

**From:** [Steve Stock](#)  
**To:** [Down Syndrome Responses](#)  
**Subject:** Request for Information RE: Down syndrome  
**Date:** Friday, April 17, 2020 3:47:53 PM

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RE: Remaining research gaps not addressed by either the 2014 NIH Research Plan on Down Syndrome, or the 2018 INCLUDE Research Plan, especially those that can be started or completed within a five- to seven-year timeframe. People with Down Syndrome are significantly underserved by technology, particularly self-support technologies and apps that can increase independence and reduce dependency on others in various areas of daily living.

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A response to notice number, NOT-OD-20-013

**On the topic: Research Infrastructure**Part One: National Registry

As a self-advocate member of the Down Syndrome Consortium, I participated in field-testing the National Down Syndrome Registry before it was officially launched in September 2013. I am glad to see that 5,000 individuals have now completed the on-line survey of the NIH/ NICHHD's "DS-Connect®". It was indicated in a DS Consortium recent meeting that a goal would be to increase the number of people with Down syndrome who are included in the registry to 10,000.

The following are some. Ideas to increase the number of people registered in DS Connects:

1. As part of a plan to increase public awareness about the importance of "DS-Connect®", work with different entities, including the national Down Syndrome organizations, to have people with Down syndrome share their own personal experience and ideas about why they have participated in the National Down Syndrome Registry. This could be accomplished through compiling short videos or photos with written statements to explain how "DS-Connect®" can help them and their families better understand why research has an impact on their own lives.
2. To set up a family-to-family campaign and enlist families who are already part of the registry to help recruit other families of people with Down syndrome who they know to also enroll in the registry. Families can then share information with other families about what registry can provide for them such as access to information about opportunities to participate in research in different areas.
3. To set up an educational campaign, working perhaps with CMS, to inform and encourage Medicaid and other Managed Care organizations to reach out to people with Down syndrome and their families/staff, who they serve, in order to provide information about "DS-Connect®": The Down Syndrome Registry. The goal would be to explain to families why might think that it is important to participate in the national registry and how they can use the website to find out about research studies available for their participation as well as other resources.

Part Two: Website

I think that it is especially important to continue with the progress from the 2014 plan to "...continue to expand the NIH website with information on Down syndrome and related research, including user-friendly information relevant to the research, clinician, and family communities, pending clinical trials, and funding opportunities. The site should also include links to information about up-to-date diagnosis and treatment guidelines adopted by nationally

recognized professional societies”. Using the same ideas listed in Part One for increasing the registry, these same ideas can be combined with educating individuals with Down syndrome, their families and professionals about what is available on the website.

**On the topic: Conducting translational research, including connecting existing resources and establishing a cohort of individuals with Down syndrome for study.**

More than twenty years ago, I wrote about some ideas I had that are also part of the 2014 Research Plan and the INCLUDE Project Research Plan. The book is *Aging, Rights, and Quality of Life: Prospects for Older People with Developmental Disabilities* by Stanley S. Herr and German Weber, Paul H. Brookes Publishing Co. (1999). The chapter is called: *Self-Advocacy for a Good Life in our Older Years*.

*“As we get older, the quality of our life can get better or worse depending upon the actions that we take throughout our lives”.....My generation of people with developmental disabilities can prepare for retirement, face real issues about aging, and create opportunities to help ourselves cope with changes in our lives”.*

Key work that I think should be continued from the 2014 Plan:

- To research about “variations in aging patterns, including consideration of lifestyle factors, among different age groups/subpopulations of individuals with Down syndrome.
- The emerging needs of people with Down syndrome as they age, and the impact on their families. ..Study whether the impact of aging on physiologic and cognitive processes is greater for those with Down syndrome than for others.
- Identify factors (medical, intellectual, social, familial) that may be protective for maximal independence and community inclusion. Such work may include: Participation by individuals with Down syndrome in higher education, employment, volunteer work; and lifestyle factors, such as close relationships.
- As the lifespans of individuals with Down syndrome continue to increase, investigate the impact on families of caring for them as they age. Such work may include: Identifying the factors that lead to effective functioning or challenges in families that include an individual with Down syndrome

Key activities in the INCLUDE Plan:

- Build a comprehensive, trans-NIH strategy to address **critical health and quality-of-life needs** for individuals with Down syndrome, leveraging the full range of resources across NIH to bring results rapidly to individuals with Down syndrome and their families. The main goals are to accelerate the development of new therapies, while simultaneously bringing promising agents already in development to individuals with Down syndrome as quickly as possible.

- To embark on this initiative in partnership with the Down syndrome community to improve the health and quality-of-life of individuals with Down syndrome, and all individuals who are impacted by many of these co-occurring condition.
- Focus on including individuals from underrepresented racial or ethnic minority groups, a range of functional abilities or underserved areas.

For me, three concepts that are very important in my life that should be included as a basis for health and quality of life in the next Research Plan are:

- *Health Self-Advocacy*- speaking up for myself with doctors and other health professionals
- *Self-Determination*-making decisions on my own or with support
- *Health Self-Management*-taking charge of my own health

Suggestion for the next NIH *INCLUDE Down Syndrome* Research Plan (2020 +):

Conduct a Cohort Research Study of individuals with Down syndrome born during the period 1970-1990 and who are now between 30 and 50 years of age. This is the first generation of individuals with Down syndrome who nearly all grew up as part of their local communities in integrated rather than segregated “institutional” settings. Like me, they have likely had the benefit of receiving early intervention & pre-school education; special education services and school inclusion; being at home with their families; participating in community social & recreational activities; independent or supported community living; and volunteer experiences and employment. This cohort should be sure to include adults with Down syndrome from diverse backgrounds and regions. An important next steps aspect and potential outcome of this research should include identifying and developing models for the inclusion of individuals with Down syndrome who are aging in community non-disability senior independent and assisted living centers. This will help address lifespan issues for people with Down syndrome and their families.

The purpose of this kind of study connects with the concept, *“As we get older, the quality of our life can get better or worse depending upon the actions that we take throughout our lives”*. It would be beneficial to have the participants with Down syndrome, as well as their families, have an opportunity to provide useful quality of life information and feedback about lifestyles in various areas, and how this may or has impacted on healthy aging with a disability. It would be valuable to learn about what individuals and families think about in terms of adult living options that are also in inclusive environments.

**Research-to-Practice** would be the goal. I was born in 1971 and was one of the first children with Down syndrome to be included in infant stimulation/early intervention, attend a community preschool with children without disabilities, school age special education supports and services combined with regular education, and a post-secondary independent living program. I also participated in community sports teams and other activities. I have been living on my own, have had good employment opportunities through the years, keep active and have access to healthcare in my own community. I have worked with other individuals with Down syndrome across the country who have had many opportunities similar to mine. I think that it is important to find out, through research, if the lifestyles for my generation of

people with Down syndrome will have an impact on aging and be different than for those people in previous generations without having the same kind of community inclusion, supports and services. This research should be focused on providing information and resources that will be useful and can be applied to recommended practices so that our lifestyles choices can positively affect outcomes for us in healthy aging. Most importantly, that we have the same choices for adult living as people without disabilities; and can all benefit from having healthy, happy and fulfilling relationships and lifestyles.

## Egan feedback: NOT-OD-20-013

- Remaining research gaps not addressed by either the 2014 NIH Research Plan on Down Syndrome, or the 2018 INCLUDE Research Plan, especially those that can be started or completed within a five- to seven-year timeframe.
  - While progress has been made in being able to image the brains of persons with Down syndrome and determine the presence of amyloid and plaques, the diagnostic and analysis of cognitive capabilities/impairments are still limited based on existing testing tools. Also the results from these tests cannot be shared with adults with Down syndrome when they are compared to children as the norm.
  - We are not aware of any research studies that examine environmental and behavioral factors to better understand cognitive decline and overall well-being
  -
- Strategies for disseminating evidence-based information from NIH-supported research more widely to health care professionals and families who may be caring for people with Down syndrome.
  - The presence of Researchers and NIH staff at the Down syndrome conferences has had a very positive impact on families to learn about the progress made in the field. There is still a bigger need to expand that information in the general population and in non-scientific journals that are read by lay people. Also based on our personal experience, the health care professionals we have interacted with have been caring, however most of them have very little information about Down syndrome and research advances. The request to health insurance to see a Down syndrome specialist has been denied as not necessary. So there is a gap in information in the health industry about the Down syndrome condition as a specialty to be addressed. The existing Down syndrome Clinics across the country are not sufficient to handle all individuals with Down syndrome. Strategic and aggressive Outreach is needed in the health care field and general population via TV ads, 60minutes or other broadcast, radio (NPR), podcast and on-line interviews. NIH DS.Connect Website is a great vehicle to post events, advances, articles etc...and would need to be expanded and linked to Medical, Health Care and Down syndrome organizations.
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- Strategies for facilitating collaborations, such as public-private partnerships, to expand the scope and number of research objectives that can be addressed.
  - Each member on the consortium should have a link to the DS Connect and update information on a monthly or at a minimum on a quarterly basis. There is a need to engage with the media.
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- Whether the following overall structure for the revised, combined NIH INCLUDE Down Syndrome Research Plan captures major goals for NIH research efforts:
  - The research plan captures all of the major goals, such as basic science, translational research establishing a cohort of individuals with Ds, and including underrepresented populations and research infrastructure.
  - As to the infrastructure, more efforts need to be focused on the DSConnect.nih.gov website with regular updates and links for outreach to a larger sector and motivation to follow the advances. Marketing and branding specialists are needed to get the website more visibility and accessibility.



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*Emma Campbell Endowed Chair on Down Syndrome  
Director, Down Syndrome Program*

Medical Geneticist, Massachusetts General Hospital  
Associate Professor, Harvard Medical School

July 8, 2020

RE: Notice Number: NOT-HD-20-013

National Institutes of Health:

Our Massachusetts General Hospital Down Syndrome Program is pleased to submit these ideas in response to NOT-HD-20-013, “Request for Information (RFI): Invitation to Comment on Updates to NIH Research Plans on Down Syndrome.”

The Mass General Hospital Down Syndrome Program integrates state-of-the-art resources with compassionate, comprehensive care through a multi-disciplinary approach. National experts from Massachusetts General Hospital, MassGeneral Hospital for Children, and Massachusetts Eye and Ear Infirmary provide five distinct **clinical services** to ensure that people with Down syndrome receive the specialty care that is specific for their age group:

- Prenatal Services: We offer consultations in a private setting for expectant parents who have received a prenatal diagnosis of Down syndrome.
- Infant and Toddler Clinic (ages birth-5): Families are educated about Down syndrome and comprehensive supports are provided for their child’s early needs.
- Child Clinic (ages 5-13): The healthcare of children is maximized so that they can achieve successes during school-aged years.
- Adolescent and Young Adult Clinic (ages 13-21): Families and youth are supported and educated about transition planning. The goal is for the person with Down syndrome to be prepared for adulthood and as engaged in their care as possible.
- Adult Clinic (ages 21 and older): Adults are supported to lead healthy lives marked by meaningful engagements with their communities.

Our Mission Statement is “We are a collaborative, multidisciplinary team, serving people with Down syndrome of all ages and their families. We provide evidence-based clinical care, education, and cutting-edge research so that individuals with Down syndrome can reach their full potential.”

