July 10, 2020

Submitted via email to DownSyndrome@mail.nih.gov

Francis S. Collins, M.D., Ph.D.
Director
National Institutes of Health
9000 Rockville Pike
Bethesda, MD 20892

Re: NOT-OD-20-013: Recommendations on Updates to NIH Research Plans on Down Syndrome

Dear Dr. Collins:

LuMind IDSC and the National Down Syndrome Society (NDSS) appreciate the opportunity to jointly submit comments on the Request for Information (RFI) issued by the National Institutes of Health (NIH) on updates to the NIH Research Plan on Down Syndrome. As the leading national Down syndrome advocacy and research organizations, we are grateful for this dedicated and ongoing collaboration between NIH, self-advocates and their families, Down syndrome organizations and the scientific, research and medical communities.

Our recommendations reflect the recent progress and knowledge gained from the INCLUDE project and other advances in Down syndrome research since publication of the 2014 research plan. While substantial progress has been made, we believe our recommendations, if adopted, will substantially improve the health and quality of life for all people with Down syndrome.

Our recommendations draw on the expertise of a broad cross-section of Down syndrome research stakeholder. We organized a group of approximately 60 researchers, scientists, clinicians, medical providers, caregivers and advocates, including self-advocates, in an effort to look at the state of Down syndrome research comprehensively and help us prepare a strategy for achieving specific outcomes for research by the year 2030. We created 12 work groups in the areas of Alzheimer's & Aging; Behavior & Autism; Cancer; Dental & Oral Health; Heart and Vascular; Immunity, Musculoskeletal, Metabolic & Obesity; Sleep and Respiratory; Speech, Language, Hearing & Vision; Basic Research (Including Cognitive Development); and Community Engaged Research.

These work groups started meeting in early 2020 to review what has been achieved since 2014, and what are the gaps and unmet needs. All of the participants, each of whom committed a substantial amount of time and intellectual capital to this project, came together as a group on April 22-23, 2020 for a virtual conference to share information and discuss findings. These work groups were instrumental in crafting our final recommendations, which we hope will give Down syndrome research the attention and funding that people with Down syndrome deserve.

We specifically want to recognize the work of Dr. James Hendrix, who directs scientific initiatives for LuMind IDSC, in organizing the working groups, facilitating the meetings and compiling the recommendations.

Thank you, Dr. Collins, for your support and leadership in elevating the research needs of those with Down syndrome at NIH. We also want to express our appreciation for the team at NICHD and other NIH institutes who are committed to addressing the persistent challenges facing people with Down syndrome across the lifespan. Our organizations are committed to working with the NIH leadership to make the updated research plan a success, and we welcome the opportunity to provide additional information or discuss these recommendations with you and your team at your earliest convenience.

Sincerely,

Kandi Pickard
President and CEO
National Down Syndrome Society

Hampus Hillerstrom
President and CEO
LuMind IDSC Foundation

Attachment

NDSS/LuMind IDSC Recommendations for 2020 Update to the NIH Down Syndrome Research Plan

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II. Priorities for Understanding Down Syndrome

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3. Longitudinal Studies

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III. Priorities for Associated Conditions Related to Down Syndrome

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C. Cancer
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E. Dental & Oral Health
F. Heart & Vascular
G. Immunity
H. Musculoskeletal, Metabolic & Obesity
I. Sleep & Respiratory
J. Speech, Language, Hearing & Vision
K. Basic Research Including Cognitive Development
L. Community Engaged Research

IV. Appendix – Working Groups and Participants

I. Introduction

The following recommendations, developed under the joint leadership of LuMind IDSC and NDSS, represent investments in research that are grounded in current scientific thinking and shared by researchers and clinicians. The two organizations engaged approximately 50 multi-disciplinary scientists and medical experts on a range of topics that could, with research advances, lead to improved healthcare and quality of life for people the Down syndrome throughout the lifespan. Scientific leaders from academia and from leading research organization, including the Jerome Lejeune Foundation and the National Task Group on Intellectual Disabilities and Dementia Practices, contributed to this effort. In addition, members of LuMind IDSC, NDSS, local Down syndrome affiliates, GiGi's Playhouse, caregivers and self-advocates were included in the process to ensure that the Down syndrome community had input into the recommendations.

These recommendations call for investments in research that cut across multiple themes and NIH institutes. To manage the multiple and diverse diseases and medical conditions common in Down syndrome, the scientists were organized in separate working groups. Each working group developed their own recommendations to advance research in their specific area. However, there were many recommendations that were not specific to an associated medical condition and these recommendations were broadly supported by many of the working groups. These broad recommendations are listed below as "Priorities for Understanding Down Syndrome." These recommendations, by definition, should be considered as high priority recommendations. They are categorized in accordance with the categories as outlined in the 2014 Down syndrome research plan, as follows:

A. Pathophysiology of Down Syndrome and Disease Progression (including Genetics)
B. Down Syndrome-Related Conditions: Screening, Diagnosis, and Functional Measures
C. Treatment and Management
D. Down Syndrome and Aging
E. Research Infrastructure

Priorities related to Section D (Down Syndrome and Aging) from the 2014 plan are covered in the Alzheimer's and Aging Working Group recommendations.

After the "Understanding Down Syndrome" priorities, we outline the recommendations each working group considered important priorities for achieving the goals of improved health and quality of life for all people with Down syndrome by 2030.

While we attempted to be comprehensive in our recommendations, some important areas are only tangentially covered. For example, we know that gastrointestinal disorders and dermatology issues are common in Down syndrome, but we hope that addressing the recommended research proposed in the immunity section will address these medical needs.

Likewise, issues of pain and pain mechanisms in the peripheral nervous system in Down syndrome are briefly touched on but, if addressed, would substantially improve the quality of life for many people with Down syndrome. Finally, studies on partial trisomy/mosaic Down syndrome are only briefly mentioned. This is a topic that deserves more attention and could

yield important knowledge about Down Syndrome biology and medicine. We encourage the NIH to consider research in these areas as well.

In the spirit of research inclusion, we also ask that, as new vaccines and treatments for COVID-19 are developed, people with Down syndrome are included in these trials. This will ensure that these treatments are also safe and effective for this vulnerable population.

To fully capture the complexity of Down syndrome research, a diverse and multi-disciplinary group of scientific leaders were needed to draft these recommendations. This same approach should apply to the NIH plan for Down syndrome research. As such, the NIH should continue to support interdisciplinarity and inter-institute research in Down syndrome such as the INCLUDE program. Furthermore, the NIH should look for interdisciplinarity in proposals for improving the health of people with Down syndrome.

Additionally, the NIH should support community engaged research efforts to intentionally and meaningfully include people with Down syndrome and their caregivers/supporters throughout the research process, starting at the very beginning with study design in order to minimize unnecessary burden to the person with Down syndrome and the caregiver. Community engaged research was not outlined as an area of focus in the 2014 Down syndrome research plan, but we feel it is critical moving forward and it supports all other research areas outlined in our recommendations. We must partner with people with Down syndrome as active participants in research, as opposed to passive subjects. Additionally, researchers must seek collaboration with caregivers, supporters, community partners, and non-profit organizations that share the goal of improving the lives of people with Down syndrome. Researchers should be required to illustrate how they have engaged people with Down syndrome and caregivers/supporters in the research process, and we encourage the use of community advisory boards to review proposed research studies to ensure adherence to ethical standards regarding research practices. We recommend that topics which bridge community and researcher agendas be considered highest priority.

An important realization is that certain important areas of medical need for the Down syndrome population were not funded or underfunded historically by the NIH, including Autism, Musculoskeletal/Metabolic/Obesity, Dental/Oral health, Speech/Hearing/Vision, Health/Wellness and Community-engaged Research. This document highlights the need for increased NIH funding in these areas.

Finally, this work will be submitted later in 2020 for publication as part of a review article on recent advances, remaining gaps, and research recommendations for Down syndrome. The article is intended to serve as a call to action to the entire biomedical research community and as a catalyst for advocacy and for giving Down syndrome research the attention and funding that people with Down syndrome deserve.

II. Priorities for Understanding Down Syndrome

A. Pathophysiology of Down Syndrome and Disease Progression (including Genetics)

1. **Standardizing Clinical and Genetic Phenotyping**
    a. Clinical phenotypes may help researchers to better define Down syndrome and could also lead to personalized medicine approaches unique to Down Syndrome from the general population. Understanding changes related to stage of life and aging including inflammation and metabolism may help to better define clinical phenotypes.
    b. **All of US for Down syndrome:** The All of Us program should include a specific sub-study of 5,000 participants with Down syndrome to provide genetic and clinical data to help define Down syndrome phenotypes. GWAS data on 5000 participants should provide enough statistical power to make meaningful phenotype and genotype connections.
    c. Expand genetic and epigenetic profiling beyond chromosome 21 to elucidate complex gene-network effects and to better incorporate existing knowledge from non-Down syndrome patient populations.
    d. A panel of Down syndrome experts (clinicians and researchers) should help define known Down syndrome phenotypes with the available clinical and genetic data to characterize patients and potential clinical trial participants. This research can then inform the development of clinical guidelines to improve Down syndrome medical care.
    e. More Unbiased -Omics data is needed:
        1) Metabolomics both globally and tissue specific metabolomics to help establish metabolic phenotypes and to discover new biomarkers of metabolic disease.
        2) Lipidomics data will be useful in better understanding the risk of diabetes and obesity in the Down syndrome population.
        3) Comprehensive 'omics' in brain samples to define genome, epigenome, metabolome, transcriptome and proteome.
        4) Microbiome (i.e. gut, oral) research in Down syndrome is needed to better understand the potential associations of the microbiome to diseases common in Down syndrome.
    f. Down syndrome data should be accumulated in an expanded DS Connect portal and compared with data from:
        1) the general population.
        2) people with intellectual disabilities but without Down syndrome.
        3) siblings of people with Down syndrome who do not have Down syndrome themselves.
        4) people with familial Alzheimer's disease (autosomal dominant Alzheimer's disease).
    g. See other recommendations outlined in the Priorities for Associated Conditions section.

