evolution of communication skills; and pathologies that affect hearing, balance, and vision.
- Explore differences *in utero* to ascertain why spontaneous fetal loss occurs only in some cases of trisomy 21, whether the placenta can provide insights on these pregnancy losses, and when the aging process begins.

Improve Clinical Research and Therapeutics

- Leverage the unique opportunities that come from prenatal screening for DS as part of routine prenatal care, and understand the role of the placenta in the developing fetus. For example, identifying fetuses with DS in continuing pregnancies creates the possibility of offering prenatal treatment(s) to the pregnant woman to minimize certain aspects of the syndrome, such as congenital heart defects. Following these pregnancies could also provide new ways to study antenatal influences, including placental function, on fetal development.
- Conduct brain-related research to determine the anatomical and morphological impacts of trisomy 21, such as relative size of different brain regions, plasticity, synaptic pruning, myelination, and glial and neuronal function.
- Apply findings about early infant/childhood development to fetuses, infants, and children with DS. Tailor newly developed behavioral interventions for typically developing infants for infants with DS to take advantage of brain plasticity during early development.
- Increase the number of individuals with DS in controlled clinical trials of experimental therapeutics and medical devices meant for the general population, taking into account differences in drug metabolism (pharmacokinetics [PK] and pharmacodynamics [PD]) in establishing drug safety, efficacy, and dosing in people with DS, and evaluate differential side effects (such as changes in toxicity). Support additional clinical research in people with DS on correct dosing and fit of therapeutics and medical devices that are already available to the public. Collect data on the relative efficacy, side effects, and interactions of therapeutics in those with DS when multiple co-occurring conditions are being treated simultaneously.

- Conduct clinical research to assess the efficacy of interventions for improved cognition, communication, hearing and balance, and vision.
- Include people with DS in clinical trials of vaccines and treatments, including COVID-19 vaccines, as they become available.
- Include people with DS and their caregivers/supporters throughout the clinical research process, beginning with study design, and develop strategies to increase the participation of people with DS of different age, sex, race/ethnicity and socioeconomic status in research.
- Consider developing public-private partnerships with biotechnology companies/pharmaceutical industry to test specific therapeutics for people with DS.
- Harmonize clinical trial protocols, when possible, with international efforts to enable meaningful data sharing. Develop sustainable diagnostic protocols and early intervention procedures that could be used in low- and middle-income countries.

Expand Research To Understand the Impact of Common Co-Occurring Medical Conditions in DS on Cognition and Overall Health Outcomes

Note: Co-occurring conditions appear in *italics* in the following list.

- Examine co-occurring *neuropsychiatric* conditions such as ADHD, ASD, depression, and developmental regression, by studying gene-brain-behavior connections, the effects of early interventions, and their long-term health effects. Study the psychological effects of untreated conditions (such as skin conditions) in people with DS.
- Study how a traumatic life change, change in health status, or event perceived as traumatic by a person with DS may affect *mental health* in people with DS. Conduct research on the effects of disaster/trauma (such as the COVID-19 pandemic) on people with DS, including loss of educational interventions, reduction in physical activity, and limits on social interactions, independence, and routine. Tailor therapeutic treatments for traumatic stress to the specific needs of people with DS.
- Define how early medical or behavioral interventions for *leukemias* alter the developmental trajectory in children with DS. Improve assessment and management of side effects experienced by people with DS during treatment (such as pain/nausea). Continue to refine treatments for leukemias in children with DS, including both chemotherapeutic agents and non-chemotherapy approaches.
- Compare markers in biological samples from individuals with cancer, both with and without DS, to look at *tumor specificity and biological signatures in cancers*. Study cancer subtypes in people with DS and in people who do not have DS.
- Characterize *congenital heart conditions* and cardiac function in individuals with DS, as well as the effects of various medical management approaches (including the risk of anesthesia for surgery), and examine the impact of differences in cardiovascular function, immune response, and hypertension across the lifespan, including factors that may protect from atherosclerotic disease. Study *neurodevelopmental outcomes* among

the large proportion of children with DS born with congenital heart conditions; these outcomes may vary even among children with DS who have the same heart defects and receive the same treatments as typically developing children.

- Study immune system differences in, and risk factors and potential treatments for, cooccurring *autoimmune conditions* most common in people with DS¹⁶, and define the full impact of autoimmunity on the health of people with DS. Study whether treatment of autoimmune skin conditions may address co-occurring autoimmune conditions. Conduct research to determine whether, in people with DS, having one autoimmune disorder predisposes them to other autoimmune conditions.
- Describe more fully *mitochondrial dysfunction* in DS, and develop targeted therapies to address it. Study how failed mitochondrial function and related oxidative stress impact the relationship between neurologic function, cognitive deficits, and AD.
- Conduct research on the long-term health impact of various types of *diabetes*, including whether having type 1 diabetes increases the chance of developing other autoimmune conditions, and whether early treatment of type 2 diabetes can reduce longer-term health issues, such as heart disease, stroke, vision problems, neuropathy, and kidney disease.
- Study the long-term health effects of *obesity* in people with DS, including: consideration of sex, race, ethnicity, and socioeconomic status; what interventions (such as diet and exercise) might assist in management; and why lipid levels in people with DS who are obese are often within a normal range.
- Study *nonalcoholic fatty liver disease* in people with DS to understand how liver dysfunction may contribute to other co-occurring conditions.
- Conduct research on nutrient absorption and metabolism in people with DS (sometimes called the gut-brain axis) to understand preventive and risk factors for *celiac disease* and related disorders.
- Conduct studies to determine more precisely the thyroid-stimulating hormone level at which *hypothyroidism* manifests; develop treatments for *thyroid disorders* in addition to standard thyroid hormone management.
- Study differential response to types of infections¹⁷, as well as risk factors and potential treatments, for individuals with DS, including antibiotics, antiviral medications, preventatives (such as palivizumab for Respiratory Syncytial Virus [RSV] pneumonia), and vaccines. Study how *infectious diseases* may influence overall health, longevity, and quality of life of people with DS.