Our Program also has a **research team** composed of enthusiastic healthcare providers committed to innovation in Down syndrome research. Our team is motivated to offer research opportunities that can help maximize the life potential for all people with Down syndrome. Working collaboratively with researchers around the globe, we are dedicated to advancing our shared understanding of biological processes associated with Down syndrome. Our past research projects have included industry-sponsored clinical trials, PCORI-funded



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innovative health platforms, and NIH-funded studies into co-occurring conditions for people with Down syndrome, such as obstructive sleep apnea.

As a team, we would like to submit the following suggestions concerning new research objectives for the NIH *INCLUDE Down Syndrome* Research Plan:

- Build sustainable in-person Down syndrome specialty clinics, with virtual options. Without these specialty clinics, we will continue to struggle to have sustainable Down syndrome research centers of excellence.
- Build Down syndrome research centers of excellence, which may or may not coincide within the Down syndrome specialty clinics.
- Over the past several years, the Down syndrome research community has produced many efficacious evidence-based projects. Now, there exists a gap in implementing these practices, including approaches that tailor and adapt these evidence-based practices for different settings, context, and health disparity subgroups. We are now at the point in the science where it is critical to dedicate funding to the study of Dissemination and Implementation (D&I) science of these evidence-based practices. We would recommend that there be a future *INCLUDE* RFAs for D&I proposals.
- We have been an active site in the International Down Syndrome Patient Database, a consortium of Down syndrome specialty clinics that has systematically collected clinical data on our patients with Down syndrome. Our consortium has now published five research papers, some of which have resulted in changes in the practice of medicine for people with Down syndrome (see references on last page). To date, this work has been unfunded. Each year, the consortium chooses a new clinical topic to study, so it has been challenging to seek project- or hypothesis-focused grants. The consortium would greatly benefit from grant opportunities to support its infrastructure. To this extent, we would like to recommend that the next *INCLUDE Down Syndrome* Research plan include funding opportunities for infrastructure supports for consortia that are doing clinical research.
- Further study of Down syndrome and aging with particular attention to family caregiver and health professional transitions, long-term care options, serious illness and end-of-life decisions, cognition/dementia
- Further study of health care practices, which foster independence, Inclusion, engagement of people with Down syndrome
- Assessment of the cross-cultural and linguistic needs of people with Down syndrome
- Study of COVID-19 risk and mitigation strategies for adults with Down syndrome in congregate living situations (e.g., group homes)
- Development of measures validated for people with Down syndrome. One limitation of prior clinical trials is that validated measures aren't sufficient in the Down syndrome population. Additional





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measures (either novel or existing) need to be validated in individuals with Down syndrome. Validating measures is a lengthy, iterative process which would be difficult to complete without substantial funding.

- Infrastructure to connect basic researchers to clinical researchers
- Support for a system for data sharing of published cohorts, such as a consistent way to present information, and share details in a publicly available, searchable format. In genetics, there are databases like ClinVar which allow geneticists to share information on variants. With the growing emphasis on data sharing, some authors share full Down syndrome datasets in the supplementary information of journals or as supplementary tables. It would be beneficial to have more researchers do so in a central, standardized way, perhaps in conjunction with the DS-Connect efforts.
- Development of a peer-reviewed journal dedicated to Down syndrome research
- Development of pathways to train additional basic scientists and clinical researchers
- Research to fund projects to bring new investigators to the field of Down syndrome and funding for the existing investigators to commit more time to research
- Inclusive opportunities to engage more scientists and researchers with the NIH, such as the INCLUDE Project Workshop in May of 2020

Thank you for the opportunity to share our suggestions. Please do not hesitate to contact me if I could offer any additional thoughts or clarifications on behalf of our team.

Sincerely,

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## Goldman, Rachel (NIH/NICHD) [C]

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**From:** Vellody, Kishore <vellodyk@upmc.edu>  
**Sent:** Wednesday, July 8, 2020 3:26 PM  
**To:** Down Syndrome Responses  
**Subject:** NOT-OD-20-013

Dear NIH,

The Down Syndrome Center at the UPMC Children's Hospital of Pittsburgh has been an active site in the International Down Syndrome Patient Database, a consortium of Down syndrome specialty clinics that has systematically collected clinical data on our patients with Down syndrome. Our consortium has now published five research papers, some of which have resulted in changes in the practice of medicine for people with Down syndrome (see references below). To date, this work has been unfunded. Each year, the consortium chooses a new clinical topic to study, so it has been challenging to seek project- or hypothesis-focused grants. The consortium would greatly benefit from grant opportunities to support its infrastructure. To this extent, we would like to recommend that the next INCLUDE Down Syndrome Research plan include funding opportunities for infrastructure supports for consortia that are doing clinical research.

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"Whatever you do, work at it with all your heart" - Col 3:23



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## **The Lifetime Trajectory of Persons with Down Syndrome**

### *T21RS Consensus Suggestions*

Down syndrome (DS) arises from having three copies of human chromosome 21, and is the most common genetic form of intellectual disability, affecting up to six million people worldwide. Furthermore, lifespan has increased dramatically such that people with DS can live well into their 60s in the developed world. **Thus, the world-wide prevalence of DS is still increasing.**

DS is not just characterized by intellectual disability but involves dysfunction and pathology in different organs/systems in different people – it is a **highly variable syndrome**. This variability can teach us about aberrant pathways associated with DS while providing potentially important information about these pathways in those without DS. In particular, there is current intense interest in the early-onset Alzheimer's disease that is a key feature of DS and ageing.

Despite the common occurrence of DS, the visibility of people with DS in all societies, and the well-known genetic cause, we have remarkably little reliable quantitative data on the life-time trajectory of persons with DS. This dearth of data severely hampers our attempts to model and understand mechanisms underlying this disorder, to optimize therapeutic, habilitative, and educational interventions, and to apply our findings to the non-trisomy 21 population.

**We are confident that it is URGENT and IMPORTANT to concentrate on long-term studies of the life-time trajectory of people with DS.** We propose the following focused RESEARCH THEMES to address key gaps in knowledge:

**THEME 1: To decipher the intrinsic variability of DS features and occurrence of comorbidities through detailed longitudinal clinical characterization of individuals linked to large-scale biobanking** We propose the collection of samples from sufficiently powered cohort(s) of individuals with DS. The cohort(s) should between them cover all ages but ensure sufficient numbers under 20 years of age. It would be important to ensure equal sex distribution in order to study sex differences, as well as sufficient numbers of individuals from different ethnic groups to allow for exploring potential differences. Of key importance is the need to undertake comprehensive clinical assessment of individuals that are linked to patient samples, to give us the full picture of life-time trajectory, and accurate numbers for prevalence of features in specific populations. Given the range of phenotypes of relevance in DS, it is likely that different cohorts may have specific priorities, but consideration should be given to comparable data collections, particularly at the clinical level, to allow for combined analyses. With this in mind, it will be necessary to link with existing cohorts and to support international collaborations. Data will give us insight into all aspects of DS including intellectual function, as well as cardiac function, otitis media, gut function, musculoskeletal function, obesity, diabetes, etc. To fully capitalize on the 'phenotypic' study of the individuals in this cohort, we need DNA sequences to give us genetic and molecular insight, cell line collection (fibroblasts, iPSCs) for validation, and we can add these to existing resources such as NIH-approved ES cells. Biomarker collection should include blood samples, and potentially other samples such as hair or saliva. There is a

great shortage of such human material especially in combination with fine-grained clinical and non-clinical assessment. Such material is essential for validating findings and capitalizing on DS variability to improve clinical outcomes. Samples must be ideally be collected longitudinally so that we can study effects of ageing.

**THEME 2: To provide robust data on neurodevelopmental trajectory, including speech and language development, oral praxis, and the co-occurrence of psychiatric disorders such as attention-deficit/hyperactivity disorder, autism, mid-life depression, or the rare cases of developmental regression with a specific focus on longitudinal neuropsychological testing** of individuals with DS and family members over their lifetime. E-health systems could be part of this effort to avoid “standalone” testing effects. Neurodevelopmental disorders with identified genetic etiologies present a unique opportunity to study gene–brain–behavior connections.

**THEME 3: To define nervous system development and function in individuals with DS through the use of current and new technologies** into the field of DS research, including advanced neuroimaging, electrophysiology, histopathology, metabolomics, microbiome studies, human iPSC studies etc. Clearly for some studies such as neuroimaging, small cohorts will be analyzed but projects must be statistically valid and with defined sex and ethnicity, to establish data to address variability in DS.

**THEME 4. Develop and expand fundamentally new approaches to researching DS**, including the discovery and development of animal and cellular models. Under this theme it would be critical to encourage the discovery and careful characterization of new developmental and neurodegenerative phenotypes in animal and cellular models, which would facilitate future preclinical research on pharmacological and genetic interventions.

**THEME 5: Define in vivo mechanisms and long-term therapy, in model systems such as mouse, rat, non-human primates, that reflect human clinical phenotypes in DS** allowing longitudinal analysis and mathematical modelling and to create opportunities for translational medicine. Note that many vitally important studies, such as brain connectomics, gene knock-down, local field potential electrophysiology, single-cell patch clamp recordings, monitoring the effects and attempts to ameliorate early-childhood stress, and large (pre-natal) developmental studies cannot be undertaken in humans.

The five themes are *priorities* to be studied under the heading: **what are the characteristics of the life-time trajectory of persons with DS?** Other aspects, such as the well-known reduction in prevalence of certain solid tumors in DS are important, but the lack of knowledge of the effects of trisomy 21 on and individual's life-time trajectory holds us back currently, and needs to be addressed immediately, for the long-term. Inadequate specific information is available about the prevalence and patterns of health conditions of people with DS, which are barriers that hold back effective interventions.

**We also believe that it is URGENT and IMPORTANT to produce information with the high potential to provide short-to-mid-term benefits to individuals with DS and their families.** To this end, we propose the following focused preclinical and clinical research themes to address these unmet needs:

1. Fund focused workgroups to study the expansion of the idea of the potential creation of Centers of Excellence for Down Syndrome Research and Care for adolescents and adults. Such centers of excellence would have a strong life-science research component and would not only provide dependable primary

and/or specialized care to adolescents and adults with DS, but would also be a reliable source of critically needed information on physical activity, diet, body composition, healthy aging, women's health (including sexual and reproductive health and early menopause), and post-school-age behavioral and psychological issues. Such centers would also provide caregiver support in the form of reliable information on research, evidence-based clinical practice, and availability of social services.

2. Fund focused clinical and pre-clinical workgroups to better understand comorbidities associated to DS, such as immunity/autoimmune issues, moyamoya disease, musculoskeletal dysfunction, cancer subtypes, ocular and other visual system disorders, obstructive sleep apnea, obesity, psychiatric comorbidities including regressive behaviors, and the molecular basis for the clinically observed protection from atherosclerotic disease.

3. Fund the expansion of current clinical care guidelines for adolescents and adults with DS.

4. Fund training programs for a new generation of clinicians and researchers (including, but not limited to, pediatricians, internists, family practitioners, basic and translational scientists) through doctoral and postdoctoral fellowships to create the workforce necessary to discover and translate new biomedical findings.

5. Fund the expansion of preclinical and clinical pharmacological research on approved drugs focused on DS. This research would involve both small safety and efficacy studies as well as pharmacokinetic and pharmacodynamics studies. Such research would address two unmet needs: (1) they would allow us to find new uses for existing drugs for those with DS; and (2) they would determine whether widely-prescribed dosages of existing drugs are appropriate for patients with DS in the context of known organ dysfunctions, altered body fat distribution, and lower metabolic rate that are commonly associated with DS.

6. Promote research on intervention strategies based on non-pharmacological approaches, including, but not limited to technological approaches to stimulate brain function.