2. **Develop and validate cellular and animal models that better translate to characteristics in individuals with Down syndrome.**

a. Animal models allow accessible anatomical/behavioral analyses of organismal brain development.
b. Current understanding of Down syndrome neurobiology is derived largely from mouse studies (Ts65Dn, Tc1). However, support for new mouse models that will minimize non-chr21 genetic changes are needed.
c. Support new models (including in mouse, rat, or non-human primate (NHP)) that best model Down syndrome. Animal models that can reflect the structural changes in human Down syndrome brain and other differences such as the immune system are needed. It is important to determine the extent of correspondence between findings in models and human biomarkers.
d. Complete comparative phenotyping including aging and lifespan of all Down syndrome mouse models.
e. Comprehensive 'omics' including the metabolome in all Down syndrome mouse models (including aging studies) are needed to better characterize these models.
f. Define and compare genetics, mechanisms and significance of dysregulated endosomes, exosomes, autophagosome, and proteostasis in all Down syndrome mouse models.
g. Map pathogenesis pathways in the Down syndrome mouse models, testing for the contribution of individual dysregulated genes.
h. Design new treatment paradigms and pathways for testing in Down syndrome mouse models (dose-response/toxicity studies).
i. Define cellular mechanisms for inflammation in Down syndrome.
j. Support development of Down syndrome patient cellular models (e.g. induced pluripotent stem cell (iPSC) neuronal cultures), exploring variation by both sex and genetic ancestry.
k. Facilitate greater cooperation between bench to bedside researchers – Greater support for sharing results and areas of need to enhance translational research in Down syndrome.
    1) Coalesce research focus from bench to bedside to ensure that clinical scientists have the tools to implement advances from bench research, and that bench discoveries are important to bedside. Identify gaps and discrepancies between basic research and clinical observations and address them.
    2) Facilitate collaborations between neuropathologists and Down syndrome clinicians to assess translational relevance of model systems and circulating biomarkers to Down syndrome neurobiology.
    3) Explore links between cellular phenotypes/mechanisms in Down syndrome mouse models with clinical findings including fluid biomarkers between different Down syndrome mouse models and humans.
    4) Translate insights from mouse models to clinic to inform possible treatments and novel trial designs
l. See other recommendations outlined in the Priorities for Associated Conditions section.

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

3. **Longitudinal Studies:** These studies provide valuable data on the population over the life course. These studies help to define clinical phenotypes and inform future research including clinical trials.
    a. There are several longitudinal studies on-going in adults and pediatrics. The NIH should continue to support and possibly expand on-going longitudinal studies to keep these important cohorts generating valuable data for more years.
    b. In addition to longitudinal studies in pediatrics and adults, the NIH should also support studies across all age groups including younger adults and adolescents.
    c. Within existing and new longitudinal cohorts, support efforts to more clearly define and chart trajectory of sex effects and contribution of comorbid conditions (e.g. thyroid function, heart disease, obesity, metabolic disorders, autoimmune disorders, obstructive sleep apnea) to health in Down syndrome. Including data on environmental influences (i.e. education, home setting, work, medications, supplements) can also add insight.
    d. Longitudinal natural history studies across the life span should include cognitive, functional, and behavioral assessments with patient and caregiver reported outcomes, and imaging, fluid and genetic biomarkers.
    e. NIH should be flexible in the management of ongoing longitudinal studies and allow for the incorporation of new technology, data, and/or samples to existing studies as appropriate. For example, as new low-cost genome sequencing technology becomes available, studies could add genomics to existing cohorts.
    f. NIH should facilitate international communication and data sharing of efforts lead by US researchers – e.g. ABC-Down syndrome/Horizon 21. Horizon 21 is a European program that is working to establish a trial-ready cohort to study AD biomarkers in Down syndrome.
    g. Develop partial trisomy and mosaic Down syndrome cohorts, including biosamples, iPSC lines and brain banks.
    h. See other recommendations outlined in the Priorities for Associated Conditions section.

C. Treatment and Management

4. **Increase Support for Randomized Clinical Trials (RTC) in the Down Syndrome Population**. To enable these trials, the following is needed:
    a. More support of traditional drug / device placebo controlled trials are needed across the lifespan in the Down syndrome population.
    b. Build and sustain clinical trial cohorts to evaluate potential treatments across the lifespan.
        1) Assess benefits across the lifespan to improve outcomes in childhood and delay declines in adulthood
        2) A better understanding of the age when an intervention would have the most benefit for people with Down syndrome.
    c. Support for more drug repurposing proposals for Down syndrome where target and mechanistic rationales exist.
    d. Support for RCT) on the efficacy of life-style interventions in the Down syndrome population across the life span is also needed. Life-style interventions could include

exercise, diet, non-regulated supplements, and behavioral interventions. Explore outcomes of physical fitness, health, behavior, cognition, and development.

1) What interventions effectively increase physical activity and reduce sedentary behavior in individuals with Down syndrome across the lifespan? Develop effective lifestyle interventions that foster healthy behaviors in individuals with Down syndrome across the lifespan.
2) Interventions that can reduce obesity and improve overall health outcomes in Down syndrome.
3) Test the efficacy of *technologies* (i.e. animal-assisted therapies, digital, wearable technology) to promote healthy behaviors in individuals with Down syndrome across the lifespan.

e. Find an appropriate control population with which to compare Down syndrome participants (related to BMI, BP, activity levels, intellectual disability, etc.)
f. Studies must build towards a large enough sample size to produce statistical power and significance to generalize the results to populations of those with Down syndrome.
g. Differences in drug metabolism (pharmacokinetics / pharmacodynamics - PK/PD) and drug safety in both children and adults with Down syndrome compared with the general population should be established for experimental drug candidates and with FDA-approved drugs.
h. Establish safety and efficacy in both children and adults with Down syndrome for FDA approved drugs that are commonly used to treat mood disorders, cognitive deficits, autoimmune disorders, and other manifestations commonly treated in this population (e.g. cholinesterase inhibitors). The side effect, safety and efficacy data in Down syndrome needs to be clearly documented including behavioral and cognitive effects of already approved prescription drug treatments to provide physicians with more precise guidance on dose and safety in the Down syndrome population.
i. Improve assessment and management of side effects during treatment. (i.e. pain/nausea during cancer therapy).
j. Support efforts to inform participants and caregivers of the value of research activities and encourage trial participation.
k. Build infrastructure to facilitate enrollment in clinical trials with disease-specific or condition-specific sub-groups. Also, expand expertise in recruiting specific age ranges particularly for adults and underrepresented groups. DS Connect may be expanded or other approaches could be built.
l. Expand support and training in the conduct of Down syndrome clinical trials to sites that may not have clinical research experience or Down syndrome clinical experience.
m. Develop and disseminate methodology for studying cognitive/behavior outcome measures in the context of large, multi-site trials.
    1) Identify the participants with Down syndrome that may be appropriate for a clinical trial given the selected outcome measures.
    2) Measures and approaches need to be developed with considerations about resource availability (some sites may not have the personnel to engage in complex assessments).

3) Develop or employ outcome measures that have demonstrable clinical and ecological utility (i.e., predict real-world changes in behavior, cognition, and/or adaptive skill independence).

n. Harmonize Down syndrome clinical protocols with European and other networks to enable more meaningful data sharing.
o. See other recommendations outlined in the Priorities for Associated Conditions section.

D. Down Syndrome and Aging (see the Alzheimer's & Aging section below)

E. Research Infrastructure

5. **Centralized Biorepository:** We recognize that centralized biorepositories are challenging and often researchers chose not to share the samples that they have collected. However, the Working Group members feel that a centralized (or virtual) biorepository of Down syndrome samples will significantly advance research.
   a. Establish a robust plan for banking of cells, plasma, serum, CSF, and brains.
   b. Expand support for brain banks and fluid biobanks for clinically characterized cases across the lifespan.
   c. Storage of fluid and tissue samples should be centralized (similar to NCRAD) or tracked via a virtual repository, and the collection and storage of the samples should be standardized.
   d. Specific cell types could be produced and stored such as peripheral blood mononuclear cells (PBMC's) and iPSC's and brain derived and peripheral exosomes.
   e. The samples should be from well-characterized participants with Down syndrome with clinical, behavioral, and functional data and with REDCap accessibility.
   f. The NIH should establish a fair and equitable process for reviewing and approving request for access to the valuable samples.
   g. Integrate biobanking efforts with existing "best practices" for genomic data-sharing, including file formats, storage/hosting solutions, and versioning protocols.
   h. Prioritize (epi)genome-wide profiling over candidate-gene profiling to address diminishing costs of throughput while preserving scarce and highly valuable tissue samples.
   i. Integrate the biorepository data with DS Connect. Linking the biorepository data to the demographic, clinical, behavioral and other data from DS Connect would increase the value of both resources.
   j. See other recommendations outlined in the Priorities for Associated Conditions section.

6. **Open Access, Centralized Down Syndrome Data**
   a. The NIH should continue their efforts to establish data standards and data sharing in the Down syndrome research community.
   b. The establishment of a centralized data repository or federated network where researcher can go as a "one-stop-shop" for Down syndrome data will be very helpful for the field.

c. DS Connect could be connected to the centralized data repository mentioned above or it could be expanded to be the "one-stop-shop" for Down syndrome data and for information on access to associated tissues and/or fluids.
d. The NIH should help long standing Down syndrome clinics to digitize their clinical data into a searchable format.
e. Support the creation of curated data sets that included assessment, survey, and transcription Down syndrome data leading to large data sets that support the use of computational modeling.
f. See other recommendations outlined in the Priorities for Associated Conditions section.

7. **Support Down Syndrome Research Training for Clinicians and Scientists**
   a. Additional training in clinical trials and clinical neuroscience in Down syndrome is needed. These efforts should help train clinicians and researchers in Down syndrome who are both established and early in their career to attract them to the field.
   b. It is estimated that only 3% of adults with Down syndrome in the US have access to Down syndrome specialist clinical care. The NIH should support the development of Master Clinics for Adults with Down syndrome (MCADS) that operate on a hub and spoke model to provide adults access to expertise across the US, train physicians in Down syndrome medical care and that enable clinical trial readiness activities for this population.
   c. See other recommendations outlined in the Priorities for Associated Conditions section.

8. **Research Inclusion**: Individuals with Down syndrome have been significantly under-represented and oftentimes excluded from all sorts of research, not just at the NIH.
   a. Develop strategies to increase the participation of people with Down syndrome in non-Down syndrome focused research.
   b. Develop strategies to increase participation in research focused on Down syndrome-specific priorities of people with Down syndrome.
   c. Increase the participation of people with Down syndrome in the design of studies for both Down syndrome and non-Down syndrome specific research.