¹⁶ These conditions include, but are not limited to: type 1 diabetes, celiac disease, Hashimoto's thyroiditis, alopecia areata, atopic dermatitis/eczema, dermatitis herpetiformis, dermatomyositis, hidradenitis suppurativa, lichen planus, lichen sclerosis, vitiligo, psoriasis, psoriatic arthritis, arthropathy, rheumatoid arthritis, vasculitis, hemolytic anemia, thrombocytopenic purpura, myositis, restless leg syndrome (rarely autoimmune), Meniere's disease, autoimmune encephalitis, inflammatory bowel disease/Crohn's disease, narcolepsy, Kawasaki disease, Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) syndrome, sarcoidosis, and systemic lupus erythematosus.

¹⁷ Types of infections may include, but are not limited to: group A streptococcus, *C. difficile* infection, recurrent otitis media (ear infections), recurrent sinusitis, RSV, pneumonia, candidiasis, croup, chronic urinary tract infection,

- Study the long-term impact of *hematological disorders* and their treatments on the health and development of people with DS.
- Study the long-term health impact of *epilepsy and seizure disorders* and their treatments for people with DS, including their role in AD progression.
- Study *moyamoya disease* to improve early detection, develop biomarkers for the condition, and determine risk of stroke associated with the disease.
- Study *hypotonia* and muscle physiology in people with DS, including the role of mitochondrial alterations.
- Study *musculoskeletal dysfunction* in people with DS, and identify fracture risk factors specific to DS, including the predictive role and value of measures of bone quality/density.
- Evaluate sources of, and potential treatments for, *visual acuity defects* in people with DS. This activity may include efforts to:
 - Evaluate corneal structure in those with DS and determine the integrity of the retinal structure
 - Map the time course for the development of refractive error
 - Evaluate visual neural processing over the course of childhood development
- Study *obstructive sleep apnea (OSA)* and other *sleep-related disorders* (e.g., circadian disturbances, insomnia), the long-term health and metabolic consequences associated with these disorders, and the efficacy of available diagnostic tools and treatments, such as medications, continuous positive airway pressure, and surgical approaches, including tonsillectomy, adenoidectomy, and hypoglossal nerve stimulator insertion.
- Conduct research to help identify types of *airway abnormalities* in people with DS that may cause aspiration (including microaspiration from reflux), dysphagia, swallowing dysfunction, and other problems.
- Study *pulmonary hypertension* in people with DS, including etiology, management, and treatments.
- Examine the impact of *dental and oral health/periodontal disease* in people with DS on cognition and development, sleep, the immune system, and synergies with common co-occurring conditions, such as potential linkages between hypodontia/microdontia and hypothyroidism.
- Assess the biomechanical and kinematic properties of the vocal tract to develop more complete information on speech physiology in DS. Conduct research on dysmorphologies of the craniofacial and laryngeal structures and *motor speech impairments* to develop clinical assessments and treatments and improve speech intelligibility.

impetigo, cellulitis, Staphylococcus (Staph) infection, cold sores/human papilloma virus, shingles, periodontitis, gout, sepsis, tuberculosis (TB) or latent TB, SARS-CoV-2, and upper respiratory infections.

- Develop preventive measures and treatments to address structural and functional abnormalities in the auditory and vestibular systems of people with DS over the lifespan to optimize *hearing and balance*.
- Develop intervention strategies using non-pharmacological approaches to manage concurrent co-occurring conditions; such approaches could include technologies to stimulate brain function, *dietary interventions* to manage type 2 diabetes and similar conditions, and *behavioral therapy strategies*, such as social engagement, physical activity, educational inclusion, to enhance cognition and behavior. Evaluate non-pharmacologic approaches in individuals with DS-AD, for both improving cognitive function and/or preventing cognitive deterioration.

Program Portrait 3: Clinical Research/Co-Occurring Conditions

Congenital Heart Disease Research Conducted by INCLUDE Scholars

Among the goals of the INCLUDE Project is fostering future generations of DS researchers. The Pediatric Heart Network (PHN)¹⁸, sponsored by the National Heart, Lung, and Blood Institute (NHLBI), is helping to achieve this goal. The PHN is a multicenter research enterprise that conducts clinical trials and other clinical research on congenital heart disease. Because approximately 50 percent of children with DS are born with congenital heart disease, the PHN was a natural home for a program focused on young investigators interested in pursuing research on DS. With support from the INCLUDE Project, this NHLBI-led effort conducted a competitive process in 2019 to fund six INCLUDE Scholars, who would conduct research related to DS and the cardiovascular system. Their projects cover a wide age span and include assessment of neurocognitive outcomes, long-term survival, and outcomes of surgery for congenital heart disease.

Another project, studying vascular health and risk factors, is premised on the fact that life expectancy among individuals with DS is increasing over historical estimates, and that cardiovascular morbidity and mortality are becoming more common as people with DS get older. The investigators are evaluating risk factors, including obesity, blood lipid abnormalities, and other metabolic abnormalities, for future cardiovascular disease in both children and adolescents with DS. Project researchers will use sophisticated, non-invasive measures of vascular health to compare cardiovascular outcomes of individuals with DS with those who do not have the condition. This study recently leveraged the funding received through the INCLUDE Project to attract additional support.

D. Living and Aging with DS/Services Research

Research studies that benefit the daily lives of people with DS and their families, such as those that inform lifestyle choices and independent living, are a high priority. People with DS are living longer than they were even a few decades ago, and this lengthier lifespan poses many new research questions and opportunities for people with and without the condition. For example, people with DS are at higher risk for developing AD than the general population, and they often develop it at younger ages than those without DS; efforts to discover new treatments for AD in those with DS may also benefit those with AD but who do not have DS.

Enhance Quality of Life

• Conduct research on the efficacy of lifestyle interventions for people with DS across the lifespan; these approaches may include exercise, diet, dietary supplements, behavioral interventions, and technologies to promote healthy behaviors, modulate conditions, such as inflammatory bowel disease or gastroesophageal reflux disease, and/or delay the onset of DS-AD.