7. Promote research to explore specific characteristics of psychiatric disorders in DS in developmental age and the effectiveness of different treatments for these disturbances in children and adolescents with DS. We know, for example that DS is associated with major language delay: production is more impaired than comprehension, but great individual variability exists. The integration of contributions deriving from different research areas as cognitive neuroscience, behavioral neuroscience, and experimental neuropsychology could provide substantial insights for the identification of early predictors of language in individuals with DS and of focused interventions, moving toward personalized medicine for DS.

8. Continue the basic and clinical studies of Alzheimer's disease molecular and cellular mechanisms to identify biomarkers and fund pilot projects of potentially disease-modifying therapies for Alzheimer's disease in persons with DS.

9. Promote care procedures, research, professional training and cultural approaches on DS in low and middle-income countries (LMICs). Given that most studies of DS are performed in high-income countries with good resources, minimal data are available on the survival and treatment of children with DS from LMICs. The joint action by scientists and clinicians coming from different countries with different incomes, would allow the development of sustainable diagnostic protocols and early intervention procedures to be administered globally.

July 10, 2020

To the DS INCLUDE Leadership Team,

I am writing to share my thoughts regarding the priorities articulated in the DS INCLUDE Project Research Plan. I am a researcher studying motor development and perceptual-motor learning in infants and young children with and without Down syndrome. I began studying early development in Down syndrome about 5-7 years ago, being mentored by experts in the field like Bob Hodapp, Elisabeth Dykens, and Debbie Fidler. As I learned about the field of research involving people with disabilities, I was very surprised to hear that research on some disabilities was much better funded than research on other disabilities. I am still surprised that this is the case.

It reminds me a little bit of the research done in one of my areas of expertise: motor development. Back in the 1940s, researchers such as Arnold Gesell and Mary Shirley did some excellent observational work in which they mapped out the normative timing of motor milestones during the first few years of life. They did such a good job that for a good 40 years or so, almost no research was done on motor development. It was as if researchers thought that knowing **when** reaching, crawling, and walking developed was all there was to know about motor development! It wasn't until Esther Thelen published some of her excellent work on variations in motor development in the 1980s that people started to take a second look at the changes happening in the motor system as potentially interesting. Now we have seen a resurgence of interest in motor development and this research has shown, among other things, that 1) there are many interesting experiential factors that contribute to the timing of motor skill development, and 2) these changes in motor skill set into motion highly impactful developmental cascades that influence many other areas of development for months and even years after the time that the behavior first appeared.

Applying this research story back to funding for Down syndrome, I think there is a temptation to think that because we understand at least some key parts of the etiology of Down syndrome, there are not other big or impactful questions to be answered about the origins of behaviors often seen in children with Down syndrome. However, like Esther Thelen, I believe there are many important questions still to be answered about variation and possible changes possible in the Down syndrome phenotype. These changes could be catalyzed not by drugs, but by early experiences. We have learned so much about typical development in infancy over the past 40 years and most of these new findings have not been brought back to the study of infants with disabilities. I believe there are many exciting new discoveries just on the horizon that could come from researchers



like myself who have made discoveries in different fields and could bring those discoveries to the study of Down syndrome. Creating early behavioral interventions that leverage the recent discoveries of infant science could yield cost-effective and safe therapies that could be administered early in development when brains can more easily benefit from experience-dependent plasticity. Such discoveries could provide almost immediate improvements in quality of life for children with Down syndrome and could lead to other improvements as development progresses.

Overall, my points are that understanding the early development of behavior (including the possible sources of behavioral change early in development) could offer many as-yet unexplored opportunities for scientific discovery and improvements in quality of life for individuals with Down syndrome. Because these discoveries would be safe, relatively inexpensive, and could be quickly integrated into infants' ongoing early intervention therapies, the potential for improvements in quality of life is huge.

Sincerely,



Amy Needham  
Professor



July 10, 2020

Submitted via email to [DownSyndrome@mail.nih.gov](mailto: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**

## **I. Introduction**

## **II. Priorities for Understanding Down Syndrome**

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

1. Standardizing Clinical and Genetic Phenotyping
2. Develop and validate cellular and animal models that better translate to characteristics in individuals with Down syndrome.

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

3. Longitudinal Studies

### **C. Treatment and Management**

4. Randomized Clinical Trials (RTC) in the Down syndrome Population.

### **D. Down Syndrome and Aging**

### **E. Research Infrastructure**

5. Centralized Biorepository
6. Open Access, Centralized Down syndrome Data
7. Support Down syndrome Research Training for Clinicians
8. Research Inclusion

## **III. Priorities for Associated Conditions Related to Down Syndrome**

- A. Alzheimer's & Aging
- B. Behavior & Autism
- C. Cancer
- D. Cognitive Development & Independence
- 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.

#### Priorities Related to Understanding Down Syndrome

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 A $\beta$  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 comorbidities, 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.

### **Prioritized Specific to Immunity**

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.

### **Priorities Related to Understanding Down Syndrome**

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.

### **Priorities Specific to Sleep & Respiratory**

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. **Human stem cell models are powerful to investigate human T21 impact at cell and organoid level**
    - 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. **Why?** 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 cell-based pathologies.
2. **Support and Expand Longitudinal Studies**
  - a. **When** 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. **Humans are gold standard to identify impacts on brain structure/function, where possible.**
  - 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. **What 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.

### **Priorities Specific to Basic Research Including Cognitive Development**

1. **Better tools are needed to enable drug discovery and development**
  - a. More biomarker research 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 Down 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.

<b>Most frequent topics of interest</b>	<b>Feedback from individuals with DS (interviews)</b>	<b>Feedback from caregivers/supporters (interviews and surveys)</b>
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



## Appendix – Working Groups and Contributors

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July 17, 2020

Lisa Kaeser, J.D.

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VIA E-MAIL: [kaeserl@mail.nih.gov](mailto:kaeserl@mail.nih.gov)

Dear Ms. Kaeser,

Please accept the following comments re: updates to the *INCLUDE Down Syndrome* research plan. As you know, the National Down Syndrome Congress is the country's oldest organization for self-advocates, their families, and the professionals who work with them. We are particularly known for hosting the world's largest annual convention related to Down syndrome, as well as our history of involving self-advocates in the leadership and direction of our organization.

Based on feedback from our members, our areas of primary concern are as follows:

1. Health issues impacting self-advocates and their caregivers.
  - a. Access to preventive health care and identifying health care providers.
  - b. Access to healthy foods, and education in the importance of maintaining a healthy diet, weight and exercise regimen.
  - c. Health impacts from being in a lower income household.
  - d. Disparities in healthcare access, provision and outcomes for all self-advocates and caregivers vs. those in the general population.
  - e. Disparities in healthcare access, provision and outcomes for self-advocates and caregivers in minority communities vs. white self-advocates and caregivers.
  - f. Physical and mental health impacts on self-advocates when their primary caregiver has a significant health challenge.
2. Caregiving for (and by) older individuals.
  - a. Health impacts of aging – including Alzheimer's disease – on self-advocates.
  - b. Health impacts on caregivers caused by caring for an older person with a disability.
  - c. Mental health issues for self-advocates who are isolated after aging out of school programs.
  - d. Mental health issues for self-advocates who are isolated and not socially engaged in a work setting.
  - e. Physical and mental health impacts on self-advocates when a primary caregiver dies.
3. Health impacts on families when self-advocates and/or their caregivers contract a disease like COVID-19.

- a. The current pandemic is unlikely to be the last; therefore, it is important to understand the physical and mental health impacts of such an outbreak on self-advocates and their families.
  - i. Access to adequate healthcare for self-advocates.
  - ii. Inappropriate rationing of healthcare services based on disability.
  - iii. Access for primary caregivers to self-advocates who are isolated in the hospital.
  - iv. Mental health impacts of isolation, loss of employment, loss of family income, and loss of family members.

Thank you for allowing us the opportunity to provide comments. If we can provide additional clarification, or be of other assistance, please don't hesitate to ask. We value our relationship with you and the NIH and appreciate all that you and your colleagues do on behalf of our community and our nation.

With best wishes,

A handwritten signature in black ink that reads "David C. Tolleson". The signature is written in a cursive, flowing style with a long horizontal stroke at the end.

David C. Tolleson  
Executive Director

**Response to NIH Request for Information (RFI):  
Invitation to Comment on Updates to NIH Research Plans  
on Down Syndrome Notice Number: NOT-HD-20-013**

**Responding Agencies:**

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**Linda Crnic Institute for Down Syndrome**

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**Anna and John J. Sie Center for Down Syndrome**

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## INTRODUCTION

This response to NOT-HD-20-013 was crafted by the following four affiliate organizations: the Global Down Syndrome Foundation (GLOBAL), the Linda Crnic Institute for Down Syndrome (Crnic Institute), the Anna and John J. Sie Center for Down Syndrome (Sie Center), and the Alzheimer's and Cognition Center (ACC) at the University of Colorado.

Working together, these agencies have created a major international epicenter for Down syndrome research and medical care, covering education, outreach, government advocacy, basic and clinical research and new clinical trials. This powerful coalition of scientists, clinicians, families, and self-advocates have transformed the Down syndrome research landscape. Today, Colorado hosts the largest geographical cluster of DS researchers in the world, with >60 research teams associated with the Crnic Institute investigating different aspects of the condition, who also hold the largest amount of NIH awards and dollars for the study of Down syndrome in the country. The ACC is the only Alzheimer's disease clinic and research center in the Rocky Mountain region, leading innovative clinical trials for immunomodulation in both typical Alzheimer's disease and Down syndrome. The Sie Center is now among the largest pediatric clinics for Down syndrome, having provided care to >1800 children with Down syndrome since 2010 through 13 multidisciplinary clinics including two first-in-kind clinics for mental wellness and K-12 education. GLOBAL is the largest Down syndrome non-profit in the U.S. and has a primary focus on research and medical care. GLOBAL has established important resources for the community including the Prenatal Testing & Down Syndrome Information pamphlet, an online medical care center finder, and the soon-to-be-published GLOBAL Medical Care Guidelines for Adults with Down Syndrome. GLOBAL has over 100 Down syndrome organizational members primarily in the U.S. with representation in every state. Working closely with Congress and the National Institutes of Health, GLOBAL is the lead advocacy organization in the U.S. for Down syndrome research and care.

Therefore, the response below coalesces a large body of experience and expertise in the field of Down syndrome research.

## EXECUTIVE SUMMARY

The four affiliate organizations contributing to this RFI – the Global Down Syndrome Foundation (GLOBAL), the Linda Crnic Institute for Down syndrome (Crnic Institute), the Anna and John J. Sie Center for Down Syndrome (Sie Center), and the Alzheimer's and Cognition Center (ACC) at the University of Colorado – were all created based on three important premises:

1. People with Down syndrome have a dramatically different disease spectrum whereby they are highly predisposed to certain life-threatening diseases (e.g. Alzheimer's disease, leukemia, autoimmune disorders) and highly protected from others (e.g. solid tumors, myocardial infarction, allergic sensitization).
2. Research into this different disease spectrum would lead to almost immediately improved medical care, improved health outcomes, quality of life, and even increased lifespan for people with Down syndrome.
3. Research into this different disease spectrum could also lead to a better understanding, treatments, and/or cures for diseases affecting the majority of the typical population in the United States and beyond.