III. Priorities for Associated Conditions Related to Down Syndrome

A. Alzheimer's & Aging

The quality of life for people with Down syndrome has significantly improved and individuals are now living longer than ever. However, with increased age in Down syndrome the risk of Alzheimer's disease is also increased. In addition, the age of onset for Alzheimer's disease occurs at much younger ages in people with Down syndrome than in the general population. There are also strong genetic drivers for Down syndrome associated Alzheimer's disease (DS-AD) with the APP gene and several other pertinent genes present on chromosome 21. Research is needed to understand the biology of DS-AD and to translate basic science advances to treatments that prevent or lessen progression of Alzheimer's disease.

<u>Priorities Related to Understanding Down Syndrome</u>

1. **Standardize Clinical and Genetic Phenotyping**
    a. Take a 'Precision Medicine' approach to integrate genetic and clinical observations for dementia risk
    b. Define DS-AD risk alleles and compare to those for sporadic Alzheimer's disease
    c. Define epigenetic changes across the life span in Down syndrome for neurons, glia, and endothelial cells, comparing them to Late Onset Alzheimer's disease (LOAD) and Familial Alzheimer's disease (FAD)
    d. Define the role(s) of hormonal changes with aging on DS-AD endotypes and phenotypes in models.
    e. Explore links between cellular phenotypes/ mechanisms and clinical markers, including neurocognitive assessments and biomarkers.

2. **Develop and validate cellular and animal models that better translate to characteristics in individuals with Down syndrome**
    a. Development and characterization of mouse, NHP, and human cellular models of aging and DS-AD.
    b. Decipher genetic, molecular, and cellular mechanisms of aging and DS-AD, including the role for increased APP gene dose in models and other copy number variations to chromosome 21 (HSA21) genes
    c. Comprehensive 'omics' of aging and Alzheimer's disease in mouse, NHP and human cell models
    d. Develop models of genetics, mechanisms and significance of dysregulated endosomes, exosomes, autophagosome, and proteostasis in aging and DS-AD.
    e. Map possible pathogenesis pathways associated with DS-AD to identify treatment targets.
    f. Elucidate conformation and toxic mechanisms of aggregating proteins from human tissue, comparing LOAD, FAD and DS-AD.
    g. Examine telomeric length and regulation in mouse models vs. human cell lines.
    h. Define age-related changes in neurons, glial and endothelial cells in mouse and human models

i. Create and compare models to assess the impact of other HSA21 genes on aging and DS-AD
j. Explore gene-gene interactions between HSA21 and other chromosomes
k. Define the impact of sex on dysregulation of genetic and cellular mechanisms
l. Define differences and similarities between models of DS-AD versus LOAD and FAD.
m. Explore molecular and cellular bases for resilience versus frailty of aging in Down syndrome
n. Examine the role of the microbiome on Alzheimer's disease pathology in Down syndrome.
o. Translate insights from model systems to clinic to inform possible treatments and novel trial designs.
p. Define the role(s) of age-related hormonal changes on DS-AD endotypes and phenotypes in mouse models.
q. Explore and translate lifestyle factors affecting Alzheimer's disease pathology and memory loss in mouse models (exercise, high-fat diets, antioxidant diets).
r. Potentially develop Down syndrome mouse models with human transgenes, leading to aggregates of amyloid and tau.

3. **Support and Expand Longitudinal Studies**
   a. Continue to support and expand longitudinal studies of the natural history of aging and Alzheimer's disease in Down syndrome – beginning in early life.
   b. Develop better and more predictive biomarkers of DS-AD. These biomarkers may help define clinical phenotypes, enable clinical trials, and improve clinical diagnosis of DS-AD.
   c. Encourage further development of multi-site, diverse cohorts for collecting and validating plasma biomarkers, discovering new biomarkers (including CSF-based) and creating cognitive and functional tools for DS-AD.
   d. Undertake epidemiological studies of post-school age adults and older adults with Down syndrome to pin-point onset, trajectories of co-morbidities and the rate of mortality related to Alzheimer's disease.
   e. Compare natural history of DS-AD to LOAD and FAD
   f. Examine gender, ethnic and race differences in DS-AD onset and progression
   g. Explore effects and mechanisms of amyloid angiopathy and breach of blood-brain barrier in Down syndrome and DS-AD.
   h. Explore the role of lifestyle factors and the impact of medical comorbidities in evolution of DS-AD by evaluating epidemiology data and data from longitudinal natural history studies. Examine and define lifestyle habits on contribution to risk and age of onset of DS-AD.

4. **Increase Support for RCT in the Down Syndrome Population**
   a. Improve methods to detect mild cognitive impairment (MCI) in Down syndrome to aid the early clinical diagnosis of DS-AD.
   b. Develop DS-AD specific assessment tools (including composites) of cognition and function that can be used in clinical trials as potential end points.
      1) Consider harmonizing assessments with clinics in the US and Europe (including Horizon 21 protocols) for trial-ready cohorts.

c. Support RCT on lifestyle factors (diet, exercise, training) and other non-medicinal interventions in clinical cohorts as a treatment or to delay the age of onset in DS-AD.
d. Research focused on treatments that specifically targets disorders of aging and DS-AD
e. Critical analysis and reexamination of utility of existing FDA-Approved Alzheimer's disease treatments in DS-AD
f. Invest in studies of functional intervention models for addressing Behavioral and Psychological Symptoms in Dementia (BPSDs) in demented adults with Down syndrome.

5. **Open Access, Centralized Down Syndrome Data:**
   a. Expand studies of populations of adult with Down syndrome to ascertain distribution, demographics, and survival rates of DS-AD.

6. **Support Down Syndrome Research Training for Clinicians**
   a. Development of research clinics in which properly trained clinicians evaluate age-related changes and DS-AD.
   b. Invest in emerging researchers who study presentation of dementia onset behavioral features in adults with Down syndrome.

Priorities Specific to Alzheimer's and Aging

1. Research to improve evaluation of age-related changes and care models for adults with Down syndrome, including impact of co-morbid conditions.

2. Development of standardized approaches to diagnosis and treatment of age-related comorbidities.

3. Encourage research in family studies to determine successful adaptations / transitions by caregivers to dementia caregiving for adults with Down syndrome.

4. Support researchers who study how adults with Down syndrome comprehend and adapt to recognized symptoms of dementia.

B. Behavior & Autism

Down syndrome is a unique but common genetic disorder whose neurobiology and multiple medical disorders result in a combination of developmental, medical, and behavioral issues. A high percentage (20-35%) of people with Down syndrome have significant mental health/behavior challenges. These challenges have very significant impacts and consequences for long-term health and quality of life.

Priorities Related to Understanding Down Syndrome

1. **Standardizing Clinical and Genetic Phenotyping**
   a. Identify behavior phenotypes in infants, toddlers, children, adolescents, and adults.

b. Further characterize phenotypes associated with cognitive, language, and adaptive functions.
c. Investigate the use neurophysiologic data with fluid, imaging, and genetic biomarkers to help establish behavioral phenotypes.

2. **Support and Expand Longitudinal Studies**
   a. Data from longitudinal studies will help define behavioral phenotypes across the lifespan.
   b. Longitudinal cohorts for children with Down syndrome to include studies of:
      1) Attention Deficit Hyperactivity Disorder (ADHD)
      2) Autism Spectrum Disorder (ASD)
      3) Compare each group to children with Down syndrome but without ADHD or ASD.
      4) Compare each group to data on children with ADHD or ASD but without Down syndrome.
      5) Study the development of infants, toddlers, and children with Down syndrome.
      6) Identify children with Down syndrome and ADHD or ASD before 6 years of age, then conduct psychological evaluations every 2 years until 18 years of age.
      7) Include the evaluation of the trajectory of behavioral, cognitive, language, adaptive functions longitudinally (every 2 years) in children with DS and ADHD or ASD.
      8) Include evaluations of sleep and the collection of biomarkers (i.e. neuroimaging and electrophysiology) in longitudinal study of children with Down syndrome and ADHD or ASD.
   c. Evaluate other medical conditions in longitudinal studies that may be contributory (i.e. autoimmune, neuroinflammatory, obstructive sleep apnea) to behavioral issues.
   d. Longitudinal Cohorts for childhood/adolescent-onset depression, anxiety, psychosis, regression / disintegrative disorder.
      1) Further characterize, associated cognitive-language-adaptive functions.
      2) Identify those with adolescent-onset (13-18 years old) and then evaluate every 2 years until young adulthood (up to age 22). Explore the incidence of depression, anxiety, and other behavioral conditions in adolescents.
      3) Include biomarkers (sMRI/fMRI) and sleep evaluations.
   e. Build Longitudinal Cohorts for Biomarker studies.
      1) Use of neuroimaging (sMRI and fMRI) studies of:
         i. Neuromaturation in typical Down syndrome infants, toddlers, children, adolescents, and adults.
         ii. Volumetrics, fiber tracts, grey/white differentiation.
         iii. Comparisons with ASD, depression, regression.
         iv. As predictor/outcome measure for sleep disorders.
         v. Hippocampal volume as a measure of progression in depression-regression syndrome and Alzheimer's disease.
      2) Employ resting state fMRI studies to measure connectivity.
      3) Use of electroencephalogram (EEG) to measure seizures and sleep disorders.
   f. Focus on Down syndrome associated autism, depression, anxiety, and regression.
      1) Further characterize, associated cognitive-language-adaptive functions.
      2) Include biomarkers (i.e. imaging, fluid, and genetic markers).
      3) Explore medical etiology (i.e. sleep, autoimmunity).

g. Contribution and impact of medical comorbid conditions such as sleep disturbances, celiac disease, thyroid disorders, and others on behavior problems such as aggression, ADHD, autism, depression, and anxiety.
h. The impact of behavior problems and psychiatric disorders on the function of individuals with Down syndrome in their daily living, academics, socialization, and overall quality of life.