¹⁸ <u>https://www.pediatricheartnetwork.org</u>

- Develop applications for mobile devices and computer-based therapies to increase independence for people with DS in activities of daily living, especially self-support technologies, to be used in telehealth, home-based, and school settings to improve learning and communication. Develop and/or adapt assistive devices, such as Global Positioning Systems and mobile devices for transportation, or devices that help to facilitate integration of an individual with DS into the workplace, residential or home environment, and community.
- Develop and validate interventions, including augmentative and alternative communication devices and other tools, aimed at improving language skills and hearing capabilities in people with DS, such as strategies to overcome difficulties in speech intelligibility and literacy.
- Evaluate the benefits of speech supplementation techniques (e.g., gestures, symbols) at different points across the lifespan to foster communicability in people with DS. Identify effective interventions and educational strategies, including the role of learning sign language early in life, to help children with DS process available linguistic input and enhance their communication skills, with the goal of matching children to the therapies best suited to their profiles. Determine the possible influences of race, ethnicity, and culture on language development in children with DS.
- Continue to conduct research on optimal educational methods for children with DS.
- Identify factors (i.e., medical, intellectual, social, familial) that may be protective for fostering maximal independence and community inclusion, with a specific focus on individuals with DS who are aging in non-disability community settings for seniors. Study what measurable skills, such as self-management skills for co-occurring conditions, are meaningful to enhancing quality of life and promoting independence among people with DS.
- Investigate the impact on families of caring for individuals with DS as they age, and as overall lifespans of those with DS continue to increase. Such work may include the following:
 - Identifying the factors that lead to effective functioning or challenges in families that include an individual with DS
 - The impact on the family, including the individual with DS, as that person leaves the school system
 - Researching the physical and mental health and lifespans of the parents, siblings, and other caregivers
- Study the impact of behavior problems and psychiatric disorders on the daily functioning, socialization, academics, and quality of life of people with DS.
- Develop tools to foster coping skills among people with DS during periods of grief/loss and disruption of routine, including accessible materials and other resources for managing depression and anxiety.

• Use lessons learned from families' experiences with the SARS-COV-2 pandemic to develop strategies that include people with DS in planning for future public health and disaster preparedness efforts, such as maintaining caregiver access to individuals with DS who may be isolated in the hospital.

Increase Inclusion of People with DS in Research

- Take into account, when designing specific research studies, how potential participants view themselves (including identities of race, gender, class, and sexual orientation) and, to the extent feasible, recruit diverse populations of people with DS into research studies.
- Develop research study materials that are accessible to individuals with DS, including study descriptions, informed consent/assent documents, and information on confidentiality and privacy of data. Engage people with DS and their caregivers in study design to increase the appropriateness of these materials and ensure that the presentation of research topics and results does not unintentionally cause psychological stress in potential participants.
- Encourage researchers to participate in DS-related outreach efforts to share the latest information and help inform individuals with DS and their families about research progress, thus encouraging additional participation in studies. Foster additional efforts to educate caregivers of people with DS about the value of participating in research.
- Working with the DS Consortium and DS-Connect[®] team, explore a variety of dissemination methods for reaching health care professionals with information about recent research findings in DS. In particular, develop and disseminate evidence-based educational materials regarding management of co-occurring conditions in DS. Encourage NIH to incorporate people with DS in its overall health education efforts.
- Consider mapping research studies to the National Institute on Minority Health and Health Disparities framework to ensure appropriate inclusion of the effects of social determinants of health.
- Study the cross-cultural needs of people with DS and apply the findings to education and recruitment efforts.

Expand Knowledge on DS, Aging, and DS-AD

- Study whether aging among those with DS has a greater impact on physiologic and cognitive processes than it does for those without DS. Such studies could include:
 - The factors that affect the risk of dementia
 - The differential impact of aging on organ systems in people with DS, such as changes in bone mass and chronic inflammatory conditions
- Support research on variations in aging patterns, including consideration of lifestyle factors, among subpopulations of people with DS.

- Explore potential protective factors for age-related dementia, including complementary and integrative health approaches, exercise, and diet.
- Study the specific impact of postmenopausal hormone replacement therapy (HRT) use by women with DS to determine if it reduces the cumulative risk for DS-AD, and if so, identify the optimal time and duration for postmenopausal HRT use in this population.
- Study how the aging process, dual diagnosis of DS and another condition (such as ASD), or mosaicism affects the progression of chronic conditions or infection.
- Explore the impact of having type 2 diabetes on the development of DS-AD.
- Study the relationship between changes in sleep, behavior, cognition, and biomarkers for DS-AD.
- Examine the impact of caring for people with DS as they age by considering the needs of caregivers in study design. Study the health impact on individuals with DS if their caregiver has a significant health issue or dies.
- Study long-term care options and end-of-life decision-making for older individuals with DS.

Program Portrait 4: Living and Aging with DS

Alzheimer's Biomarker Consortium-Down Syndrome (ABC-DS)

Adults with DS are at high risk for developing AD. Virtually all adults with DS have neuropathological changes consistent with AD by age 40, including deposits of amyloid-beta (A β) in diffuse and neuritic plaques, and most will develop clinical dementia by their late 60s. The high risk for DS-AD has been attributed, at least in part, to triplication and overexpression of the gene for amyloid precursor protein (*APP*) on chromosome 21, leading to elevated levels of A β peptides. However, there is wide variation in age at onset of dementia among those with DS, ranging from younger than 40 to older than 70 years of age. This age range suggests that additional genetic, biological, and environmental factors modify the rate and degree of A β deposition or clearance and that these factors may be important modifiers of risk, accelerating or slowing disease progression. Development of empirically supported methods for early diagnosis of dementia in DS, biological characterization of the preclinical and early phases of DS-AD, and identification of risk factors for AD progression are critical to the early diagnosis of dementia and for the development of effective interventions and treatments.