**In our estimation, the importance of the 2018 trans-NIH INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndrome (INCLUDE) Project is the singular and most transformative program benefitting people with Down syndrome in nearly two decades.**

**We applaud the NIH, especially the leadership of Dr. Francis Collins, Dr. Lawrence Tabak, Dr. Diana Bianchi, and Dr. Gary Gibbons who established and manage INCLUDE. We are deeply grateful and indebted to the dedicated, hard-working staff at the Eunice Kennedy Shriver NICHD, NHLBI, NIA and other participating ICs for organizing important work groups and conferences.**

**INCLUDE has created a funding plan and model that made an immediate impact since 2018 and is also investing in the long-term future through a data coordination center, clinical trials, and specific research areas that hold the most promise.**

**The recruitment of 18 NIH institutes focused on diseases with disproportionately increased or decreased prevalence in the Down syndrome population is a brilliant cornerstone of INCLUDE. We hope that additional institutes where co-occurrence of institute-specific diseases or conditions will eventually join the project.**

We are honored to participate in this historic RFI. We have provided eight key research areas that build upon NIH's past plans and the outstanding INCLUDE project: (1) Immunity, (2) Development, Brain and Mind, (3) Heart, Lung and Blood, (4) Eyes and Vision, (5) Ear, Nose, Throat, (6) Endocrine System, Diabetes and Metabolism (7) Skin, Muscles and Bones, (8) Gut, Kidney and Bladder. In each section, there are important scientific questions that are asked in the areas of epidemiology, natural history, diagnostics, therapeutics, and mechanistic investigations. We sent a survey to our self-advocates and families reflecting these priorities and received over 1,000 responses in a three-day period with 98% agreeing that these areas of focus are "extremely important" or "very important" to them. Eighty-two percent selected "extremely important." The results of the survey are attached including topline demographics and additional areas of interest directly from the families.

In addition, we believe there are three other areas that are crucial for the future success of Down syndrome research over the next seven years:

1. Medical Innovation Networks: Galvanizing individuals with Down syndrome, their families and medical care providers through the establishment of Medical Innovation Networks.
2. Research that Directly Informs Health Guidelines: Targeting research that directly informs pediatric and adult medical care guidelines for individuals with Down syndrome. Since the 1980s, the lifespan of people with Down syndrome has more than doubled, and since 2002, the live birth rate in the U.S. has increased substantially. Research on the aging Down syndrome population is also critical.
3. Engaging the Population with Down syndrome in Research: Mitigating challenges/paving the way for clinical trials with a focus on less invasive research and easy to understand communication.

Finally, while we don't dedicate a section to this per se, having a clear understanding of how COVID-19 and other future pandemics affect people with Down syndrome and other intellectual and developmental disabilities is something we should somberly consider.

We hope that the information provided herein assists the NIH as you look to combine your past Down syndrome research plan and your INCLUDE Project into one NIH *INCLUDE Down Syndrome Research Plan* that will address important gaps and exciting new research over the next seven years.

Again, we are deeply grateful to the NIH for your dedication to enhancing health, elongating lifespan, and reducing illness for people with Down syndrome. NIH's work over the last sixty years for this unique population is being built upon in a way that is truly life-changing and life-saving, and is being duly recognized by our community, congressional champions, and indeed society as a whole.

## **RFI Questions 1-4 (Review of NIH Plans & Progress)**

### **RFI QUESTION 1: Have any of the objectives from the 2014 NIH Research Plan on Down Syndrome been achieved, in full or in part.**

Building upon the 2007 Down Syndrome Research Plan, the 2014 NIH Research Plan on Down syndrome was very detailed, thorough, and all-encompassing. It included five major areas: (1) Pathophysiology of Down Syndrome & Disease Progression, (2) Down Syndrome-Related Conditions: Screening, Diagnosis, and Functional Measures, (3) Treatment and Management, (4) Down Syndrome & Aging, and (5) Research Infrastructure. Each section was further broken down into short term or longer-term objectives. While many of the areas were the same or similar to the 2007 NIH plan, “Down Syndrome & Aging” was a new section and there were longer lists of areas to study including proteomics, epigenetics, environmental factors affecting the health and cognition of people with Down syndrome, participation of people with Down syndrome in NIH-funded clinical trials, a need to assess sex, age, race and other factors in research, and an acknowledgement that understanding co-morbidities and related diagnosis and treatment could require support from other institutes at NIH. Given the relatively flat and low funding of Down syndrome research at the NIH it is a testament to all involved that modest progress was made between 2014 and 2018 in many areas of the plan. In addition, four exceptional initiatives stand out:

- The NIH Biomarkers of Alzheimer’s Disease in Adults with Down Syndrome Initiative co-organized and funded by the NIA and NICHD in 2015 with an initial investment of \$37M over five years. The resulting Alzheimer’s Biomarkers Consortium – Down Syndrome (ABC-DS) has 11 clinical research sites and is now funded at ~\$50M by the NIA and NICHD with many exciting and promising results for the field and hope for the families.
- DS-Connects® is a powerful resource that aims to stimulate Down syndrome research by creating a bridge between people with Down syndrome and their families to researchers (including educational, lifestyle and therapeutic research) in order to measurably improve the lives of people with Down syndrome. Established in 2013 and growing to over 3,000 participants by 2014 and over 7,000 today, DS-Connects® was a result of the first NIH Down syndrome conference held in December 2010 “Down Syndrome: National Conference on Patient Registries, Research Databases, and Biobanks.” This registry is truly a game-changer for Down syndrome research at the NIH.
- The recruitment of Dr. Diana Bianchi as the Director of NICHD in 2016 including her renowned lab work focused on developing prenatal treatments for people with Down syndrome that would reduce oxidative stress and inflammation, improve brain growth and function and improve health and lifespan outcomes. As a leading Down syndrome researcher Dr. Bianchi brings the acumen, passion and compassion needed to move the science forward with a focus on improving health outcomes and lives.
- Between 2014 and 2017 the NHLBI also made great progress on their Pediatric Heart Network and clinical trial networks with a national footprint. Those networks and studies included patients with Down syndrome and their historical and longitudinal benefit in helping answer Down syndrome research questions is very valuable.

### **RFI QUESTION 2: What are the achievements to date (in full or in part) under the INCLUDE project, and have any of the goals of its 2018 Research Plan been met?**

The four affiliate organizations contributing to this RFI agree that the trans-NIH Investigation of Co-occurring conditions across the Lifespan to Understand Down syndromE (INCLUDE) Project is the singular and most transformative program benefitting people with Down syndrome in nearly two decades.

GLOBAL, our self-advocates with Down syndrome and family members, membership organizations, congressional champions, and leadership at NIH all contributed to a congressional directive in the fiscal

year (FY) 2018 Omnibus Appropriations legislation, which called for a new trans-NIH research initiative on critical health and quality-of-life needs for individuals with Down syndrome. NIH launched the INCLUDE project in June 2018 in support of this initiative.

It is our assessment that the trans-NIH INCLUDE Project has been a definitive success because INCLUDE:

- (1) Builds upon the last 60 years of Down syndrome research at NIH, as well as the 2007 and 2014 NIH Down syndrome research plans;
- (2) Has attracted 18 NIH institutes and centers which participate in the project with much to offer and much to gain from Down syndrome research (including several institutes that had never funded Down syndrome research in the past);
- (3) Has a trans-NIH model that has allowed for significantly increased funding mechanisms that are both centralized and decentralized, as well as short-term (e.g. supplements) and long-term (data coordinating centers and clinical trials);
- (4) Has a dual goal of improving health outcomes and increasing the lifespan for people with Down syndrome and for typical people who suffer from diseases that the Down syndrome population is highly predisposed to or protected from; and
- (5) Funds intelligent, strategic, and promising research areas defined as, “3 components:”
  - Conduct targeted, high-risk, high-reward basic science studies on chromosome 21
  - Assemble a large study population of individuals with Down syndrome
  - Include individuals with Down syndrome in existing and future clinical trials

Based on the science funded by INCLUDE annotated on the NIH website, it is clear that the NIH is well on its way to delivering on the 2018 INCLUDE Project plan.

**RFI QUESTION 3: What seminal publications have resulted from research on Down syndrome supported by NIH since 2014, including the INCLUDE Project.**

Please see the Bibliography section, which highlights seminal and landmark findings and publications we used to support our recommended key areas of research and follow-on scientific questions. Many of these publications are associated with generous NIH and INCLUDE Project grants.

**RFI QUESTION 4: List revised research objectives aimed at expediting research on Down syndrome, including unmet needs in basic, translational, or clinical research, and identifying whether each is a short- or longer-term priority.**

We cover this question below under the section “Recommendations for Down syndrome Research at the NIH (7 Year Plan)” that highlights eight key research areas with future research questions.

## RFI Question 5 (Impact Research 5-7 years forward)

**RFI QUESTION 5: What are the remaining research gaps not addressed by either the 2014 NIH Research Plan on Down Syndrome, or the 2018 INCLUDE Research Plan, especially those that can be started or completed within a five- to seven-year timeframe.**

**A cohort study across the lifespan.** We believe Component 2 of the INCLUDE Project is undoubtedly one of the highest priority projects for the field. The assembly and study of a large cohort of individuals with Down syndrome through deep phenotyping, multi-dimensional biobanks, and myriad pan-omics datasets, as well as other molecular and cellular assays, will profoundly accelerate the pace of discoveries that will improve health outcomes for people with Down syndrome. Efforts such as the ABC-DS, the Crnic Institute Human Trisome Project™, and the Gabriella Miller Kids First program lay a strong foundation for the INCLUDE Cohort in terms of research participants already enrolled, human expertise developed to study such a large cohort and generation of key datasets. The harmonization and expansion of these cohorts, plus inclusion of other smaller cohorts, is deemed a necessary step toward this goal.

**A definitive assessment of the impact of immune dysregulation in Down syndrome.** We applaud the renewed interest in immune dysregulation in Down syndrome by NIH and the community more broadly, leading to incorporation of NIAID in the INCLUDE Project, and funding of several grants focused on immune dysregulation in people with Down syndrome. A sustained investment in this area over the next 5-7 years should illuminate the mechanisms and consequences of immune dysregulation in this population, paving the way for immune-based diagnostic and therapeutic strategies.

**Tissue-specific impacts of trisomy 21.** Another high priority project is the elucidation of the impacts of trisomy 21 on diverse human tissues and organs through the study of induced pluripotent stem cells (iPSCs) and iPSC-derived cell types and organoids. With the advent of new protocols to differentiate iPSCs into myriad cell types, as well as the progress in the generation of three-dimensional heterotypic organoids, it is now possible to investigate the impacts of trisomy 21 on gene expression programs, as well as proteomic and metabolomic signatures, in different human tissues and organs. An orchestrated effort to assemble a large panel of iPSCs with and without trisomy 21, including a large number of isogenic pairs, and to differentiate these into different cellular fates would illuminate novel biological processes affected by the extra chromosome, which in turn may reveal new pathways toward advanced diagnostic and therapeutic approaches.

**Clinical trials.** The funding of the first 5 clinical trials in 2019 as part of Component 3 of the INCLUDE Project represents a significant landmark for the field. With sustained investment in this area, over the next 5-7 years we should be able to identify promising therapeutic avenues for diverse comorbidities using more refined interventions in larger cohorts. We applaud the funding of a network of sites for trials for Alzheimer's disease in Down syndrome by the INCLUDE Project, and believe that similar networks should be created for other highly prevalent comorbidities affecting this population (e.g. autoimmune disorders, autism spectrum disorders, pulmonary conditions).