3. **Increase Support for RCT in the Down Syndrome Population**
   a. **Drug efficacy trials:** Establish efficacy in persons with Down syndrome for experimental drug candidates and with FDA-approved drugs to treat mood disorders, maladaptive behaviors, psychiatric syndromes, sleep disturbance, cognitive deficits and other manifestations commonly used to treat this population.
      1) Conditions: autism, anxiety, depression (mood), psychosis, ADHD, DS-associated Alzheimer's disease (DS-AD).
      2) Commonly used drugs should be evaluated in Down syndrome clinical trials such as: selective serotonin reuptake inhibitor (SSRIs) (i.e. fluoxetine, citalopram), atypical antipsychotics (AAPs) (i.e. aripiprazole, risperidone), cholinesterase inhibitors, stimulants, alpha agonists, and antiepileptic drugs.
   b. **Behavioral therapy trials:** Non-pharmacological treatments: need to study / validate behavioral therapy strategies in Down syndrome for behavior / learning as well as for Down syndrome with ASD or other co-occurring neurological disorders (ND) in rigorous clinical trials. Include a focus on treating cognitive-language and maladaptive behavior.
      1) Include research on the value of social engagement between Down syndrome peers and with typical peers without Down syndrome.
      2) Explore the value of physical activity with Down syndrome peers and with typical peers without Down syndrome.
      3) More rigorous research is needed to test the value of educational inclusion strategies on cognition and behavior.

4. **Support Down Syndrome Research Training for Clinicians**
   a. Support training of Clinical Neuroscience specializing in Down syndrome.
   b. Support training for specialists in behavior and mental health in Down syndrome.

C. Cancer

This variable landscape of cancer raises important questions about the role of immune system and cancer surveillance. Individuals with Down syndrome have higher rates of mortality from infections and greater susceptibility to autoimmune diseases. This raises questions about what protects individuals with Down syndrome from solid malignancies, and the role of the immune system in cancer. It is important to acknowledge the full landscape of cancer research as it relates to Down syndrome, and the research recommended here is focused on the forms of cancer that are prevalent in the Down syndrome population such as myeloid leukemia (ML-DS) and acute lymphoblastic leukemia (DS-ALL).

Priorities Related to Understanding Down Syndrome

1. **Standardizing Clinical and Genetic Phenotyping**
    a. Biological samples from cancer patients should be analyzed for tumor specificity and genomic data to compare Down syndrome and the general population. This data will help to identify phenotypes and, risk factors, and may inform the development of targeted treatments.

2. **Support and Expand Longitudinal Studies**
    a. Characterize neurocognitive, behavioral, and quality of life outcomes beginning during therapy and continuing into survivorship, in order to identify risk factors for poorer outcomes and potential targets for interventions. Characterization of neurocognitive, behavior, and quality of life outcomes will also inform recommendations for supportive care and provide families with psychoeducation about expected outcomes.
        1) An example: children treated for ALL undergo three years of immunosuppressive therapy, which results in frequent hospitalization and decreased community participation, meaning limited early intervention, school, and rehab services. This is particularly true in DS-ALL, given increased vulnerability to treatment toxicity/morbidity. However, we also know that these early and intensive interventions promote neurocognitive development. We need to better understand the role of community participation during treatment to develop evidence-based recommendations.
        2) Neurocognitive monitoring studies should begin during therapy and continuing into survivorship, to align with the standard of care recommendation for the general population of childhood cancer survivors treated with CNS-directed therapy.

3. **Centralized Biorepository**
    a. Biological samples should also be obtained and banked from Down syndrome cancer patients including tumor specificity and genomic data.

Priorities Specific to Cancer

a. The cancer screening and diagnosis particularly in children and infants should be modernized. For example, a better understanding of the role of inherited genomic variation in DS-ALL, to ultimately improve risk stratification for treatment.
b. New research should lead to earlier detection and intervention with improved outcomes for the DS population.
c. Support for epidemiology research on the prevalence of cancers in DS should be expanded. This will be valuable in defining the diagnostic needs.
d. Comparisons of survivability in DS to the general population in cancer treatment
e. Decrease treatment toxicity and treatment related mortality
    1) Examine outcome variability to identify prognostic factors (clinical, genetic, etc.) and inform treatment modifications (reductions of cytotoxic chemotherapy to decrease toxicity)

2) –omics studies to clarify mechanisms, provide basis for targeted treatment/precision medicine
3) Genetic susceptibility to inform treatment targets, surveillance/genetic counseling

D. Cognitive Development & Independence

Given the broad nature of this topic, research is needed to better understand how trisomy 21 impacts people from both the biological and clinical perspective. Research is needed to better understand neurodevelopment and function in Down syndrome. An improved understanding of cognitive development may allow research on aspects of cognitive decline that are preventable or potentially correctable. Clinical interventions and improved diagnostic tools will lead to better outcomes for cognition and independence. The role of new, digital technology to enable greater independence also needs to be explored.

Priorities Related to Understanding Down Syndrome

1. **Support and Expand Longitudinal Studies:** There is a need for large, multi-site, longitudinal studies on specific areas of cognitive outcomes and independence to understand natural development for the purposes of establishing reliable and valid outcome measures.
   a. Identify how different aspects of executive functioning and cognition are best measured at different life stages, yet also allow for consistency in use of measures across lifespan.
   b. Identify how clinically *meaningful* independence is measured throughout the lifespan and recommended as a variable in behavioral studies of individuals with Down syndrome.
   c. Identify what factors influence independence and how they can be modified to support greater independence.
   d. Consider the aspects that influence or improve cognition and independence that are Down syndrome-specific, or more broadly related to IDD.
   e. Identify how to measure outcomes at younger ages to support potential interventions that require earlier introduction (prenatal, or as an infant or toddler), and how to follow outcomes during this earlier period of development to evaluate the impact of interventions.

Priorities Specific to Cognitive Development

1. Further refinement of reliability and validity of cognitive outcome measures for use across the lifespan.
2. Stronger understanding of how cognitive skills impact functional and patient-centered outcomes is needed.
   a. Collaboration across behavioral disciplines is needed to ensure use of reliable and accurate measures.
   b. Focus has been on youth and aging, with young adulthood missing from the literature.

3. Evidence-based guidance for using neurocognitive tools, such as MRI, EEG, TMS, in Down syndrome across the lifespan. Identify how to link neurocognitive performance with underlying brain structure.
4. Extend research to better understand impact of common medical conditions in Down syndrome on cognitive outcome measures (i.e. ADHD, anxiety, AML/ALL, ASD) and any within-syndrome heterogeneity.

Priorities Specific to Independence

1. **Measurement** – Define independence and develop validated methods to measure successful independence. Independence is different from daily living skills and may include methods such increased use of Goal Attainment Scaling.
2. **Meaningful change** – What measurable skills are meaningful to patient, and range of what is currently being achieved vs range of what can be achieved in Down syndrome?
3. **What can we do to achieve meaningful change?** What factors impact independence; can they be modified? What intervention strategies can be used to modify independence (i.e., digital technology)? When do those interventions need to occur?

E. Dental & Oral Health Research Recommendations

Issues of dental and oral health are very common in Down syndrome and are often relate directly to quality of life. More research is needed to understand the impact of dental and oral health in Down syndrome and the association with development, sleep disorders, the immune system and other common co-occurring conditions. This research could lead to greater insights in the role of oral health on the overall health of people with Down syndrome and lead to better treatment options.

Priorities Related to Understanding Down Syndrome

1. **Develop and validate cellular and animal models that better translate to characteristics in Down syndrome individuals.**
    a. Employ Down syndrome mouse models allowing the genetic contribution of chromosome 21 (HSA21) to the Alzheimer's disease related pathology associated to periodontal bacteria: Use various periodontal bacteria alone and in combination to induce periodontal disease. Outcomes: brain infection, Alzheimer's disease pathology, cognition.
        1) timing of brain Aβ deposition, tau pathology, and neurodegeneration.
        2) periodontal disease related inflammatory and bacterial mechanistic pathways.
        3) periodontal disease induced amylogenic mechanistic pathways (synthesis vs. clearance of pathological Alzheimer's disease proteins).
        4) periodontal disease peripheral mechanistic pathways (i.e. contribution of periodontal disease to peripheral amyloid).
        5) the effect of periodontal treatment on brain infection, brain pathology and cognition.

2. **Support and Expand Longitudinal Studies:** Need for large, multi-site, longitudinal studies on issues of dental care and oral health in Down syndrome to better understand caries, eruption on teeth, periodontal disease, and hypodontia in Down syndrome.
    a. **Caries in Down syndrome:** Characterize the caries experience of individuals with Down syndrome over the lifespan.
        1) Do 20% of the children with Down syndrome have 80% of the caries, as is true with typical children?
        2) Characterize the caries experience of aging adults with Down syndrome
        3) **Identify the risk factors for dental caries** in children, young adults, and aging adults with Down syndrome (including race, ethnicity, and health disparities). Past dental caries, low socioeconomic status, recent immigration, mother/caregiver's caries status are some of the risk factors for dental caries in the general population. Do these risk factors hold true for people with Down syndrome or are there additional factors that are specific to people with Down syndrome across the lifespan?
    b. **Characterize the eruption sequence for primary teeth in children with Down syndrome** and determine the factors that promote abnormal eruption times. Investigate how delayed eruption of primary teeth affects the caries experience.
        1) How does this delay of primary teeth affect eating and nutrition, when mastication, in and of itself, is often an issue in very young children with Down syndrome?
        2) Is there an association between the delay of eruption of primary teeth with co-morbidities, such as hypothyroidism?
        3) When a child becomes euthyroid do their teeth then erupt?
    c. **Periodontal disease in Down syndrome:** Support longitudinal cohort studies of Down syndrome adults (including young adults) with/without periodontal disease and with range of periodontal severity.
        1) Study the association of periodontal disease (inflammation and microbiome) and Alzheimer's disease in Down syndrome. Measure cognitive decline and Alzheimer's disease biomarkers (Imaging and fluid biomarkers). Study periodontal disease peripheral and central mechanistic pathways (including clearance of pathological Alzheimer's disease proteins) in people with Down syndrome.
        2) Study the independent and synergistic effect of periodontal disease measures and other common comorbid conditions in Down syndrome (i.e. diabetes, sleep apnea, Alzheimer's disease).
        3) Examine the independent and synergistic role of periodontal and systemic inflammation and oral (subgingival, salivary) microbiome in Down syndrome people. Explore cognition and brain biomarkers (imaging and fluid biomarkers).
        4) Investigate the association of immune system dysregulation with periodontal (gum/bone) disease in individuals with Down syndrome.
            i. Severe periodontal breakdown with horizontal bone loss is often present in the mandibular anterior teeth. The large amount of plaque and calculus alone cannot explain the severity of periodontal disease in individuals with Down syndrome.