ABC-DS is a multidisciplinary, multisite longitudinal study examining biomarkers of DS-AD in a large cohort of adults with DS, ages 25 and older. The National Institute on Aging (NIA) and the NICHD initiated ABC-DS in 2015 with the funding of two groups of research collaborators—Neurodegeneration in Aging Down Syndrome (NiAD, U01AG051406) and Alzheimer's Disease in Down Syndrome (ADDS, U01AG051412). In September 2020, the continuation of ABC-DS was funded by the NIA, NICHD, and the INCLUDE Project (U19AG068054). The ABC-DS researchers will follow the cohort of people with DS to conduct three projects:

- Investigate how DS-AD parallels and differs from sporadic AD within an amyloid, tau, neurodegeneration framework, and to identify modifiers of risk of conversion/progression
- Identify genetic modifiers of the development of DS-AD
- Translate outcomes to a precision medicine framework and expedite clinical trials

Importantly, the next iteration of ABC-DS includes an emphasis on increasing the diversity of individuals in the cohort of adults with DS. The AD/DS Outreach, Recruitment, and Engagement Core will rapidly disseminate information to DS communities and engage underrepresented racial ethnic groups.

E. Research Infrastructure and Tools

Diagnostic and screening measures used for DS and related conditions have continued to evolve in recent years. However, 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 DS.

In the near term, the scientific community needs to further improve tools, techniques, methods, and measures to move toward a minimum set of common measures for use across studies, age groups, and developmental and behavioral domains. The field may benefit from an agreement on common domains and on a core set of standardized tests and measures that can be assessed in clinical research on DS to allow for comparability across studies, noting that domains appropriate for one stage of life may not be appropriate for others. In addition, making common research resources available to researchers, such as new models for DS, research infrastructure, and data and tissue repositories, will allow research to move forward more rapidly.

Expand Research Tools

- Develop additional new model systems for studying DS 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, glia, and synapses in brain organoids, as well as in model organisms such as *C. elegans* and Drosophila.
- Develop and support new animal (i.e., mouse, rat, or NHP) models for conducting preclinical research on DS, including testing pharmacological and genetic interventions, and conducting anatomical and behavioral analyses of brain development. Prioritize the development of models that minimize non-chromosome 21 genetic changes, and those that can reflect the structural changes in the human brain and immune system without introducing extraneous genetic material.

- Develop and support new human cellular/organoid cultures for conducting preclinical research on DS.
- Design new treatment paradigms and pathways for testing in DS mouse models (specifically, dose-response and toxicity studies).
- Develop nanotechnology and other small-molecule approaches to enhance contrast of amyloid imaging reagents for finer resolution studies in younger individuals with DS.
- Develop human DS cellular models (e.g., iPSCs differentiated into neuronal cultures) to study variations by sex and ancestry.
- Use both *in vivo* and *in vitro* model systems to study cardiovascular function and therapy response.
- Refine outcome measures already validated for studying people with DS, and disseminate these outcome measures to the research community. Emphasize measures that have demonstrable clinical utility, such as identifying changes in language, behavior, cognition, or adaptive skills. Build on the NIH Toolbox Cognitive Battery to develop or adapt additional outcome measures for studying low-functioning, very young children, or adolescents with DS. Track outcomes during early development to allow evaluation of the impact of interventions at different stages.
- Link cognitive phenotypes of DS to validated developmental measures, including speech and language, auditory function, behavioral, and psychological abnormalities. Use Magnetic Resonance Imaging (MRI), functional MRI (fMRI), diffusion-tensor imaging (DTI), and other emerging imaging modalities in conjunction with specific neurocognitive assessment measurements to examine major pathways and determine how those pathways differ in persons with DS. For example, this research could address the correlation among cognitive function/language impairment/behavior issues in individuals with DS and co-occurring ASD.
- Develop biomarkers and other assessment tools to diagnose and analyze developmental delays and cognitive impairments (including dementia) that also permit tracking the effectiveness of early interventions. Specifically, identify the clinical, cognitive, genetic, and biochemical biomarkers of DS-AD for use in detection and management of disease progression. Develop or improve methods to detect mild cognitive impairment in DS to aid in the early diagnosis of DS-AD.
- Develop diagnostic/screening tools and biomarkers for autoimmune conditions in people with DS, including celiac disease and arthropathy, prior to the development of symptoms.
- Assess how asthma diagnostic criteria and screening tools should be applied to individuals with DS.
- Develop screening tools and biomarkers for infectious diseases that occur more commonly in people with DS (e.g., pneumonia).
- Conduct research to identify new biomarkers for hypothyroidism in addition to antithyroid antibodies in people with DS.

- Develop screening tools for depression, anxiety, and other co-occurring mental health conditions in people with DS.
- Develop diagnostic and screening tools for hematologic disorders in people with DS to permit tailored treatment.
- Refine the diagnostic and screening tools for vision-related conditions in people with DS.
- Develop or improve methods to assess auditory and vestibular function over the lifespan of people with DS for use in screening during routine health examinations.
- Refine the diagnostic and screening tools for type 1 diabetes in people with DS.
- Assess the value of and develop additional screening tools and technologies (such as wearables) for OSA in people with DS to improve diagnosis without the necessity of sleep studies in medical facilities.
- Facilitate collaboration between neuropathologists and DS clinicians to assess the usefulness of current model systems and biomarkers for DS neurobiology.
- Develop functional intervention models that address behavioral and psychological symptoms. Use neurocognitive tools and brain imaging technologies (i.e., MRI, fMRI, DTI, electroencephalogram) to link neurocognitive performance and health status in DS with underlying brain structure.

Improve Research Infrastructure

- Increase public awareness of and registration in DS-Connect[®]: The DS Registry to relay personal experiences from the DS community, such as videos and other outreach methods describing why individuals have chosen to participate in research and explaining how research has impacted their lives.
- Set up a family-to-family outreach campaign allowing families who are already enrolled in the DS-Connect[®] registry to explain to others why they joined and raise awareness about opportunities to participate in research.
- Ensure that participants receive the overall study results from any research projects in which they participated, in accessible language.
- Expand the DS-Connect[®] website to promote non-DS-Connect events and articles. Expand and update the DS-Connect[®] and/or the NIH DS websites with listings of upcoming clinical trials and treatment guidelines.
- Work with the Centers for Medicare and Medicaid Services to provide information and materials about the DS-Connect[®] registry and upcoming research studies that are seeking participants from healthcare organizations that accept Medicaid.