**A definitive test battery for neurodevelopmental and behavioral phenotypes across the lifespan.** The field continues to be impeded by the lack of a definitive test battery to assess neurodevelopmental and behavioral phenotypes in this population at different age ranges. The elucidation of this battery should be considered a top priority, as this would enable more definitive investigations of the mechanisms and factors modulating these highly variable phenotypes, but also enable clinical trial outcomes measures.

**A targeted study to understand the potential disparity in lifespan for Black or African Americans with Down syndrome.** In 2007, life expectancy for Black people with Down syndrome was estimated to be half compared to Caucasians with Down syndrome (NIH Down Syndrome Working Group, 2007). More recently a 2016 study showed that infant survival rate of Black babies with Down syndrome was considerably less than that of Caucasian babies with Down syndrome (Kucik et al., 2013). Research over a 5-7-year period and recruiting a large cohort of African Americans would allow for a deep understanding of differences in this population and provide a roadmap to immediately improve health outcomes and

eventually lifespan. A definitive epidemiological study that defines the impact of genetic makeup and other endotype features versus socio-economic status, access to medical care, lifestyle, diet, and geography is paramount. In addition to African Americans, understanding the impact of trisomy 21 on race and ethnicity more broadly is an important and worthy study.

**A targeted study to understand what existing or revised learning programs work for school-aged children with Down syndrome.** There is strong evidence that ABA and other evidence-based learning programs are effective for a large number of students with autism spectrum disorder (Medavarapu et al., 2019). There is also evidence that remedial programs in math, reading, and comprehension have benefit for those with intellectual and developmental disabilities. A longitudinal, targeted study in one or two areas of academics with pre-, during-, and post- assessments multiple times throughout the year in at least two socioeconomically diverse systems could be extremely useful for students with Down syndrome, teachers, and families.

**Compliance with healthcare guidelines.** In a 5-7-year period, multiple centers providing health care to patients with Down syndrome could aggregate important data on adherence to pediatric and adult medical care guidelines for individuals with Down syndrome. Existing tools such as the “Reach Out and Read” program could be applied, and results measured. Simultaneously, clinician adherence to referrals and patient compliance to referrals can be measured. An important result of such a study would be a proactive plan to dramatically improve guideline and referral compliance.



## RFI Question 6 (Dissemination, Education & Outreach)

**RFI QUESTION 6: What strategies are there for disseminating evidence-based information from NIH-supported research more widely to health care professionals and families who may be caring for people with Down syndrome.**

Consider your constituent/audience.

There are two key issues to consider when contemplating disseminating evidence-based information from NIH-supported research to health care professionals, individuals with Down syndrome and families:

- (1) Is the information actionable and therefore more likely to be perceived as useful by the health care professional and/or the individual with Down syndrome and his/her family?
- (2) Is the information modified or modifiable so that an individual with Down syndrome can digest and use such information in a safe and reliable manner?

Guidelines and information for the clinician with little-to-no Down syndrome experience

To the extent the NIH-supported research is useful and actionable for health care professionals, having the information published in high impact medical journals is important to inform the majority of clinicians who may see only one or two patients with Down syndrome in their caseload. These journals are a natural “go-to” for guidance in assessment and treatment.

Research supporting guidelines and actionable information.

INCLUDE should consider investing in research that bolsters and fills gaps associated with the American Academy of Pediatrics Healthcare Supervision Guidelines for Children with Down Syndrome (Bull, 2011) and the Global Down Syndrome Foundation Medical Care Guidelines for Adults with Down Syndrome (expected 2020). This would help ensure a virtuous cycle of translational research.

Research supporting modification and patient toolkits.

The NIH and INCLUDE should also consider investing in creating the best modification of information and guidelines directly for individuals with Down syndrome or other intellectual and developmental disabilities. Best practices in modification of complex information, checklists and toolkits that support independence is something families routinely look for. The saying, “never for us without us,” goes a long way as society works to empower every individual to access medical care and, through good health, their own potential.

A task force approach to dissemination.

Creating, separately or together, a national and local task force that includes Down syndrome organizations, broad based disability organizations, health care system enterprises, health care specialty associations, medical centers, and schools would provide a leveraged, coordinated approach to disseminating NIH-supported research to health care professionals, individuals with Down syndrome and their families.

Incorporate Down syndrome and/or intellectual and developmental disabilities as a constituency in existing NIH education and awareness campaigns.

The NIH has several education and awareness campaigns under the Office of the Director and under many of its institutes and centers. It may be possible to dovetail with those endeavors specifically for individuals with Down syndrome and/or other intellectual and developmental disabilities. For example:

- The Office of Communications and Public Liaison (OCPL) has its *Clear Communication* program to reach individuals with literacy challenges or individuals with disabilities and disorders.
- The National Eye Institute has developed materials and resources to help health educators reach populations who are at high risk for eye disease and vision loss in addition to important information about glaucoma awareness, and the relationship between diabetes and blindness.

- The National Heart Lung Blood Institute has a national education program, *Learn More Breathe Better*,<sup>SM</sup> that raises awareness on lung disease and, *The Heart Truth*, that does the same for heart disease prevention. In addition, *We Can! (Ways to Enhance Children's Activity and Nutrition®)*, is focused on healthy weight through behavior.
- The National Institute of Dental and Craniofacial Research has a program called Developmental Disabilities and Oral Health that provides dental professionals with basic information needed to deliver quality oral health care to people with special needs.
- The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development organizes *The National Child & Maternal Health Education Program* with more than 30 of the nation's most prominent maternal and child health care provider associations, federal agencies and other partners.

Create national campaigns to reach small but important groups of individuals with Down syndrome

Race, ethnicity, mosaicism, and co-occurrences such as autism.

Continue to grow and expand DS-Connect<sup>TM</sup>. This database is arguably the most powerful resource we have nationally that connects people with Down syndrome and their families who are interested in research with scientists and clinical researchers. Continued investment, coordination with other data sets, and ensuring a robust number of non-invasive and translational research opportunities will certainly help cast the net wider.

## RFI Question 7 (Collaborations & Partnerships)

### **RFI QUESTION 7: What strategies are there for facilitating collaborations, such as public-private partnerships, to expand the scope and number of research objectives that can be addressed.**

We believe that one of the most powerful and immediate strategies towards dramatically expanding the breadth and depth of science funded by the NIH INCLUDE Project is the creation of an INCLUDE Medical Innovation Network (Network).

An INCLUDE Network would be similar to the 33 Alzheimer's Disease Research Centers administered by the NIA, or the 15 Eunice Kennedy Shriver Intellectual & Developmental Disabilities Research Centers administered by the NICHD.

It would consist of research and medical care centers housed at major medical institutions across the United States, focused on developing a large cohort study of individuals with Down syndrome across the lifespan with deep phenotyping, multi-dimensional biobanks, and myriad pan-omics datasets, as well as other molecular and cellular datasets. The centers would participate in longitudinal studies to define the role of genetic makeup and endotype features (e.g. epigenome, transcriptome, metabolome, immune maps), as well as lifestyle and environmental factors on the developmental and clinical course of Down syndrome. The centers would also harmonize and expand data, pursue clinical applications from basic research for patients with Down syndrome and co-occurring conditions, develop diagnostics and pursue outcomes measures for interventions and treatments. Importantly, all the centers would engage in clinical trials.

In the United States, Down syndrome medical care centers, some with strong research ties and many with research aspirations, already exist with annual patient visits ranging from 200 to 4,000. .

An INCLUDE Network could be funded by a P30 Center Core Grants or P50 Specialized Center grant mechanism. However, we envision a Network to be highly leveraged on several fronts (possible examples that could be advanced):

1. Each INCLUDE Network center will have to budget for integrated all-center long-term research efforts such as longitudinal studies and clinical trials to ensure coherence and collaboration.
2. Centers for Medicare & Medicaid Services (CMS)/Center for Medicare and Medicaid Innovation (CMMI) 5-year demonstration programs applied to each of the INCLUDE Network centers
  - Demonstrate that free or considerably reduced cost in medications for patients with Down syndrome can improve health outcomes thereby saving money for the medical institution, healthcare system, and insurance companies. A specific example would be providing Palivizumab (brand name Synagis™) to all children with Down syndrome during RSV season which could dramatically reduce emergency room visits and improve health outcomes. While the drug is covered by insurance for patients with Down syndrome who have congenital heart issues, it is otherwise unaffordable (Beckhaus and Castro-Rodriguez, 2018).
  - Care coordination, interoperability, telemedicine and clear health outcome and financial measures would be key. Chronically ill patients and underserved populations would be a priority.
3. Targeted treatment and clinical trial investment from medical innovation companies such as Inspire Medical Systems, Inc (OSA treatment) and pharmaceutical companies such as those that manufacture JAK inhibitors for treatment of autoimmune disorders.
4. Matching funds from the major medical institutions where the INCLUDE Network centers are housed.
5. Matching local government funding from the state or district where the INCLUDE Network centers are house.

6. Matching funds from local, state and national Down syndrome and Intellectual and Developmental Disabilities (IDD) fundraising and advocacy organizations/philanthropic funds.
7. Matching funds from disease specific non-profits for said disease-related research at the INCLUDE Network centers (e.g. Heart, Cancer).
8. Engaging people with Down syndrome, their families, local stakeholders, State Medicaid agencies, etc.

Engaging sufficient numbers of people with Down syndrome and their families in research is paramount to any INCLUDE Project advancement as well as any public-private partnerships that leverage resources, space, talent, funding, technology, data, samples and more.

Down syndrome focused public-private partnership could better include the CDC, the Agency for Healthcare Research and Quality, expertise and standards from the intellectual and development disability community, from disease specific non-profits and networks, and from Congress and the White House. The NIA, Alzheimer's Association, patient advocates and biotech/pharma partnerships are certainly a strong role model for the Down syndrome community.

## RFI Question 8 (Review of INCLUDE)

**RFI QUESTION 8: Does the following overall structure for the revised, combined NIH INCLUDE Down Syndrome Research Plan capture the following major goals for NIH research efforts:**

- Conducting basic science studies on chromosome 21 and areas highly relevant to Down syndrome
- Conducting translational research, including connecting existing resources and establishing a cohort of individuals with Down syndrome for study
- Including individuals with Down syndrome in existing and future clinical trials, including individuals from underrepresented racial or ethnic minority groups, a range of functional abilities, or underserved areas, and including research on co-occurring conditions

Yes, the structure does seem to capture the major research effort goals. We do believe that additional institutes added to INCLUDE, additional funding, and the ultimate goal of reaching over \$200M a year in Down syndrome research funding will best ensure the success of the INCLUDE project and certainly result in improved medical care, improved health outcomes and elongated life for those with Down syndrome. In addition, it will most certainly contribute to the understanding of life-threatening diseases in the typical population and contribute to diagnostics and treatments.

GLOBAL and our affiliates will continue to work with our congressional champions, self-advocates with Down syndrome and their family members, and other national and local Down syndrome organizations across the United States. We also look forward to any opportunity to support international Down syndrome initiatives with the NIH.

## **Recommendations for Down Syndrome Research at the NIH (7 Year Plan): KEY RESEARCH AREAS AND SCIENTIFIC QUESTIONS**

Led by the Linda Crnic Institute for Down Syndrome (Crnic Institute), the four affiliate organizations contributing to this RFI – the Crnic Institute, the Global Down Syndrome Foundation (GLOBAL), the Anna and John J. Sie Center for Down Syndrome (Sie Center), and the Alzheimer’s and Cognition Center (ACC) at the University of Colorado organized key research areas by eight biomedical ‘systems’:

- (1) Immunity
- (2) Development, Brain and Mind,
- (3) Heart, Lung and Blood,
- (4) Eyes and Vision,
- (5) Ear, Nose, Throat,
- (6) Endocrine System, Diabetes and Metabolism
- (7) Skin, Muscles and Bones,
- (8) Gut, Kidney and Bladder.