ii. Many contributing factors have been reported; abnormal capillary morphology, disorders in connective tissue and anatomical aspects of teeth are some of those considered to be of influence.
iii. Alteration in immunological response may also play a role in the progression of the disease process. Disorders in the polymorphonuclear leucocyte function and monocyte function have been reported in individuals with Down syndrome. T-cell lymphocyte counts are low, and an immature subset of T-lymphocytes is present.

d. **Study hypodontia in children with Down syndrome:** Children with Down syndrome have a reported prevalence of permanent tooth hypodontia (missing less than 6 teeth) or oligodontia (missing 6 or more teeth) between 53.5%-63% compared to 1-11% in the general population.
   1) Explore the potential association of hypodontia and the onset of hypothyroidism, including the use and dose of medications while documenting which teeth are missing. Determine if threshold values of thyroid hormone are not reached in children prior to the age of five years, does this affect permanent tooth development for late-developing teeth such as the premolars.

e. **Study microdontia in children with Down syndrome:** People with Down syndrome have significantly smaller permanent teeth than typically developing individuals.
   1) Explore the potential link of hypothyroidism to the timing of permanent teeth organogenesis in Down syndrome.
      i. In rats, absence of the thyroid hormone, thyroxine, during odontogenesis results in smaller teeth. This is thought to be a result in a decrease in the vascularization of dental structures and hampered proliferation and histodifferentiation of epithelial tissues.
      ii. Since the organogenesis of permanent teeth begins in week 20 of gestation, when nerve growth is critical, if hypothyroidism begins in this period and continues during the long period of tooth formation, can this explain the microdontia seen in the permanent teeth.

3. **Increase Support for RCT in the Down syndrome Population**
   a. **Periodontal Treatments:** Investigate the effect of periodontal treatment (scaling and root planning alone or in combination with antibiotics or other treatment modalities) in adults with Down syndrome on cognition and Alzheimer's disease biomarkers (fluid and imaging).
   b. **Sleep Apnea Treatments:**
      1) Better characterize how orthodontic dental correction impacts obstructive sleep apnea in children with Down syndrome.
      2) Individuals with Down syndrome have a relative macroglossia with a midface hypoplasia and Class III malocclusion due to a maxilla that is narrower than the mandible and is set back in the cranium and often have anterior and posterior crossbites. How does the improvement of the malocclusion with orthodontics affect obstructive sleep apnea in children with Down syndrome?

F. Heart & Vascular

Individuals with Down syndrome face a variety of heart and cardiovascular problems. There is a significant risk of congenital heart malformations which may require medical management and/or correction by surgery or minimally invasive procedures. Aside from this, there are differences in cardiovascular function (such as blood pressure, heart rate, and peripheral vascular resistance) that have ongoing effects over the lifespan. Research into these areas can have a major impact in the health and wellness of individuals with Down syndrome.

Priorities Related to Understanding Down Syndrome

1. **Standardizing Clinical and Genetic Phenotyping**
    a. Identify dysregulated developmental pathways leading to abnormal heart structure and function and resultant outcomes.
        1) Genomics approach: Interrogate nuclear and mitochondrial genes and their possible interactions with genes on chromosome 21.
        2) Integration of -omics approaches to identify perturbed pathways: gene expression, epigenomics, etc.
2. **Develop and validate cellular and animal models that better translate to characteristics in individuals with Down syndrome**
    a. Use of *in vivo* and *in vitro* Down syndrome model systems to study cardiovascular function and therapy responses (efficacy and side effects) to the cardiovascular system.
3. **Support and Expand Longitudinal Studies**
    a. Support longitudinal natural history studies in adults and epidemiology research with available medical records to better understand the effects of aging on the cardiovascular system.
        1) Study adults with Down syndrome and congenital heart disease regarding survival and late complications to better understand comorbid conditions (i.e. many adults with Down syndrome have pacemakers).
        2) The impact of cardiovascular function on the development of Alzheimer's disease in Down syndrome also needs to be studied.
        3) Support longitudinal natural history studies in all ages and epidemiology research with available medical records to better understand the interaction of medical comorbidities (thyroid, diabetes, immune dysfunction, sleep apnea) on heart, blood pressure and vascular function.

Priorities Specific to Heart & Vascular

1. Evaluate cardiovascular function in "normal", abnormal, and repaired hearts of those with Down syndrome, including EKG abnormalities.
    a. Evaluate sex, race, and ethnic differences in cardiac structure/function. For example, it is known that menopause occurs on average 5 years earlier in Down syndrome than in the general population. Does this difference impact cardiovascular function?
    b. Identify environmental risk and protective factors that alter cardiovascular function across the lifespan such as lifestyle (i.e. adiposity, activity level, alcohol consumption, use of chronic prescription meds).
    c. Effect of exercise on cardiac, intellectual, and autonomic functioning.

2. Characterize the differences in vascular resistance, arterial stiffness, BP, and Heart Rate (HR) in those with Down syndrome and determine the associated etiology.
3. Further research on Moyamoya to advance early detection, develop fluid and imaging biomarkers, and better understand the relation to stroke.
4. Examine the effects of anesthesia on cardiovascular function (and co-occurring conditions such as cognition and dementia) in those with Down syndrome, considering the increased number of surgeries typically experienced from infancy to adulthood, as compared to the non-Down syndrome population.
5. Optimization of surgical approaches and associated outcomes of cardiac repair in Down syndrome is needed.
6. Less common forms of complex congenital heart disease in Down syndrome, such as single ventricle, need to be better documented and studied.
7. Study the safety of commonly used unregulated dietary supplements in people with Down syndrome across the lifespan particularly on the impact of heart and cardiovascular safety.

G. Immunity

The need to better understand the role of the immune system in Down syndrome has never been more urgent than now with the global pandemic of COVID-19. Research on the basic biology of the immune system in trisomy 21 is needed to develop animal models and new therapeutic approaches for Down syndrome. In addition, the recognition of differences in the immune system in individuals with Down syndrome is vital to understanding the safety and efficacy of new treatments including the development of a vaccine for COVID-19.

Priorities Related to Understanding Down Syndrome

1. **Standardizing Clinical and Genetic Phenotyping**
   a. **Innate immune cell functional assessment:** There is a serious gap in understanding the function of all innate immune phenotypes in Down syndrome. Deeper understanding of dendritic cell biology, natural killer (NK) cell biology, granulocyte biology, monocytes biology is needed.
   b. **Adaptive immune cell functional assessment:** Significant gaps remain in understanding adaptive immune phenotypes in Down syndrome, including cell-intrinsic & -extrinsic factors regulating T helper (Th) cell differentiation, T cell activation, T cell exhaustion, functional differences, B cell differentiation/activation, B cell function. More research is needed in this area.
   c. **Genetics of immune disorders:** There is a severe paucity of research in phenotype divergence in Down syndrome in terms of immune dysfunction. Inherited genetic variants may well explain some of this and thus this needs to be studied in detail. It is important to determine if standard disease SNPs have similar effects in Down syndrome (e.g. NOD2, ATG16L1T300A) and whether established disease SNPs are reproduced in Down syndrome.
   d. **Trajectory towards autoimmunity.** Studies, for example by Trialnet, show the ability to prospectively identify people at risk of developing type 1 diabetes (T1D). People with Down syndrome show increased risk of T1D at early ages, whether this

trajectory is altered in Down syndrome is unknown. Research to determine the rate of developing disease after autoantibodies appear in Down syndrome is needed. Longitudinal studies to understand alterations in immune cell populations and/or response to perturbations may identify individuals at imminent risk of autoimmunity who may benefit from targeted therapy.

e. **Response to medications.** Better understanding of the efficacy, safety and dosing of medication in DS is needed. It is essential to understand if drugs used in autoimmunity show the same efficaciousness and safety in DS, and if biomarker assays support the need for altered dosing. Conversely, it is important to evaluate whether medications used in DS for non-immune conditions have increased incidence of immune-related side effects, including autoimmunity.

2. **Develop and validate cellular and animal models that better translate to characteristics in individuals with Down syndrome**
   a. There have been several murine models of Down syndrome developed, largely based on ploidy of chr21 genes, that represent potentially useful systems. These models have generally been characterized neurologically; it is essential to characterize them immunologically to understand which aspects of Down syndrome immunopathology are recapitulated in which model systems. Models may recapitulate neurologic and/or immunologic phenotypes in full or in part. This also presents important opportunities to develop and test models of autoimmunity to test mechanistic and therapeutic hypotheses. Researchers can also leverage model alleles of immune-relevant genes to investigate genetic interactions in the immune system.

3. **Support and Expand Longitudinal Studies**
   a. **Immunological atlas in Down syndrome:** Currently we do not understand how the immune system matures in Down syndrome from infancy to adulthood, how this differs from people without Down syndrome and how this impact immune-related diseases in Down syndrome. We need to survey a large Down syndrome population and map the immune system at all ages and create longitudinal studies where the same individuals can be followed over a period of 20+ years. These studies should also incorporate responses to perturbation, both in vitro and in vivo (e.g. vaccines, below).

4. **Increase Support for RCT in the Down syndrome Population**
   a. **Vaccine responses in Down syndrome:** We need to understand well how individuals with Down syndrome respond to canonical vaccines beyond small-scale titer measurements. Is this response durable, is it protective? Do the kinetics differ?
      1) Individuals with Down syndrome need to be included in clinical trials overall and for vaccines specifically.
      2) It is critically important to include people with Down syndrome in the development of new COVID-19 vaccines to ensure that they are safe and effective in the Down syndrome population.

<u>Prioritized Specific to Immunity</u>

1. **B cell biology**: A few reports have documented the lower number of B cells in individuals with Down syndrome. We need to examine in depth the function and development of B cells in individuals with Down syndrome including: B cell differentiation, immunoglobulin subset development, antigen presenting function, and B cell memory.