- Work with DS organizations and experienced clinical trial specialists to create accessible and appropriate recruitment materials for DS studies, that use language that is easily understandable to people with DS and their families; consider both visual and non-visual materials. Study how health care practice may best foster the engagement and independence of people with DS. Identify ways to foster community-engaged research, collaborating where possible with people with DS, caregivers/supporters, and community partners; use community advisory boards to augment ethical reviews of research by institutional review boards.
- Augment systems for data sharing of published cohorts and make results available in a searchable format, including fostering international data sharing. Consider establishing a publicly available, centralized repository for DS data, either through or in conjunction with the DS-Connect[®] registry, so that researchers may compare those data with data on the general population, people with intellectual and developmental disabilities other than DS, siblings of people with DS, and people with AD. Develop training and other support for DS clinics to allow them to digitize their clinical data for submission to a centralized repository/database, and encourage the use of global identifiers that allow data sharing between databases without revealing personally identifiable information.
- Through the INCLUDE Data Coordinating Center, create a large cohort study of individuals with DS across the lifespan to accelerate research into co-occurring conditions. Provide researchers and the broader DS community with access to the cohort data and data mining and analysis tools, and facilitate data sharing and linkages of datasets using unique identifiers that preserve individual confidentiality.
- Expand the research infrastructure for DS by establishing or augmenting collaborations among existing clinical sites and research networks at medical/academic institutions across the country that conduct research related to DS and its co-occurring conditions. Encourage this federation of sites to conduct large studies, such as a longitudinal cohort study or multisite clinical trials. To facilitate the translation of basic and translational research to clinical practice, such sites should:
 - Support an interdisciplinary team of researchers and clinicians, including the development of new researchers in DS, some of whom may conduct implementation science projects to ensure that the underlying research results benefit the DS community.
 - Facilitate enrollment of condition-specific subgroups, age ranges, or underrepresented populations of people with DS into research studies.
- Develop a range of trial designs to enhance reproducibility of data in the DS population, for which sample size may be limited.

- Establish a federation of biorepositories that will permit biobanking of cells, plasma, serum, cerebrospinal fluid, and brain and other tissues for research purposes, ¹⁹ including samples from individuals with cancer with DS. Integrate biorepository data with the DS-Connect[®] research registry as feasible. Standardize sample collection and processing methodologies and policies for consistent, equitable sample distribution, and establish review and distribution processes for researcher access to the samples/data. Identify and address barriers and motivating factors to donation. Consideration should also be given to:
 - Linking the DS repository with the NIH NeuroBioBank²⁰ and the existing AD Research Centers Brain Banks²¹, so that tissue from people with DS can be compared to those obtained from individuals with AD and other disorders
 - Collecting neurotypical control samples
- Expand federally funded research training programs to ensure a vibrant pipeline of researchers doing work in DS, and host scientific workshops that bring emerging investigators together with established scientists in the field for training in clinical trials.

Program Portrait 5: Research Infrastructure and Tools

Using the Pediatric Trials Network (PTN) to Test Therapeutics for Children with DS

Only a small percentage of drugs and devices approved by the U.S. Food and Drug Administration (FDA) have been labeled for pediatric use. NICHD established the PTN in 2010 to conduct clinical research and collect data to assist the FDA in revising medication labels for safer and more effective use in children. Working with research sites around the country, the PTN studies the formulation, dosing, efficacy, and safety of drugs, as well as medical devices, for use in children. This structure allows the network to address many of the challenges facing clinical trials in children, such as having a limited number of subjects at one site, competing research priorities, and a lack of trained investigators.

Recently, NICHD funded an expansion of the PTN's trial structure to develop prospective trials to assess the safety and efficacy of therapeutics prescribed for children with DS. The PTN PK, PD, and Safety Profile of Understudied Drugs Administered to Children per Standard of Care effort will train investigators at a core set of sites on clinical pharmacology-based research and clinical trials in DS to evaluate the PK/PD of drugs administered to children with DS as part of the standard of care. This approach will allow the collection of these data in a real-world setting,

¹⁹ A large range of biospecimens may be considered, such as buccal DNA, hair, blood, cord blood, brain, cerebrospinal fluid, saliva, tissues from surgeries, urine, stool, skin, amniotic fluid, placenta, and dried bloodspots collected during newborn screening.

²⁰ <u>https://neurobiobank.nih.gov/</u>

²¹ https://www.nia.nih.gov/health/alzheimers-disease-research-centers

permitting researchers to understand differences in how children with DS may metabolize drugs and to evaluate the influence of genetic factors.

In addition, the PTN is engaging in another study to help children with DS and the co-occurring condition, ADHD, called the Guanfacine for Hyperactivity in Children with DS study. Millions of children are affected by ADHD, which is often associated with behavioral problems, learning disorders, psychiatric comorbidities, such as depression, and increased risk of injury. ADHD puts children with DS at a high risk for these comorbidities, yet FDA-approved treatment options for ADHD have been studied almost exclusively in typically developing children. Moreover, clinicians may be using these medications for treatment, but with no data to drive their dosing decisions. Guanfacine is one of the most commonly used medications for treating ADHD, but no PK/PD data exist for its use in children with DS. This prospective, randomized, placebo-controlled trial, in children with DS ages 6 to 12 years, will provide the data needed to determine the safety and efficacy of the treatment in this specific population.

Conclusion: Emerging Research Opportunities

The field of DS research has undergone some remarkable changes since the last NIH research plan was published in 2014. In that research plan, *Down Syndrome Directions*, the research objectives were significantly expanded in comparison to the first DS-specific plan published in 2007, with a more balanced perspective on the health needs and multiple co-occurring conditions of DS beyond just intellectual disability, including the addition of a new section focused on DS and Aging. Although not all of the objectives have been met from the 2014 research plan, there has been significant progress in DS-related research.

- With regard to basic science discoveries, the development of iPSC and cerebral organoid culture systems has provided new tools to probe early neurodevelopment, and the availability of rapid, efficient gene-editing tools, such as CRISPR/Cas9, have revolutionized the ability to engineer cellular and animal models in ways unimaginable just 7 years ago.
- Although a few significant, single genes on chromosome 21 are still the subject of intense scrutiny, newer studies are likely to take a more nuanced view of the impact of multiple genes on the entire chromosome, as well as the role of genes on other chromosomes and even environmental factors; in fact, many of these studies are incorporating 'omics technologies that provide a systems biology approach that was not even feasible a decade ago.
- The recent recognition of DS as an "interferonopathy" due to altered immune system regulation in the condition has resulted in a more complete model of the interplay between the immune system, oxidative stress, bioenergetics, and neurogenesis on cognition and many other aspects of DS, although these integrative studies are still in their infancy.