These key research areas are critical to improving the lives of those with Down syndrome and align with the research scope of many NIH institutes, with numerous clear areas of synergy and connectivity. For example, research areas and scientific questions about ‘Heart, Lung and Blood’, which fall under the scope of the National Heart, Lung and Blood Institute (NHLBI), are clustered together in one section, but this section also includes questions that interconnect with other ‘systems’, such as questions about the role of inflammation in pulmonary hypertension, which would involve research on immune dysregulation more relevant to the mission of the National Institute of Allergy and Infectious Diseases (NIAID).

Under each key research area, we follow the same sequence of inquiries and proposed areas of research emphasis:

- Epidemiology
- Natural History
- Diagnostics
- Therapeutics
- Mechanistic Investigations

Throughout, we cite important papers that we believe have advanced each field, many of them funded by generous and much appreciated NIH grants. Where appropriate, we also point to activities that we believe should be of high-priority for Component 1, 2 and 3 of the INCLUDE Project, i.e. basic science, cohort study and clinical trials, respectively.

These research questions arise from over six years of monthly meetings by members of the Working Group, a notable group of experts covering the entire range of expertise for each of these systems.

GLOBAL has recently submitted the *Global Down Syndrome Foundation Medical Care Guidelines for Adults with Down Syndrome* for publication. The nine areas of the guidelines also align with our key research areas organized here. Furthermore, the guidelines include a “Future Research Needed” section for all nine areas.

Lastly, each section contains a section addressing research challenges and opportunities for individuals with Down syndrome.

## I. Immunity

Immune dysregulation is a major cause of morbidity and mortality in people with Down syndrome. Our epidemiological studies through the Crnic Institute Human Trisomy Project™ (HTP) revealed that >60% of adults with Down syndrome have been diagnosed with one or more autoimmune disorders ([www.trisomy.org/explorer](http://www.trisomy.org/explorer)). Bacterial lung pneumonia and sepsis are leading causes of death among children and adults with Down syndrome (Ram and Chinen, 2011; So et al., 2007), which is likely due to immune dysregulation leading to inadequate anti-bacterial responses (Cocchi et al., 1978; Izumi et al., 1989; Rascon Trincado et al., 1988). Immune dysregulation overall, and neuroinflammation more specifically, are also likely contributors to neurological disorders in this population. Neuroinflammation is obvious and chronic in Down syndrome (Wilcock, 2012; Wilcock and Griffin, 2013), and a known driver of neurological conditions in the typical population (Chitnis and Weiner, 2017). In the general population, immune-metabolic dysregulation, most prominently activation of the interferon-driven kynurenine pathway, has been associated with the progression of Alzheimer's disease, autism spectrum disorders, seizure disorders and various neurological conditions more prevalent in those with Down syndrome (Aarsland et al., 2015; Akesson et al., 2018; Beal et al., 1990; Braidy and Grant, 2017; Bryn et al., 2017; Chen et al., 2009; Chen et al., 2010; Davis and Liu, 2015; Evangelisti et al., 2017; Guillemin and Brew, 2002; Gulaj et al., 2010; Hartai et al., 2005; Jacobs et al., 2019; Lapin, 1973, 1981; Laugeray et al., 2011; Lim et al., 2010; Majlath et al., 2014; Oxenkrug, 2010; Savitz, 2017; Stone and Darlington, 2013; Vecsei et al., 2013). Furthermore, chronic immune dysregulation can cause severe neurodevelopmental issues, as evidenced by monogenic Type I Interferonopathies and other inborn errors of immunity (Rodero and Crow, 2016). Altogether, these observations justify a stronger investment in the research activities elucidating the multidimensional impacts of immune dysregulation in children and adults with Down syndrome.

### 1) Autoimmune conditions.

Despite the increasing appreciation of the elevated rates of autoimmunity in the population with Down syndrome, larger and more sophisticated epidemiological studies are needed to fully understand the broader impacts of immune dysregulation caused by trisomy 21.

#### a. What is the prevalence of the following autoimmune conditions in people with Down syndrome across the lifespan? Are there variations by age, sex, race/ethnicity, and geography?

- Type 1 diabetes
- Celiac disease
- Hashimoto's disease
- Alopecia areata
- Atopic dermatitis/eczema
- Dermatitis herpetiformis
- Dermatomyositis
- Hidradenitis suppurativa
- Lichen planus
- Lichen sclerosis
- Vitiligo
- Psoriasis
- Psoriatic arthritis
- Arthropathy
- Rheumatoid arthritis
- Vasculitis
- Hemolytic anemia
- Thrombocytopenic purpura
- Myositis

Restless legs syndrome  
Meniere's disease  
Autoimmune encephalitis  
Inflammatory bowel disease/ Crohn's disease  
Narcolepsy  
Kawasaki disease  
PANDAS  
Sarcoidosis  
Systemic lupus erythematosus

- b. What are the protective and risk factors for diverse autoimmune conditions in people with Down syndrome?** As also explained in the sections about autoimmune thyroid disease (AITD) and celiac disease, GWAS studies in the typical population have identified genetic risk factors associated with development of autoimmunity, including various HLA alleles (Pearce and Merriman, 2006; Wellcome Trust Case Control et al., 2007), components of the interferon pathway (Hall and Rosen, 2010), and even SNPs in other genes encoded on chromosome 21, such as UBASH3A (Ge et al., 2017). Many of these genetic variants have important diagnostic values in the typical population, such as HLA alleles in celiac disease, but their utility in diagnosing these various autoimmune conditions in Down syndrome remains to be defined. We propose that a definitive study of genetic variants contributing to autoimmunity in Down syndrome should be a key aspect of Component 2 of the INCLUDE Project (cohort study). We applaud the key partnership between INCLUDE-funded researchers and the Gabriella Miller Kids First program, who have embarked on the sequencing of >2,000 genomes of individuals with Down syndrome. Although the primary focus of these genome sequencing efforts is on congenital heart disease and leukemias, we believe the scope should be expanded to investigate genetic variants predisposing to autoimmune disorders and other comorbidities more common in Down syndrome. Nevertheless, we would like to emphasize that non-genetic factors are likely to be equal or more important. In this regard, we propose that Component 2 should emphasize the study of immune and inflammatory signatures in Down syndrome, which are likely to modulate the development of myriad comorbidities in this population, including autoimmune disorders, Alzheimer's disease, pulmonary conditions, and neurological disorders. These studies would include analyses of cytokines, immune cell signatures, as well as transcriptome, proteome and metabolome signatures that could help assess the risk of developing autoimmune conditions in Down syndrome. Additionally, a deep analysis of the autoantibody repertoire in Down syndrome is also needed. Although it is clear that autoantibodies are involved in the etiology of the most common autoimmune disorders in this population (e.g. AITD, celiac disease), their role in the development of other autoimmune conditions remains to be elucidated. The importance of this line of research cannot be overstated, as the identification of autoantibodies would not only illuminate mechanisms of disease but could also enable the development of diagnostic tools. With the advent of genome-wide technologies for autoantibody mapping, it is now possible to reveal autoantibodies against any tissue or organ from plasma/serum samples, and these efforts could be readily incorporated in Component 2 of the INCLUDE Project. Repeatedly, the microbiome has been involved in modulation of the host immune response, with many examples where variations in the gut, oral and skin microbiome have been tied to the etiology of immune disorders (Human Microbiome Project, 2012). Therefore, a deep investigation of the microbiome in Down syndrome is warranted, across the lifespan, encompassing multiple comorbidities, and including analysis of key sites of action for bacterial and fungal species (gut, mouth, skin, inner ear).
- c. What is the long-term impact of autoimmune conditions in people with Down syndrome?** The development of autoimmunity signals a loss of 'self-tolerance' and the appearance of autoreactive immune cells and auto-antibodies. It is well known that the development of one autoimmune disorder predisposes to other autoimmune disorders. Therefore, people with Down syndrome are at high risk of developing consecutive and sequential autoimmune disorders across the lifespan, with potential involvement of multiple organs. The full impact of this predisposition to autoimmunity remains to be defined and should be considered a high priority area of research. Autoimmunity can have far



reaching impacts, even on comorbidities and phenotypes that at first impression may not seem immune-related. One tantalizing possibility is that of developmental regression in Down syndrome, a phenomenon of unknown etiology, that could potentially be tied to immune dysregulation. Seizure disorders common in people with Down syndrome could be potentially tied to autoimmunity as well, with anti-NDMA encephalitis providing a clear example of an unexpected autoimmune mechanism targeting the brain (Dalmau et al., 2008).

- d. What are the most appropriate diagnostic(s)/screening tool(s) for autoimmune conditions for people with Down syndrome?** The lack of appropriate diagnostics tools in this area is likely to be imposing a disproportionate burden on the population with Down syndrome in terms of morbidity and decreased quality of life. With the exception of AITD, which is easily screened by measuring thyroid hormones, and autoimmune skin conditions, which are readily apparent in most cases, most other autoimmune conditions affecting this population are likely to be grossly underdiagnosed. Most prominent among these are celiac disease and the arthropathy of Down syndrome, two conditions with long pre-symptomatic or pre-clinical development phases. Effective screening criteria for celiac disease in Down syndrome are lacking and would require further additional research. Celiac disease symptoms including diarrhea, constipation, and behavioral issues may be difficult to differentiate in this population making celiac disease diagnosis and monitoring even more challenging. While T cell dysregulation is associated with IFN hyperactivity and likely subsequent autoimmunity in Down syndrome (Araya et al., 2019), the inflammatory profile has not been investigated extensively in those with celiac disease. There are likely important additional factors that accelerate the development of celiac disease in this population. Furthermore, individuals with DS have been described to develop another form of immune enteropathy that is still poorly characterized (Nanjo et al., 2014). This enteropathy appears to differ from classic celiac disease as it is not associated with the typical autoantibody and HLA risk profile of celiac disease and, in our experience, is refractory to the gluten-free diet (Nanjo et al., 2014). The arthropathy of Down syndrome is likely to be another underdiagnosed autoinflammatory condition for which definitive diagnostic criteria are missing (Foley et al., 2019).
- e. What are the best treatment modalities for autoimmune conditions in Down syndrome?** With the exception of AITD, which is treated to an extent by thyroid hormone management, most autoimmune conditions highly prevalent in those with Down syndrome do not have definitive and effective standards of care. Even for celiac disease, the benefits of a gluten-free diet remain to be fully documented. Our studies of autoimmunity in Down syndrome revealed that ~25% of adults have been diagnosed with one or more autoimmune skin conditions, such as alopecia areata, psoriasis, hidradenitis suppurativa, vitiligo and atopic dermatitis. Although some of these conditions are treated in the typical population with FDA-approved immune-modulatory agents (e.g. anti-IL17 agents for psoriasis) their efficacy in Down syndrome remains to be defined. In this regard, we applaud the investment from the INCLUDE Project on a first-in-kind clinical trial for a JAK inhibitor for autoimmune skin conditions in Down syndrome (NCT04246372). Nevertheless, we believe a stronger investment is needed in this area, with many potential interventions to be tested. In addition to targeting JAK/STAT signaling with FDA-approved JAK inhibitors, we believe there are many other interesting immune-modulatory strategies that should be investigated in this population. One prominent example is the well documented elevation of mTOR signaling in Down syndrome (Di Domenico et al., 2018; Iyer et al., 2014; Perluigi et al., 2014), which could be counteracted with FDA-approved anti-inflammatory drugs such as rapamycin, everolimus, and sirolimus. In an animal model of Down syndrome, rapamycin reduced toxic metabolic intermediates in the CNS (Duval et al., 2018). Many patho-cytokines with clear ties to autoimmunity are also elevated in Down syndrome, including many for which FDA-approved antagonists are available, such as IL-6, TNF- $\alpha$ , IL22, IL10, and IL17 isoforms (Sullivan et al., 2017), to name a few. The role of these cytokines in autoimmunity in Down syndrome remain to be defined, and additional research in this area is warranted, which could pave the road for new clinical trials in this field. Natural products with anti-inflammatory properties, such as apigenin, which is currently being investigated in the intramural NICHD program (Guedj et al., 2016), also warrant deeper investigations. Lastly, the recent discovery that inhibitors of the integrated stress

response (ISR), which acts downstream of interferon signaling, can reverse some phenotypes in animal models of Down syndrome also deserves further investigation (Zhu et al., 2019).