2. **T cell biology:** Only recently the function of certain T cells has been implicated in Down syndrome, albeit with different results (i.e. regulatory T cells (T regs)). More research on T cell biology in Down syndrome needed specifically on the following:
   a. Th differentiation (Th17, Treg, Th1, Th2) regarding cell-intrinsic and cell-extrinsic factors.
   b. Treg function.
   c. T effector resistance to Treg suppression.
   d. Type 1 regulatory (Tr1) biology.
   e. CD8 T cell biology involving selection, activation, and exhaustion.
   f. Memory (CD4 & CD8) cells.
   g. The dysregulation in thymic selection. AIRE is on chr21 but there is conflicting data on AIRE expression in medullary thymic epithelial cells (MTECs).
   h. Effects of thymectomy on T cell repertoire ("holes").

3. **Inflammation:**
   a. Inflammatory features are omnipresent in Down syndrome. We need to better understand inflammation at every level including skin, blood, brain, other organs.
   b. More research is needed on the role of interferon (IFN) and how IFN drives innate and adaptive (dys)function in Down syndrome.
   c. Research is needed to interrogate the role of individual IFNs in Down syndrome. This is critical for development and selection of therapeutics to restore immune homeostasis without excessive immunosuppression.

H. Musculoskeletal, Metabolic & Obesity

Today, there is an improved understanding of physical activity levels in Down syndrome. There is emerging evidence about benefits of increasing physical activity for managing Down syndrome comorbidities, and there is an improved understanding of physiologic contributors to and morbidities associated with obesity in Down syndrome. Further, there are ongoing international efforts underway to better understand metabolic dysregulations in Down syndrome. However, research is needed to better understand the etiology and timing of weight status changes across the lifespan, the prevalence and prevention of obesity-related secondary conditions, and effective interventions for reducing obesity in this community. In addition, hypotonia is very common in Down syndrome yet it is not well understood, and more research is needed.

<u>Priorities Related to Understanding Down Syndrome</u>

1. **Support and Expand Longitudinal Studies**
   a. Research on the etiology and timing of weight status changes in Down syndrome across the lifespan is needed.

b. The causes of obesity in individuals with Down syndrome across the lifespan is not well understood.
c. Prevalence and prevention of obesity-related secondary conditions (i.e. cardio-metabolic sequela and psychosocial impact). What are the adverse outcomes of obesity in Down syndrome and how can these be prevented?
d. A better understanding of hypotonia and muscle physiology across the lifespan is needed.
e. Longitudinal research studies on motor development and on motor function across the lifespan are needed.
f. How environmental and psychosocial factors impact exercise and metabolism in Down syndrome should be better understood.

2. **Increase Support for RCT in the Down Syndrome Population-** Conduct randomized controlled trials on:
   a. The impact of physical activity and exercise on metabolic health outcomes – including obesity – in individuals with Down syndrome across the lifespan.
   b. The impact of dietary interventions for reducing obesity in individuals with Down syndrome across the lifespan.

Priorities Specific to Musculoskeletal, Metabolic & Obesity

1. A stronger understanding of the metabolic changes over the lifespan associated with Down syndrome is needed related to obesity, inflammation, immunity, insulin resistance, glucose intolerance and risk for diabetes.
   a. The study of common metabolic mechanisms in Down syndrome is needed
   b. The NIH should foster collaboration with global studies like the European effort (GO-DS21) and others.

2. Study the *causes* of low physical fitness in Down syndrome. Explore physiological, behavioral, and environmental factors. The studies need to be well-designed and properly powered to reach meaningful conclusions.

3. Support the study of hypotonia in Down syndrome. Little is known about the genetic or biochemical basis of hypotonia. Include exploring the role of mitochondrial alterations in hypotonia.
   a. What is the etiology of hypotonia in Down syndrome?
   b. Research on muscle development and weight gain in children with Down syndrome is needed.
   c. Are age-related muscle and weight loss processes different in Down syndrome than in the general population?

4. Study the relationship between physical activity and physical wellness in Down syndrome. These may offer ways to improve the quality of life.
   a. What are the determinants of physical activity in individuals with Down syndrome across the lifespan?
   b. Sedentary behavior.

1) What are the levels and patterns of sedentary behavior in individuals with Down syndrome across the lifespan?
2) What are the determinants of sedentary behavior in individuals with Down syndrome across the lifespan?

c. Relationships between physical activity, physical fitness, and health in Down syndrome
1) What is the impact of *physical fitness* on health outcomes in Down syndrome?
2) What is the impact of *sedentary behavior* on health outcomes in Down syndrome?
3) What are the *interactions* among physical fitness, physical activity, and sedentary behavior and their collective impact on health outcomes in Down syndrome?

I. Sleep & Respiratory

Sleep disorders such as obstructive sleep apnea (OSA) are common in both adults and children with Down syndrome. It is known that sleep disorders may be associated with cognitive impairment and progression to dementia. More research is needed to understand these associations in Down syndrome, while also developing new diagnostic tools and treatments for sleep disorders. There are also many serious respiratory issues that impact individuals with Down syndrome. For example, pulmonary hypertension (PH) is a significant cause of morbidity in children and infants with Down syndrome. More research is needed in PH to provide clinical guidance to prevent the PH in Down syndrome.

Priorities Related to Understanding Down Syndrome

1. **Standardizing Clinical and Genetic Phenotyping**
   a. Establish clinical and/or genetic phenotypes related to normal sleep patterns and sleep/circadian rhythms disorders. For example, there is no normative data regarding recommended hours of sleep in individuals with Down syndrome.
   b. Characterize the clinical and molecular phenotypes that distinguish Pulmonary hypertension (PH) in children with Down syndrome from PH in children without Down syndrome that would allow the development of pharmacological clinical trials, and guidelines for monitoring and management of pulmonary hypertension in children with Down syndrome.

2. **Support and Expand Longitudinal Studies**
   a. Conduct epidemiologic research using available medical records to determine the prevalence and severity of all sleep and circadian rhythm disorders in Down syndrome. Currently, studies have been limited to mostly obstructive sleep apnea (OSA).
   b. Support multi-centered, methodological homogeneous studies, to evaluate the importance of sleep and the impact of sleep disturbances with objective sleep measures on:
      1) Learning and brain development children with Down syndrome;

2) Cognitive impairment in children and adults with Down syndrome. Develop a battery to assess the cognitive impact of sleep disturbances in Down syndrome (specifically for children, adults, and in adults with cognitive impairment);
3) Whether sleep disorders are worse (conatal) with neuropsychological deficits in individuals with Down syndrome; and
4) The progression to Alzheimer's dementia in adults with Down syndrome.

c. Explore the relationship between changes in sleep, behavior, cognition, neuroimaging, and Alzheimer's disease biomarkers.

3. **Increase Support for RCT in the Down Syndrome Population -** There is a need for randomized controlled clinical trials in the Down syndrome population to evaluate the efficacy of different types of sleep treatments and diagnostic tools in children and adults with Down syndrome, such as.
   a. **OSA:**
      1) Test the efficacy of OSA treatments such as adenotonsillectomy, continuous positive airway pressure (CPAP), mandibular advancement devices, hypoglossal nerve stimulation, weight loss, and others in Down syndrome across the lifespan.
      2) Explore whether OSA treatments can minimize cognitive/behavioral impairment in children and adults with Down syndrome, and progression to dementia in adults with Down syndrome.
      3) Study the relationship between changes in cognitive parameters and sleep architecture.
      4) Study the feasibility and validation of at-home diagnostic tools including actigraphy, home sleep apnea testing, and wearable technologies.
   b. **Circadian Disturbances:** Evaluate the efficacy of treatments for circadian disturbances, such as light therapy, melatonin, and others in Down syndrome across the lifespan.
   c. **RLS/PLMD:** Establish the efficacy and safety of Restless Legs Syndrome (RLS) and Periodic Limb Movement (PLMD) treatments such as iron, gabapentin, and others in Down syndrome.
   d. **Insomnia:** Conduct cognitive behavioral and pharmacological treatment clinical trials for insomnia, including sleep behavior in child with Down syndrome.

<u>Priorities Specific to Sleep & Respiratory</u>

1. **Micro-aspiration and airway abnormalities:** Research on the evaluation of micro-aspiration and airway abnormalities in Down syndrome is needed.
   a. Research is needed to determine the age when children with Down syndrome should be tested for micro-aspiration and airway abnormalities.
   b. More research on the identification of children with Down syndrome needing early laryngeal evaluation is needed.

2. **Pulmonary hypertension (PH)** is a significant cause of morbidity in children and infants with Down syndrome. More research on PH in children with Down syndrome is needed.
   a. Support PH research that will lead to the development of clinical guidelines for airway evaluation in children with Down syndrome that incorporate multi-disciplinary aerodigestive programs starting in infancy.

3. **Evaluation:**
    a. Design and validate **sleep questionnaires** and sleep scales, to screen for sleep disorders in the Down syndrome population.
    b. Develop evidence-based **Sleep Guidelines** to screen and treat OSA **in children and adults** with Down syndrome. There is a need to characterize sleep patterns and assess the prevalence and type of sleep disorders in adults with Down syndrome. Adults with Down syndrome should be routinely asked and evaluated for sleep disorders, most frequently OSA.

4. **Education:**
    a. Healthcare and caregiver **sleep education** to increase awareness about the presence of sleep disturbances, their impact on quality of life, and potential treatment in children and adults with Down syndrome.
    b. Clinicians and researchers' education need to be supported to develop these guidelines.

5. Assess acute and long-term health consequences of OSA in individuals with Down syndrome. Does OSA impact cardiovascular health, cognitive decline, Alzheimer's disease, metabolic disorders, etc.?

6. Develop evidence-based medical guidelines for management of sleep disorders other than OSA in Down syndrome.

J. Speech, Language, Hearing & Vision

Communication is a critical element for any person's quality of life. Childhood development is clearly linked to the development of speech, language, hearing and vision. Research on these issues in individuals with Down syndrome is needed to develop new tools and methods that will improve communications skills, independence, and quality of life.

Priorities Related to Understanding Down Syndrome

1. **Standardizing Clinical and Genetic Phenotyping**
    a. Identify Down syndrome behavioral and genetic phenotypes and environmental factors to inform our understanding of natural development, the timing, and targets of interventions for cognition; communication (i.e., speech, language, and augmentative/alternative communication (AAC)); hearing and balance; and vision.