- In addition, due to several large cohort studies, researchers have a better understanding of the pathophysiology of DS-AD,²² but more recent recognition of a worrisome "regression" phenotype reminds us of how much we have yet to learn about some of these co-occurring neurological conditions.
- While in the recent past there has been a paucity of medication trials tailored to people with DS (with the exception of several exploring the optimal chemotherapy for childhood leukemia in DS, and some failed trials to improve cognition or even prevent dementia),²³ this situation is improving, particularly with support from the INCLUDE Project.

The impact of the INCLUDE Project cannot be underestimated, as it has infused the field with new funding, brought new investigators into DS research, and encouraged new and "out-of-thebox" approaches to this well-known chromosomal disorder, fundamentally changing the culture of DS research conducted and supported by NIH. The emphasis on support of trainees and junior faculty engaging in DS-related research, through institutional training grant supplements, Clinical and Translational Science Awards training supplements, the PHN Scholars program (see <u>Program Portrait 3</u>), and individual fellowship and career development awards, is resulting in younger scientists joining the DS research community. The additional emphasis on transformative research is encouraging new and established investigators to broach exciting new areas of inquiry in the basic science domain. All of these measures increase the pool of investigators involved in DS research and fulfill the congressional mandate to "expand the current pipeline of DS research" (see <u>Appendix E</u>).

Despite only being in its infancy, with the first supplements funded a short time ago, the INCLUDE Project can still cite a limited number of specific outcomes and discoveries in this research plan. In addition, some of the promising DS projects funded through INCLUDE and other NIH sources allow identification of aspirational scientific goals that may lead to exciting discoveries in the future.

One of the recurrent concerns of investigators studying systems that model features of DS is a lack of robust and reproducible cell-based (especially iPSC) and rodent models to facilitate cutting-edge research. Moreover, the most commonly used mouse model in DS research (Ts65Dn), is also incomplete with regard to the number of human-equivalent genes triplicated and contains additional genetic material that does not correspond to human chromosome 21. One aspirational goal for the DS research field is the development and availability of improved rodent models for DS that investigators could use to pursue their studies. Another aspirational goal is continued advances in the realm of prenatal treatments to prevent certain aspects of the condition, such as cognitive impairment,²⁴ immune disorders, or AD; while more preclinical studies are needed prior to engaging in human trials, the possibilities are intriguing. Finally, the concept that an extra copy of a chromosome could be selectively "turned off" or "silenced" in a cell was only recently achieved in a cell culture environment²⁵; testing this chromosome

²² <u>https://pubmed.ncbi.nlm.nih.gov/30733618/</u>

²³ https://pubmed.ncbi.nlm.nih.gov/28884975/; https://pubmed.ncbi.nlm.nih.gov/24573065/

²⁴ https://pubmed.ncbi.nlm.nih.gov/33098770/

²⁵ <u>https://pubmed.ncbi.nlm.nih.gov/30518921/</u>

silencing in a mouse model of DS to prevent amyloid plaque deposition in the brain and onset of dementia symptoms would be a striking accomplishment and a breakthrough in the field.

On the clinical side, improved treatments for some of the most challenging aspects of DS is a worthy goal, for which community input is critical. Parents often report that poor communication and speech articulation, as well as poor sleep quality (including breathing pauses and snoring), are some of the most vexing problems for families because they can have a major impact not only on the well-being of the person with DS, but also that of other family members. Many families also fear the possibility of developmental regression in their teens and young adults with DS, and the onset of dementia as their loved ones with DS age. The broader DS community could engage with researchers to improve understanding of the causes and range of clinical presentations for these issues, with the primary goal of developing clinical trials of these conditions specifically in DS. Some researchers already are developing an AD prevention trial using an anti-amyloid therapy, and the success of such a trial would be a significant benefit for individuals and families.

The unique challenges posed by the COVID-19 pandemic also provide opportunities to understand the heightened risk factors for more severe outcomes in those with DS infected with the SARS-CoV-2 virus. Through supplemental awards and other mechanisms, investigators could learn about the role played by immune factors in COVID-19 infection that may help understand risks and resiliencies in the general population as well. Eventually, the knowledge gained will help the DS community prepare for the next pandemic or other emerging health threats that may have a disproportionately negative impact on those with DS.

Perhaps most important, the environment for DS research also has changed since the last plan was published due to the enhanced engagement and partnership with the DS community. The NIH commitment to research participation by individuals across the lifespan, including those with intellectual disabilities and DS,²⁶ is a welcome development and is changing the clinical research landscape away from the past, when these groups were often excluded from research because it was deemed too time-consuming or too complicated to develop informed consent protocols that accommodated their needs. INCLUDE Project leadership has acknowledged the important role of self-advocates with DS and their family members, and all workshops hosted since 2019 (see Appendix D) have included the voice of the participant, parent, and/or self-advocate in their speaker rosters. These presentations have been some of the most dynamic and provocative and have served as touchpoints for subsequent discussions.

Inviting a wider range of individuals to engage in clinical research—both as participants and as clinicians leading the studies—is a cornerstone of the PTN efforts to understand drug metabolism in children with DS who are already taking medications, and in its stand-alone trial of guanfacine in children with DS and ADHD (see <u>Program Portrait 4</u>). It is hoped that these efforts will culminate in the recruitment of a larger number of PTN investigators and clinical trialists who understand the unique needs of the DS population, can develop relevant therapies for them, and are comfortable proposing new clinical trials to test the therapies in this population. Likewise, the more recent emphasis on studies focused on developing outcome measures and biomarkers to serve as endpoints for clinical trials is paving the way for future

²⁶ <u>https://pubmed.ncbi.nlm.nih.gov/29285540/</u>

trials of interventions not just for cognition and dementia treatments, but also for immune disorders, sleep apnea, eye disorders, and many other conditions. These efforts underscore the importance of diversity, equity, and inclusion in our workforce and in the research participants recruited for DS studies.