- f. What are the mechanisms by which trisomy 21 increases the risk and/or severity of autoimmune conditions? Are there any specific genes on chromosome 21 or downstream signaling pathways that contribute to this class of comorbidities in Down syndrome?** This is a key area of research demanding increased investment. We applaud the recent inclusion of NIAID to the NIH Working Group in Down Syndrome with the creation of the INCLUDE Project and the significant and increasing investment by NIAID, NIAMS and NHLBI on studies of immune dysregulation in Down syndrome. The renewed interest in studies of the interferon pathway in Down syndrome is lauded and much warranted. Although the first observations that trisomy 21 increases interferon signaling were made more than 40 years ago by Epstein and colleagues (Epstein et al., 1987; Epstein and Epstein, 1976; Tan et al., 1974), and despite the pioneering work of Maroun and colleagues demonstrating the detrimental impact of interferon receptor triplication in early mouse models of Down syndrome (Hallam et al., 2000; Hallam and Maroun, 1998; Maroun, 1980, 1995, 1996; Maroun et al., 2000), the field lost track of these important discoveries. More recently, unbiased experimental approaches have revealed that interferon dysregulation is rampant in both humans with trisomy 21 (Araya et al., 2019; Powers et al., 2019; Sullivan et al., 2017; Sullivan et al., 2016; Waugh et al., 2019), as well as in multiple mouse models of Down syndrome carrying triplication of the interferon receptor gene cluster (Aziz et al., 2018). The role of interferon signaling in the development of autoimmunity in the typical population is well studied (Green et al., 2017; Hall and Rosen, 2010; Oppenheim et al., 2004), but its contribution to autoimmunity in Down syndrome remains to be defined. Even if interferon hyperactivity is demonstrated to drive autoimmunity in Down syndrome, what are the specific mechanisms? How does interferon hyperactivity in Down syndrome lead to such profound and widespread loss of 'self-tolerance' in this population? These mechanistic investigations are a pre-requisite for the identification of safe intervention strategies that could target the underlying pathways without compromising the anti-viral and anti-tumoral roles of interferon signaling. For example, as stated above, many interferon-inducible patho-cytokines are elevated in Down syndrome, such as IL-6, TNF- $\alpha$ , IL22, IL10 and various IL17 isoforms. What is their role in autoimmunity and other developmental and clinical hallmarks of Down syndrome? This could be tackled through a combination of studies in all three components of the INCLUDE Project, from basic science approaches in animal models to clinical trials, including a dissection of the contribution of Type I, II and III interferon ligands, all of which employ receptors encoded on chromosome 21. Beyond the interferon receptors, other genes on chromosome 21 with a role in immune control could contribute to autoimmunity in Down syndrome, such as AIRE, DYRK1A and UBASH3A, to name a few, all of which deserve further investigation. The fact that immune dysregulation and interferon hyperactivity has been observed in mouse models of Down syndrome carrying extra copies of interferon receptors opens up many opportunities for mechanistic investigations and pre-clinical testing of various immune-modulatory strategies (Aziz et al., 2018).

## **2) Infections.**

A dysregulated response to common infectious agents is a major cause of morbidity and mortality in the population with Down syndrome. Most prominently, individuals with trisomy 21 show more severe consequences during lung viral infections, such as increased rates of hospitalization during respiratory syncytial virus (RSV) and H1N1 influenza A infections (Beckhaus and Castro-Rodriguez, 2018; Perez-Padilla et al., 2010), as well as increased rates of mortality from bacterial pneumonia and sepsis (Bloemers et al., 2010; Garrison et al., 2005). In the current COVID19 pandemic, it is predicted that individuals with Down syndrome will develop more severe pathology upon SARS-CoV-2 infection (Espinosa, 2020), and initial epidemiological studies indicate that this is indeed the case (Malle, 2020). A stronger investment in this research area is much needed.

- a. What is the prevalence of the following infectious diseases in people with Down syndrome across the lifespan? Are there any differences by age, sex, race/ethnicity, or geography?**

Group A streptococcus  
C. difficile infection  
Recurrent otitis media (ear infections)  
Recurrent sinusitis  
Respiratory Syncytial Virus (RSV)  
Pneumonia  
Candidiasis  
Croup  
Chronic urinary tract infection  
Impetigo  
Cellulitis  
Staph infection  
Cold sores  
Shingles  
Periodontitis  
Gout  
Sepsis  
Tuberculosis (TB) or latent TB

- b. What are the protective and risk factors for these infectious diseases in people with Down syndrome?** More specifically, what is the role of other comorbidities in the predisposition to infectious diseases? For example, what is the impact of dysphagia and pulmonary hypertension on acquiring and/or improperly resolving lung infections? What is the impact of hematological disorders common in this population (e.g. TMD) in the maturation and function of myeloid cell types involved in the anti-bacterial defense? What is the impact of OSA and its various treatment modalities (e.g. CPAP, tonsillectomy) on the risk of acquiring and/or improperly resolving lung infections?
- c. What is the long-term impact of these infectious diseases in people with Down syndrome?** Generally, how do infectious diseases impact overall health, longevity, and quality of life indicators from participation in education, the workforce and social activities? More specifically, what is the role of these more prevalent infectious diseases in the development of autoimmunity in people with Down syndrome? It is well established that common infectious are often involved in the priming of the immune system toward an autoimmune state, such as in the case of reovirus infections in the etiology of celiac disease (Bouziat et al., 2017). Therefore, what is the link between greater risk of infections and autoimmunity in Down syndrome? Given the fact that inflammation can induce metabolic pathways producing neurotoxic intermediates, such as quinolinic acid (Guillemin, 2012), what are the long term neurological impacts of repeated infections in Down syndrome?
- d. What are the most appropriate diagnostic(s)/screening tool(s) for infectious diseases for people with Down syndrome?** Given that some infections are significantly more common in Down syndrome (e.g. RSV, bacterial pneumonia), we believe that specialized screening protocols should be developed for this population for these conditions. For example, in the case of bacterial lung pneumonia, the leading cause of death among adults with Down syndrome (Ram and Chinen, 2011), a significant research investment could produce novel tools to detect early signs of infections as well as biomarkers of prognostic value. In this sense, the current research investment in this area is disproportionately small. Children with Down syndrome have a >60-fold higher rate of pneumonia than typical children (So et al., 2007), and bacterial pneumonia is a leading cause of mortality in adults with DS (Ram and Chinen, 2011), more so than Alzheimer's disease.
- e. What are the best prophylactic and treatment modalities for these infectious diseases in Down syndrome?** More specifically, for those pathogens for which vaccines are available, what is the efficacy of these vaccines in the population with Down syndrome? Should vaccination protocols be adjusted for this population? We believe that new, more effective vaccines for grave infections such as RSV and bacterial pneumonia should be considered a top priority for the field. Given the clear dysregulation in cellular and humoral immunity in Down syndrome, it is possible that some vaccines

are less effective in this population, and there is evidence to support this notion (Joshi et al., 2011), which demands increased research investment into vaccine research and development. Research into the mechanisms that underlie the greater risk of developing severe complications during infections, including lung infections and sepsis, could illuminate immune-modulatory strategies to normalize the host response without impeding the anti-viral and anti-bacterial defense. In addition, analysis from some pediatric medical care centers for Down syndrome indicates that children with Down syndrome may be more inclined to not vaccinate against diseases such as chicken pox and measles as compared to the typical population. This is clearly an important area where data should be aggregated in terms of prevalence and health outcomes over long periods of time.

**f. What are the mechanisms by which trisomy 21 increases the risk and/or severity of infectious diseases in people with Down syndrome? Are there any specific genes on chromosome 21 or signaling pathways that contribute to this phenotype in Down syndrome?** Of importance to bacterial infections in those with Down syndrome, exacerbated production of Type I IFNs during the anti-viral response is known to increase the risk of secondary bacterial infections in mouse models. Indeed, knock-out of one of the Type I IFNRs encoded on chromosome 21 improved survival and clearance of *S. pneumoniae* (Shahangian et al., 2009). These harmful effects of Type I IFN signaling seem to be driven by impairment of macrophage and/or neutrophil function by IFN-induced cytokines, most prominently among them the anti-inflammatory cytokine IL-10 (Pittet et al., 2010; van der Sluijs et al., 2004). IL-10 is involved in the dampening and resolution of an immune response, and is consistently elevated at baseline in people for Down syndrome (Sullivan et al., 2017). Furthermore, one of the subunits of the IL-10 receptor, IL10RB, is encoded by one of the four genes in the IFNR cluster on chromosome 21. IL10RB not only serves as a subunit for the IL-10 receptor, but also for the Type III IFNs, IL-22, and IL-26 receptors (Pestka et al., 2004). These findings beg the question: what is the impact of elevated IL-10 signaling in Down syndrome? This is important, because the suppressive effects of IL-10 on the anti-bacterial branch of the immune system could increase the risk of secondary bacterial infections (van der Sluijs et al., 2010; van der Sluijs et al., 2004). The role for IL-10 in this phenomenon has been well investigated for pneumococcal pneumonia and tuberculosis. In a mouse model of influenza A, treatment with anti-IL-10 neutralizing antibodies before inoculation with *S. pneumoniae* resulted in reduced bacterial outgrowth and reduced lethality during secondary bacterial pneumonia (van der Sluijs et al., 2004). In the case of tuberculosis, Type I IFN signaling was shown to actually promote *M. tuberculosis* bacterial expansion and pathogenesis (Moreira-Teixeira et al., 2018), which was explained by IFN-dependent induction of IL-10 and consequent impairment in bacterial killing (McNab et al., 2014). Altogether, these observations support the notion that Type I IFN hyperactivity and increased downstream IL-10 signaling could be drivers of the known susceptibility to bacterial pneumonia in people with Down syndrome. Noteworthy, several reports have documented impaired neutrophil function in DS (Cocchi et al., 1978; Izumi et al., 1989; Rascon Trincado et al., 1988). Therefore, increased research in the field of immunology, with a focus on dysregulation of the anti-bacterial defenses, is amply justified.

### **3) A Case for Down Syndrome Medical Innovation Networks.**

There is a great need for more accurate, aggregated data with a larger magnitude of power and power analysis specific to Down syndrome. Harnessing the largest and fastest growing Down syndrome clinics in collaboration with national networks studying autoimmune diseases and immunity could more quickly answer questions associated with intra-Down syndrome and typical population comparables along the lines of prevalence, risk and protective factors, diagnostics, treatments and therapies. Establishing natural history and epidemiological studies at such centers across the United States with biomarkers, proteomics, epigenetics, microbiomes and other important inputs could help cure autoimmune diseases in people with Down syndrome and in the typical population as well.