2. **Support and Expand Longitudinal Studies**
    a. Research is needed to examine the relationships among breathing, sleep apnea, and speech production, to identify common factors that could be addressed in treatment.

3. **Increase Support for RCT in the Down Syndrome Population**

a. RCT's with larger samples are needed to accurately assess the efficacy of new interventions for improved cognition; communication (i.e., speech, language, and AAC); hearing and balance; and vision. A rigorous program of clinical trials that combine augmentative and alternative communication approaches with parent responsiveness training should be created.
    1) A recent comprehensive review of intervention studies for children with Down syndrome indicated that high levels of parent responsivity during early childhood can enhance communication growth when combined with intensive augmented communication and language interventions. In contrast to young children with autism, and despite the seriousness of their communication and language delays, only a very few small clinical trials have been conducted with this population.

Priorities Specific to Speech, Language, Hearing & Vision

1. **Language:**
    a. Validate language measures that are sensitive to change in those with Down syndrome.
    b. Support the development and validation interventions across multiple contexts (i.e., parent-implemented, telehealth, and school-based), thus increasing access to high-quality interventions for those with Down syndrome. This includes developing strategies that persons with Down syndrome can use to overcome failures in speech communication. Examples of strategies are slowed speaking rate, use of supplementary cues such as manual signs, recasting the utterance, and enhancing the communicative environment.
    c. Investigations of language/communication intervention intensity to identify recommendations for the length and dosage of interventions for optimal outcomes. This includes identification of alternative intervention agents, such as peers, teaching, and parents.
    d. Research on literacy interventions and outcome measures for communication competence. Promotion of these skills will support independence and quality of life, as well as, transition from school to the workforce. Develop treatment strategies to improve phonological awareness. Such treatments may lead to improved speech production and literacy.

2. **Speech Intelligibility:** The reduced speech intelligibility that often occurs in children and adults with Down syndrome can greatly hamper communication with other people and can interfere with use of voice-activated technologies (e.g., Alexa and Google Home).
    a. Difficulty with intelligibility often arises from two general aspects of the speech disorder: dysmorphologies of the craniofacial and laryngeal structures, and motor speech impairments (e.g., dysarthria, childhood apraxia of speech). Research is needed to distinguish the effects of these two factors and to develop personalized clinical assessments and treatments.
    b. Research has shown that speech production in persons with Down syndrome is affected by dysfunctions in the subsystems of speech production (e.g., respiratory, phonatory, articulatory, resonatory, and prosodic). A better understanding is needed for the interaction among these subsystem dysfunctions, their patterns of change

during development and aging, and their combined contribution to reduced speech intelligibility.

c. Assess the biomechanical and kinematic properties of the vocal tract to obtain more complete and accurate information on speech physiology in Down syndrome. These forms of data would deepen the understanding of speech motor impairments common in individuals with Down syndrome. Examples are:
    1) assessing the distribution and severity of hypotonia in the speech production system (possibly by measuring perioral biomechanical stiffness).
    2) determining the kinematic properties of articulatory movements.
    3) measuring the muscular and aerodynamic forces developed during speech production.
d. Develop apps and computer-based therapies that can be used in telehealth, home-based, and school-based treatment programs to improve intelligibility. These should be designed to accommodate different levels of cognitive or linguistic ability.
e. Evaluate the benefits of different speech supplementation techniques at different points in the lifespan. Speech supplementation is the use of additional cues such as context, gestures, or visual signs and symbols.
f. Determine the relationships between speech domains (especially intelligibility and prosody) and receptive and expressive language.
g. Quality of speech often is affected in Down syndrome, even in individuals who are intelligible, but the reasons for atypical quality are not well understood. Research is needed to assess phonatory and resonatory factors related to speech quality, with the goal of developing treatment strategies.

3. Hearing and Balance:

a. Given evidence of structural and functional abnormalities in the auditory and vestibular systems over the lifespan, it is important to gain a better understanding of the emergence of these abnormalities and possible changes with aging. This information is critical background for advances in assessment and treatment.
b. There is a need for treatments (e.g., pharmacological, genetic, RCT) designed to account for developmental and aging effects, as well as complications related to overall health and to specific dysmorphologies.
c. The sensory systems of vision and audition develop in concert and in relation to foundational body-centered senses to support balance, posture, and motor coordination. More information is needed to formulate strategies of prevention that can be followed to reduce the occurrence of vestibular and sensory integration disorders.
d. Establish guidelines for assessment of auditory and vestibular function during the lifespan, to include screening tests that can be used in routine health examinations.
e. Data are needed on the relationship between anatomic and physiological features of the auditory-vestibular complex and functional measures of hearing and balance.
f. Design modifications of hearing aids to address issues such as stenosis of the external auditory canal and dysmorphologies of the pinna.
g. Determine the relationship between hearing disorders and general patterns of communication and education.

4. Vision:

a. Studies are needed to evaluate specific sources of visual acuity deficits to assist in the development of appropriate treatment strategies that can target specific deficits. Potential topics for investigation include evaluation of corneal structure, mapping the time course for development of refractive error, determining the integrity of the retinal structure, and evaluating visual neural processing.
b. Clinical trials evaluating treatments to improve acuity are needed, particularly in young children prior to the development of neural adaptations from early poor visual experiences.
c. Studies are needed that will evaluate corneal structure and the longitudinal stability of corneal structure. These studies are critical to understanding the elevated risk for keratoconus in persons with Down syndrome, and to guide the timing of potentially invasive treatment strategies, such as corneal crosslinking, when keratoconus is suspected.
d. Evaluating the relationship between visual acuity and commonly observed binocular vision and functional vision abnormalities (e.g. strabismus, nystagmus, reduced ocular accommodation, reduced stereoacuity) may be beneficial in identifying common neural deficits negatively impacting multiple aspects of the visual system, as well as guiding whether the treatment of visual acuity alone can positively impact binocular and near visual performance.
e. Ocular imaging is a non-invasive means to observe vascular and neural manifestations of systemic disease. Studies that evaluate the use of ocular biomarkers (e.g. retinal structure) may lead to new strategies for the diagnosis of systemic disease, or for monitoring progression of disease when other objective strategies are otherwise unavailable, such as in Alzheimer's disease.
f. Histological studies of corneal tissue that evaluate the anatomical structure of the corneal layers will further understanding of structural differences in the cornea of persons with Down syndrome and whether they share similar features to the corneas from typical individuals who developed the disease keratoconus.

K. Basic Research Including Cognitive Development

Many gaps remain in our fundamental understanding of the biological impact of Trisomy 21. It is important to support research that will increase the understanding of the impact of Trisomy 21 on the brain to identify best targets and critical timeframes for most effective biological therapies. The main questions are summarized as 1) Where/What? 2) When? and How/Why?

- **WHERE/WHAT?** What regions and cells of brain are most impacted? How do these connect to cognitive phenotypes? Do other systems (e.g. congenital heart, inflammation, thyroid) contribute?
- **WHEN?** When do deficits in neurodevelopment and function arise? When are these deficits preventable or potentially correctable? *How much is neural cell development vs. function*?
- **HOW/WHY?** How mechanistically does trisomy for *normal* Chr21 genes impact neural cells and cognition in Down syndrome? How many (and which) Chr21 genes are dosage-sensitive?

Priorities Related to Understanding Down Syndrome

1. **Develop and validate cellular and animal models that better translate to characteristics in individuals with Down syndrome.**
    a. **<u>Human stem cell models</u> are powerful to investigate <u>*human*</u> T21 impact at <u>cell and organoid level</u>**
        1) Support research to identify cell pathologies that allow mechanistic manipulations.
        2) Evolving experimental designs for better reproducibility needed.
        3) Support more research on the inducible silencing of one chromosome 21 which could have a large impact on DS research and therapy development.
        4) Support the use of human iPSC models to reveal the timing of specific steps in cellular pathogenesis.
    b. Study brain development over time in DS mouse models and compare with human studies of brain development.
    c. **<u>Why?</u>** Support more mechanistic studies on the links between T21 and cognition. **Studies have implicated:**
        1) Several Chr21 candidate genes including some that are involved in neurodevelopment.
        2) Developmental signaling pathways (e.g. Shh, NOTCH, NFAT).
        3) Multiple mechanisms of stress.
        4) Oxidative/mitochondrial stress.
        5) General aneuploid/proteomic stress.
        6) Integrated Stress Response (ISR).
    d. Identify functional deficits caused by trisomy 21. Studies have reported aberrant synapses with imbalances, cell stress pathways activated, mitochondrial deficits and endosomal enlargement, but a deeper understanding is needed.
    e. Research on the role of many more unstudied or understudied Chr21 genes (and RNAs) is needed.
    f. How do we factor in DS variability or gene interaction effects? More genetic and -omics studies from a larger number and more diverse number of DS participants is needed.
    g. Better tools are needed to enable drug discovery and development. Human cell/organoid models can be used to test drugs for <u>cell-based</u> pathologies.

2. **Support and Expand Longitudinal Studies**
    a. **<u>When</u>** do biological differences that underlie cognitive deficits first arise? Children often score more mildly impacted than adults, indicating progressive decline. This question is critical for the testing of therapeutic candidates but not sufficiently studied. Therefore:
        1) Longitudinal studies across the lifespan are needed that include non-invasive brain imaging, especially of pre- and postnatal brain development, biomarker analysis and genomic studies to better understand the cognitive variability in DS.

3. **Centralized Biorepository**
    a. **<u>Humans</u> are gold standard to identify impacts on brain structure/function, <u>where possible.</u>**
        1) More support for DS brain banks is needed because studies with autopsy tissue are extremely valuable, but small sample sizes and variable status limit their impact. Include access to fluid sample and DNA from DS individuals.
        2) Increased support for prenatal studies is needed where possible.
    b. **<u>What</u>** brain regions and cells are most impacted in DS? **Define anatomical impacts of trisomy 21.**
        1) Limited studies are based on small sample sizes have reported smaller cortex and cerebellum, hippocampal synaptic plasticity, myelination, reduced neurons, more glia and dendritic spine defects.
        2) The cellular basis for smaller brain regions is not clear due to small sample sizes, variables are not well controlled leading to inconsistent conclusions and contradictory conclusions which remain unresolved.