Appendix A: The Down Syndrome Consortium

In 2011, the National Institutes of Health (NIH) joined with governmental and private organizations interested in Down syndrome to form the Down Syndrome Consortium. The goal of the Consortium, which is led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), is to encourage the exchange of information about Down syndrome research and healthcare among Consortium members, including:

- 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
- LuMind IDSC Down Syndrome Foundation
- Global Down Syndrome Foundation
- International Mosaic Down Syndrome Association
- Alzheimer's Association
- National Task Group on Intellectual Disabilities and Dementia Practices
- Jerome Lejeune Foundation
- Linda Crnic Institute
- National Down Syndrome Congress
- National Down Syndrome Society
- Down Syndrome International
- Special Olympics
- T21 Research Society
- Self-Advocates

NIH Down Syndrome Working Group

- National Cancer Institute (NCI)
- National Heart, Lung, and Blood Institute (NHLBI)
- National Human Genome Research Institute (NHGRI)
- National Institute on Aging (NIA)
- National Institute of Allergy and Infectious Diseases (NIAID)

- *Eunice Kennedy Shriver* National Institute on Child Health and Human Development (NICHD)
- National Institute on Deafness and other Communication Disorders (NIDCD)
- National Institute of Dental and Craniofacial Research (NIDCR)
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
- National Institute of Mental Health (NIMH)
- National Institute of Minority Health and Health Disparities (NIMHD)
- National Institute of Neurological Disorders and Stroke (NINDS)
- National Center for Advancing Translational Sciences (NCATS)

Appendix B: Input into Development of the Revised Plan

On April 13, 2020, 21 National Institutes of Health (NIH) Institutes, Centers, and Offices (ICOs), including the Office of the Director, issued the Request for Information (RFI): Invitation to Comment on Updates to NIH Research Plans on DS (NOT-HD-20-013) in response to direction from NIH leadership to combine previously published plans relevant to the Down syndrome (DS) and update them to create the *NIH INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) DS Research Plan.* NIH asked for comments from the public concerning the effectiveness of the previous plans, advances made since 2014, remaining research gaps, and suggestions concerning new future research objectives. The RFI was widely disseminated by Down Syndrome Consortium members and organizations, through research and professional societies, and to investigators funded by the INCLUDE Project.

A total of 11 responses were submitted, which together combined input from 154 members of the DS community. Responses came from self-advocates, family members, professional societies, researchers, clinicians, and other members of the DS community. They were grouped according to each of the plan's categories: Basic Research, Cohort/Epidemiology, Clinical/Co-Occurring Conditions, Living and Aging with DS/Services Research, and Research Infrastructure.

Ten out of the eleven received responses have been <u>published in whole on the INCLUDE Project</u> <u>website</u> for public comment. (One respondent could not be reached to provide permission for posting.)

Appendix C: INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) Project Funding Opportunity Announcements Since 2018

Fiscal Year 2018

- <u>NOT-OD-18-194</u>: Notice of Availability of Administrative Supplements for NIH Grants that are NOT Focused on Down Syndrome to Address Specific Down Syndrome Research Objectives
- <u>NOT-OD-18-195</u>: Notice of Availability of Administrative Supplements for NIH Grants Focused on Down Syndrome to Address Specific Down Syndrome Research Objectives

Fiscal Year 2019

- <u>NOT-OD-19-071</u>: Notice of Availability of Competitive Supplements/Revisions for the INCLUDE Project (Competitive Supplement/Revision Clinical Trial Optional)
- <u>RFA-OD-19-018</u>: Clinical Trials Development for Co-Occurring Conditions in Individuals with Down syndrome: Phased Awards for INCLUDE (R61/R33 Clinical Trials Required)
- <u>RFA-OD-19-016</u>: Transformative Research Award for the INCLUDE Project (R01 Clinical Trial Not Allowed)
- <u>RFA-OD-19-015</u>: INCLUDE Clinical Trial Readiness (R21 Clinical Trial Not Allowed)
- <u>NOT-OD-19-084</u>: Notice of Clarification of Application Submission Information for NOT-OD-19-071: "Notice of Availability of Competitive Supplements/Revisions for the INCLUDE Project"

Fiscal Year 2020

- <u>RFA-OD-20-007</u>: Development of the INCLUDE Project Data Coordinating Center (U2C)
- <u>NOT-OD-20-022</u>: Notice of Special Interest (NOSI): Administrative Supplements to National Center for Advancing Translational Sciences (NCATS) Clinical and Translational Science Awards (CTSA) Program KL2 Institutional Career Development Awards as part of the INCLUDE Project
- <u>NOT-OD-20-017</u>: NOSI: Development of Animal Models of Down Syndrome and Related Biological Materials as Part of the INCLUDE Project
- <u>NOT-OD-20-023</u>: NOSI: Competitive Supplements/Revisions (R01) Available for INCLUDE Project (Competitive Supplement/Revision Clinical Trial Optional)

- <u>NOT-OD-20-024</u>: NOSI: Availability of Administrative Supplements for the INCLUDE Project
- <u>NOT-OD-20-025</u>: NOSI: NIH Research Project Grants on Down Syndrome (R01) for the INCLUDE Project
- <u>NOT-OD-20-020</u>: NOSI: Ruth L. Kirschstein National Research Service Award (NRSA) Fellowship Awards to Support Training in Research Related to Down Syndrome as Part of the INCLUDE Project
- <u>NOT-OD-20-021</u>: NOSI: Mentored Career Development Awards to Foster the Careers of Investigators Pursuing Research Related to Down syndrome as Part of the INCLUDE Project
- <u>RFA-OD-20-006</u>: Small Research Grants for Analyses of Down Syndrome-related Research Data for the INCLUDE Project (R03 Clinical Trial Not Allowed)
- <u>RFA-OD-20-005</u>: Transformative Research Award for the INCLUDE Project (R01 Clinical Trial Not Allowed)
- <u>RFA-OD-20-004</u>: INCLUDE Clinical Trial Readiness (R21 Clinical Trial Not Allowed)
- <u>RFA-OD-20-003</u>: Clinical Trials Development for Co-Occurring Conditions in Individuals with Down Syndrome: Phased Awards for INCLUDE (R61/R33 Clinical Trial Required)
- <u>NOT-OD-20-129</u>: NOSI regarding the Availability of Urgent Competitive Revisions and Administrative Supplements for Research on Coronavirus Disease 2019 (COVID-19) in Individuals with Down Syndrome for the INCLUDE Project