<u>Priorities Specific to Basic Research Including Cognitive Development</u>

1. **Better tools are needed to enable drug discovery and development**
    a. More <u>biomarker research</u> is needed to advance drug development. Biomarkers that can enable the transition from the lab to the clinic will be most valuable. For example, there are limited EEG studies of Ds individuals to examine functional activity.
2. **When is a Cognitive Deficit Still Amenable to Improvement? When is a cognitive deficit still reversible or substantially correctable (by any means)? Could address this with:**
    a. model systems of inducible "trisomy silencing."
    b. specific gene silencing (e.g. APP).
    c. other specific genes might be shown to contribute to early cognitive deficits. If so, gene-based therapies could be used.
    d. Non-genetic correction or therapies for improvement of cognition. For example, drug targeting an affected molecular pathway such as Integrated Stress Response.

L. Community Engaged Research

To best understand Down syndrome, we must ask people with Down syndrome about their lived experience. Through community engaged research, we can incorporate the perspectives of people with Down syndrome and caregivers/supporters, the two key stakeholders in Down syndrome research. Historically, community concerns and interests have been left out of the research agenda due to poor communication between communities and medical researchers. **Engagement is critical to building trust between the Down syndrome community and medical researchers.** Without community engagement, research topics will not reflect the priorities of the community, research studies will not be effective in recruiting participants, and research findings will not be disseminated effectively back to the community and incorporated into practice. We recommend that topics which bridge community and researcher agendas be considered highest priority.

The Community Engaged Work Group gathered feedback in two ways: 1) workgroup recommendations through a series of phone calls, 2) phone interviews with self-advocates with Down syndrome. Themes from these efforts are presented as General Recommendations and Specific Recommendations regarding research focus areas of interest to adults with Down syndrome and caregivers/supporters. Additionally, we present take-aways from LuMind IDSC-supported surveys with 2700+ caregiver participants.

General Recommendations

1. **Selection of research topics**
    a. **Research across the lifespan:** Historically, Down syndrome research has focused on pediatric populations. Recent efforts regarding Alzheimer's disease and aging reflect improvements in life expectancy for the Down syndrome population and important topics suggested by caregivers. However, self-advocates voiced concern over a lack of research about topics of importance during adulthood. We recommend that Down syndrome research utilize a lifespan approach, ensuring that areas of research focus are distributed across the lifespan, as opposed to only addressing topics at the beginning and end of life. Our discussions revealed that only through a lifespan approach will concerns of the entire community—people with Down syndrome and caregivers/supporters—be addressed.
    b. **National Institute on Minority Health and Health Disparities Research Framework:** Given that people with Down syndrome experience health disparities and are impacted by social determinants of health, we recommend the use of the NIMHD framework. Proposed research studies and areas of focus should be mapped to this framework, to ensure efforts across domains of influence (biological, behavioral, physical/built environment, sociocultural environment, health care system) and across levels of influence (individual, interpersonal, community, societal).

National Institute on Minority Health and Health Disparities Research Framework

		Levels of Influence*			
		Individual	**Interpersonal**	**Community**	**Societal**
Domains of Influence *(Over the Lifecourse)*	**Biological**	Biological Vulnerability and Mechanisms	Caregiver–Child Interaction Family Microbiome	Community Illness Exposure Herd Immunity	Sanitation Immunization Pathogen Exposure
	Behavioral	Health Behaviors Coping Strategies	Family Functioning School/Work Functioning	Community Functioning	Policies and Laws
	Physical/Built Environment	Personal Environment	Household Environment School/Work Environment	Community Environment Community Resources	Societal Structure
	Sociocultural Environment	Sociodemographics Limited English Cultural Identity Response to Discrimination	Social Networks Family/Peer Norms Interpersonal Discrimination	Community Norms Local Structural Discrimination	Social Norms Societal Structural Discrimination
	Health Care System	Insurance Coverage Health Literacy Treatment Preferences	Patient–Clinician Relationship Medical Decision-Making	Availability of Services Safety Net Services	Quality of Care Health Care Policies
Health Outcomes		**Individual Health**	**Family/ Organizational Health**	**Community Health**	**Population Health**

National Institute on Minority Health and Health Disparities, 2018
*Health Disparity Populations: Race/Ethnicity, Low SES, Rural, Sexual/Gender Minority
Other Fundamental Characteristics: Sex/Gender, Disability, Geographic Region

2. **Approach to research**
   a. **Dyad approach to research:** Given the structure of support networks for people with Down syndrome, we recommend that research utilize a dyad approach when feasible. People with Down syndrome and caregivers/supporters do not exist in isolation; their needs must be considered simultaneously when designing studies.
   b. **Intersectional approach to research:** Down syndrome is only part of an individual's identity. The extent to which a person with Down syndrome identifies with Down syndrome varies. Respect for how people with Down syndrome view themselves is lacking in research studies. Studies should view people with Down syndrome as people, acknowledging that multiple identities (race, gender, class, sexual orientation) overlap within a single person and contribute to one's lived experience.

3. **Representation in research**
   a. Efforts should be made to improve representation in Down syndrome research, for the research agenda to represent the concerns of the entire Down syndrome community. Representation with respect to race, gender, sexual orientation is lacking not only in participants with Down syndrome and participants who are caregivers/supporters, but also in researchers. This issue contributes to the inadequate recruitment of diverse populations of people with Down syndrome in research studies. Given that building trust with the Down syndrome community is critical, we encourage NIH to: (1) Increase funding for research, training programs,

and outreach initiatives focused on minority and non-English speaking researchers, scientists and clinicians interested in Down syndrome research; and (2) increase minority representation among non-governmental organizations participating in the NIH Down Syndrome Consortium.

4. **Meaningful engagement of self-advocates and caregivers/supporters at each step of the research process**
   - **a.** Self-advocates and caregivers/supporters voiced concern over research study materials not being written in a way that is accessible and easily understandable. This includes study descriptions, informed consent/assent documents, information provided related to confidentiality and privacy of data, and materials for dissemination.
   - **b.** Early engagement of participants in study design will ensure that communications are accessible. Materials should incorporate principles of universal design, so that documents are accessible for all and do not require adaptations based on an individual's unique needs. It is the researchers' responsibility to adapt to the needs of the community, not the other way around.

Specific Recommendations

In addition to the four general recommendations above, we recommend three specific research focus areas. Discussions with self-advocates (adults with Down syndrome) and with caregivers/supporters suggested the following topics as high priority research areas:

1. **Mental Health & Wellness:** This topic was highlighted by every self-advocate we spoke to, as the current pandemic has presented unique challenges for people with Down syndrome, including loss of independence, loss of routines, loss of in-person programming, and loss of physical fitness activities. Given that crisis can trigger regression symptoms, a proactive approach is critical.
   - **a.** Tools to foster coping skills regarding grief/loss, disruption of routines.
   - **b.** Efforts aimed at preventing crisis.
   - **c.** Screening tools and instruments for depression and anxiety.
   - **d.** Accessible resources regarding managing depression and anxiety.
   - **e.** Holistic approach to wellness, recognizing that associated conditions outlined in these recommendations (sleep, nutrition, oral health, obesity) do not manifest in isolation.
   - **f.** Provider training regarding diagnostic overshadowing.
   - **g.** Researcher training regarding how research topics and results are presented, as the way in which research agendas are presented can unintentionally elicit psychological distress in participants with Down syndrome.
   - **h.** Self-advocates voiced that healthy relationships with friends is critical for mental health.
2. **Independence & Empowerment:** Self-advocates and caregivers/supporters suggested multiple research topic areas that promote independence and empowerment of people with Down syndrome. This reflects the aging of the Down syndrome population and the desire of adults with Downs syndrome to be treated like adults. Narratives regarding how people with Down syndrome have 'exceeded expectations' simply illustrate

pervasive low expectations, which is a problematic barrier to the independence and empowerment of people with Down syndrome.

   a. Taking ownership of one's health, goal setting.
   b. Employment: supports and barriers.
   c. Transportation: supports and barriers.
   d. Self-advocates called for research addressing the physical and mental health of caregivers/supporters.
   e. Consent/assent processes in research should be made accessible, which demonstrates respect for participants.

3. **Disaster Preparedness**
   a. All self-advocates voiced concern over being left out of ongoing discussions regarding coronavirus response.
   b. Lessons learned during the pandemic can inform strategies for future disaster preparedness efforts.

Caregiver Survey Results

Finally, we present results from caregiver surveys supported by LuMind IDSC that had >2,700 participants. Survey topics were:

1. Behaviors, attitudes, and knowledge towards research (N=256) (with Nicole White, Antioch University, Anna Esbensen, Cincinnati Children's).
2. Three other separate short surveys on research (N= 367).
3. Sleep apnea (N=800).
4. Independence (N=400).
5. Topics of interest (N=400).
6. Focus groups adult caregivers (N=40) (with Eli Lilly and NDSS).
7. COVID19 survey (N=459) (with T21RS).

Highlighted results include:

1. 92% wishing to see new drugs and interventions for their loved one with Down syndrome.
2. Multiple surveys showed consistently the following as key research needs: Alzheimer's, Cognition, Independence, Sleep apnea, Behavior, Speech/Communication.
3. Alzheimer's is the most important topic of interest for caregivers/supporters of individuals with DS of all ages.
4. 89% want their loved one with DS to be as independent as possible (9% additional said some independence).
5. Sleep apnea treatment options with CPAP mask only appropriately treats 17% of those diagnosed with sleep apnea.
6. Need more data on COVID19 cases in DS - how the virus affects people with DS based on pre-existing co-morbidities and any safety differences compared to the general population.
7. Caregivers/supporters frequently have extra challenging day to day situations, so efforts should be taken by researchers to minimize the burden for the individual with Down

syndrome and the caregivers/supporters to remove barriers and maximize research participation.

In summary, it is important to recognize that research areas of interest to people with Down syndrome and to caregivers show similarities and differences, as illustrated in the table below. To engage the Down syndrome community, the NIH must support research on a variety of topics, encompassing both biomedical and functional perspectives.

Most frequent topics of interest	**Feedback from individuals with DS (interviews)**	**Feedback from caregivers/supporters (interviews and surveys)**
Empowerment	X	X
Independence	X	X
Mental Health & Wellness	X	X
Exercise/Nutrition	X	X
Alzheimer's disease		X
Cognition		X
Sleep apnea		X
Speech/communication		X
COVID19/disaster preparedness	X	X

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