Fiscal Year 2021

• <u>NOT-OD-21-001</u>: NOSI: Administrative Supplements to NCATS CTSA Program KL2 Institutional Career Development Awards as part of the INCLUDE Project

Appendix D: Down Syndrome Research-Related Meetings Since 2014

[In Progress]

Appendix E: Congressional Directives

Recent Appropriations Report Language on Down Syndrome Research

Fiscal Year 2018: House Report 115-244

Trisomy 21.--The Committee continues to recognize that the presence of a third copy of human chromosome 21, which causes Down syndrome, predisposes individuals to significant immune system dysregulation. This dysregulation is associated with the occurrence of Alzheimer's disease as individuals with Down syndrome age and the high incidence of autoimmune disease as well as protections against most solid tumor cancers and cardiovascular disease. These findings present a rich research opportunity and, based on the NIH's recently released report on the Feasibility of a Multi-Year Study on Trisomy 21 in Humans, the Committee encourages NIH to pursue a multi-year, trans-NIH research initiative examining immune system dysregulation and trisomy 21, with the aim of yielding scientific learnings that could significantly improve the health of individuals with Down syndrome as well as millions of typical individuals.

Fiscal Year 2018: Senate Report 115-150

Trisomy 21.--The Committee recognizes that the presence of a third copy of human chromosome 21 may be linked to significant immune dysregulation and Alzheimer's disease, while protecting against most cancers and cardiovascular disease among individuals with Down syndrome. The Committee strongly encourages NIH to pursue an initiative on this topic that will yield scientific learnings that could significantly improve the health of individuals with Down syndrome as well as millions of typical individuals.

Fiscal Year 2019: House Report 115-862

Trisomy 21.--The Committee applauds the NIH for significantly increasing its investment in Down syndrome research and for the NIH Director's leadership in advancing the trans-NIH initiative the Committee included in the fiscal year 2018 appropriation. The Committee directs NIH to continue to make new investments in Down syndrome research that prioritize funding for both new research grants that will significantly expand the current pipeline of Down syndrome research, as well as the implementation of the new trans-NIH initiative. In addition, the Committee encourages NIH to prioritize funding for research to improve the health and neurodevelopment of individuals with Down syndrome and typical individuals at risk for immune system dysregulation, Alzheimer's disease, cancer, cardiovascular disease, and autism.

Fiscal Year 2019: Senate Report 115-289

Trisomy 21.--The Committee applauds the NIH for significantly increasing its investment in Down syndrome research and for the NIH Director's leadership in advancing the trans-NIH initiative the Committee included in the fiscal year 2018 appropriation. The Committee directs NIH to continue to make new investments in Down syndrome research that prioritize funding for both new research grants that will significantly expand the current pipeline of Down syndrome research, as well as the implementation of the new trans-NIH initiative. In addition, the Committee encourages NIH to prioritize funding for research to improve the health and neurodevelopment of individuals with Down syndrome and typical individuals at risk for immune system dysregulation, Alzheimer's disease, cancer, cardiovascular disease, and autism.

Fiscal Year 2019: Conference (House) Report 115-952

Trisomy 21.--The conferees applaud the NIH for significantly increasing its investment in Down syndrome research and for the NIH Director's leadership in advancing the trans-NIH initiative the Committees included in the fiscal year 2018 appropriation. The conferees direct NIH to continue to make investments in Down syndrome research that prioritize funding for both research grants and early-stage investigators that will expand the current pipeline of Down syndrome research, as well as the implementation of the new trans-NIH initiative. In addition, the conferees encourage NIH to prioritize funding for research for emerging scientific opportunities to improve the health and neurodevelopment of individuals with Down syndrome and typical individuals at risk for immune system dysregulation, Alzheimer's disease, cancer, cardiovascular disease, and autism.

Fiscal Year 2020: House Report 116-62

Trisomy 21.--The Committee commends NIH for its support of the Investigation of Co-Occurring Conditions Across the Lifespan to Understand Down Syndrome (INCLUDE) Initiative. The Committee includes no less than \$60,000,000 within the Office of the Director for the INCLUDE Initiative, an increase of \$22,000,000 above the expected fiscal year 2019 funding level. The Committee expects that this multi-year, trans-NIH research initiative may yield scientific discoveries that could significantly improve the health and quality of life of individuals with Down syndrome as well as millions of typical individuals.

Fiscal Year 2021: House Report 116-450

Trisomy 21.-- The Committee commends NIH for its continuing support of the INvestigating Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) Initiative. The Committee includes no less than \$65,000,000, an increase of \$5,000,000 above the fiscal year 2020 level, within the Office of the Director for the INCLUDE Initiative. The Committee expects that this multi-year, trans-NIH research initiative may advance scientific discoveries that will dramatically improve the health and quality of life of individuals with Down syndrome as well as millions of typical individuals. The Committee requests the Director provide a plan within 60 days of enactment of this Act that includes a timeline description of potential grant opportunities and deadlines for all expected funding opportunities so that young investigators and new research institutions may be further encouraged to explore research in this space. This plan should also incorporate and increase pipeline research initiatives specific to Down syndrome.

Fiscal Year 2021: Conference Report 116RCP68-JES-Division H

Trisomy 21. – The agreement commends NIH for its continued support of the INvestigating Cooccurring conditions across the Lifespan to Understand Down syndromE Initiative. The Committee includes no less than \$65,000,000, an increase of \$5,000,000, for this initiative. The agreement reiterates the directives under this heading in House Report 116-450. In addition, the agreement encourages this project to consider complementary and integrative health approaches to address co-occurring conditions in individuals with Down syndrome, such as traditional Chinese medicine on development, and Applied Behavioral Analysis and Applied Verbal Analysis on development and language acquisition.

Appendix F: Selected Research Accomplishments/Bibliography

[In Progress]