### **4) Addressing Research Challenges & Opportunities for individuals with Down syndrome.**

Are there additional considerations for treatment of autoimmune conditions or infections for specific subgroups of the population with Down syndrome, including aging adults, those with the dual diagnosis of autism and Down syndrome, or those with mosaicism? What are the harms versus benefit of screening

asymptomatic people with Down syndrome for autoimmune conditions due to the high prevalence? What are the costs to families associated with annual screening and how might financial burden be reduced? What would be the cost savings for families and hospitals, and the years-of-life savings for individuals with Down syndrome be if pneumonia vaccine compliance was 100% in people with Down syndrome?

Does access (within state) to a Down syndrome clinic result in improved outcomes (lifespan, quality of life, reduced hospitalizations, ADL performance) for people with Down syndrome? Is access to a Down syndrome clinic or specialist feasible for most families? How is this impacted by race, geography, age, care giving arrangement?

What are the common barriers to accessing medical care facing people with Down syndrome and their families? Would provision of a food voucher or transportation stipend reduce burden of care and increase access?

## II. Development, Brain, and Mind

Undoubtedly, research on the topics of development and neurosciences remains a high priority for the field. Scientific research that could illuminate interventions to improve development, neurological function, and mental health across the lifespan would have tremendous benefits for the population with Down syndrome. Likewise, research aimed at reducing the burden of neurological comorbidities (e.g. Alzheimer's disease, autism spectrum disorders, seizure disorders) will advance the mission of extending lifespan and improving quality of life for individuals with Down syndrome.

### 1) Developmental delays.

#### a. What is the prevalence of the following developmental delays in people with Down syndrome across the lifespan? Are there differences by race/ethnicity, sex or geography?

Speech/Language delay  
Fine motor delay  
Gross motor delay  
Sensory motor delay

Although it is clear that these various forms of developmental issues are more prevalent in the population with Down syndrome, these are highly variable phenotypes, and the factors driving this heterogeneity have not been elucidated. A definitive epidemiological study would illuminate patterns in the variation of these phenotypes, with potential to reveal the impacts of lifestyle, diet, socio-economic status, and diverse types of interventions. We believe a thorough assessment of these conditions should be included in the activities of Component 2 of the INCLUDE project. A key challenge in this area is the identification of a suitable test battery that could be used broadly, which in itself is worthy of a significant research investment.

#### b. What are the protective and risk factors for various developmental delays in people with Down syndrome? In parallel to a definitive epidemiological study, research should be aimed at identifying genetic- and non-genetic risk factors modulating the appearance and severity of developmental delays, with special emphasis on factors that may be operating during pregnancy and early infancy. Early interventions will be key to improve development, but our understanding of the very early events that are dysregulated by the extra chromosome await elucidation. Are there medical comorbidities early in life that correlate or predict patterns of developmental delays later on in life? This research should be holistic and integrative, as there are myriad factors that could impact early development including variations in the endotype (e.g. genome, transcriptome, proteome, metabolome), diet, microbiome and peri-natal comorbidities (e.g. TMD, CHD). Given the renewed emphasis on immune dysregulation, particularly interferon hyperactivity, these studies must include analysis of the role of immune dysregulation in early development. The fact that interferon hyperactivity causes developmental delays and neurological issues in Type I Interferonopathies highlights the importance of this topic (Crow and Manel, 2015; Rodero and Crow, 2016). We follow with great interest the studies of JAK inhibition in children with Type Interferonopathies at NIH (Sanchez et al., 2018), and we applaud the activities within the NICHD intramural program to study natural compounds with immune-modulating activities that could potentially be used pre- and/or peri-natally, such as apigenin (Guedj et al., 2016). We believe a significant investment should be made in the study of early immune-modulatory strategies to improve development.

#### c. What are the long-term impacts of these various developmental delays in people with Down syndrome? A longitudinal study defining the various developmental tracks and 'natural histories' of developmental delays is warranted. For example, are there neurological conditions later in life that can be linked to early delays in development? This question is of key relevance for conditions such as autism spectrum disorders (ASD), attention deficit disorders, and seizures disorders, for which early interventions could produce vast improvements. How does early childhood stuttering and the onset of stuttering later in life, a major impediment to speech and communication, evolve and relate? Being able to map differences in early developmental milestones to later neurological conditions

would be of great value for this population. More broadly, the impact of diverse types of developmental delays in various aspects of social life, including school performance and work placement, should be investigated critically, so that individual development plans and work placement efforts can be customized to the need of the individual following evidence-based practices.

- d. What are the most appropriate diagnostic(s)/screening tool(s) for various developmental delays in Down syndrome?** Once again, early diagnosis is key to reduce the burden of the developmental delays via early intervention strategies, and additional research in this area is needed. One obvious example is the use of eye tracking technology to detect early signs of autism in the typical population, which enables early intervention strategies. What other early biomarkers for developmental delays could be employed in those with Down syndrome? Special emphasis should be put on understanding how deviation of very early developmental milestones could indicate risk of more serious developmental issues later in life. Research is needed on existing batteries and tools currently in use for people with IDD to determine their usefulness and sensitivity in people with Down syndrome, as well as what modification to these existing tools might make them more valid in Down syndrome. Given the wide range of variation of developmental skill and delay seen in Down syndrome, it is likely a screening tool specific to Down syndrome would be needed to increase accuracy and earlier identification of developmental delays in this population.
- e. What are the best therapies and interventions for developmental delays in Down syndrome?** Earlier detection and diagnosis are critically important, but incomplete without an understanding of what treatment/intervention options work best for this population. What therapies have shown effective for this population? What modifications to existing interventions increase their effectiveness in Down syndrome? Should therapy modality, frequency, and/or duration differ depending on the severity of the delay? Does earlier intervention correlate with improved outcomes in people with Down syndrome? Longitudinal studies are needed to determine whether improvements or gains in skills made during treatment for developmental delays in childhood are long lasting, or whether there may be benefit to interventions throughout teen and adulthood. Expectedly, the use of speech therapy, feed therapy, neuromotor reflex integration and other types of early intervention would have tangible benefits for those with Down syndrome. However, the full impact of these interventions in the developmental trajectory remains to be elucidated. We believe that cross-sectional and longitudinal studies as part of Component 2 of INCLUDE should aim to elucidate the value of these and other interventions, leading to a progressive growth and evolution in the suite of intervention strategies available to families and practitioners. These studies should include the assessment of a wide range of intervention modalities amenable to families of vastly different socio-economic status and cultural backgrounds. Although we welcome the assessment of intervention modalities that require advanced technology (e.g. computer assisted learning), we believe that low tech interventions should be studied in greater detail and depth (e.g. neuromotor reflex integration).
- f. What are the mechanisms by which trisomy 21 increases risk and/or severity of developmental delays Down syndrome?** Answering this question will likely require a synergistic portfolio of activities across all three components of the INCLUDE Project. Basic science studies could focus on two major aspects: cell-based studies of key iPSC-derived cell types potentially involved in developmental phenotypes (e.g. neurons, glia, oligodendrocytes) and gene-mapping efforts in animal studies. Careful analyses of developmental and behavioral phenotypes in popular mouse models of Down syndrome has paved the road for more sophisticated gene mapping efforts (Aziz et al., 2018). With the advent of CRISPR-based genome engineering technology, it is now possible to envision collaborative efforts to rapidly define the impacts of dozens of genes to developmental and behavioral phenotypes. However, experiments in mouse models, which are very time and resource consuming, should be highly attuned to results obtained through human research in Components 2 and 3. In this regard, -omics studies in the cohort study in Component 2 may identify signaling pathways differentially dysregulated in those with Down syndrome and specific neurodevelopmental profiles. Are these pathways also dysregulated in mouse models of Down syndrome? If so, what genes are involved? Answering these questions may reveal strategies for pre-clinical testing of interventions to be later tested in humans in Component 3. Using the aforementioned example of interferon hyperactivity, the fact that this phenomenon is

observed both in mice (Aziz et al., 2018) and humans (Sullivan et al., 2016), and that is has been mapped in human cells to the triplicated interferon receptors (Powers et al., 2019), opens up myriad possibilities for pre-clinical testing of immune-modulatory strategies that could be translated to the clinic.

## 2) Neurological and Psychological Conditions.

### a. What is the prevalence of the following neurological and psychological conditions in people with Down syndrome across the lifespan? Are there variations by race/ethnicity, sex or geography?

Alzheimer's Disease / Dementia / Memory loss  
Autism Spectrum Disorders  
Anxiety  
ADD/ADHD  
Depression  
Bipolar Disorder  
PTSD  
Schizophrenia  
Obsessive-compulsive disorder  
Parkinson's disease  
Traumatic Brain Injury  
Cerebral Palsy  
Stroke  
Brain malformation  
Movement disorder  
Moyamoya syndrome  
Seizure disorders, including infantile spasms and epilepsy  
Autoimmune encephalitis

Whereas epidemiological data is very strong for some of these conditions more prevalent in those with Down syndrome (e.g. Alzheimer's disease), it is very poor, yet tantalizing, for others (e.g. Moyamoya, autoimmune encephalitis). Stronger epidemiology for these conditions could be achieved through Component 2.

### b. What are the protective and risk factors for these various neurological conditions in people with Down syndrome? Naturally, this question is of the utmost importance for Alzheimer's disease, and we applaud the efforts of the Alzheimer's Biomarkers Consortium - Down syndrome (ABC-DS) in this area. We look forward to the results of this massive investment and to a sustained effort in this consortium. Given the many established ties between inflammation and Alzheimer's disease, we are particularly interested in the identification of immune-modulatory factors that could influence the onset and development of Alzheimer's disease in Down syndrome, which in turn could enable development of novel diagnostic and therapeutic strategies. We believe that immune-modulatory strategies hold much promise in this field, and we are investing heavily in this area, including clinical trials for the immune modulator GM-CSF (Boyd et al., 2010; Jim et al., 2012). After Alzheimer's disease, we believe that special emphasis should be placed in autism spectrum disorders and seizures disorders, both of which affect a sizable fraction of the population with Down syndrome. Our team has produced one of the most comprehensive analyses of infantile spasms in Down syndrome to date (Daniels et al., 2019), but much remains to be defined in terms of identification of risk factors. If mental health conditions appear to be more common in people with Down syndrome, then it would be critically important to understand the unique vulnerabilities in the population driving this increase as well as what protective factors might help mitigate future pathology. One question is how might the common medical comorbidities contribute to mental health conditions? For example, with increase in autoimmune conditions causing increased inflammation, how might this be impacting mental health? Which risk factors are modifiable, and which may be genetically driven by the 21<sup>st</sup> chromosome? A better understanding is also needed to understand how phenotypic variation may or may not be



correlated with later expression of mental health conditions in the population. The onset of one specific condition, regression, has been reported by families to begin after a traumatic experience or life change, or the presence of an infection, but different clinical terminology, small sample sizes and a lack of specified diagnostic tools have made it difficult to draw any conclusions. Tragically, we also know people with IDD including Down syndrome are high-risk for all forms of abuse (physical, sexual, emotional and financial), but how these factors contribute to their overall mental health has been greatly overlooked and this must be rectified.

- c. **What is the long-term impact of neurological conditions diagnosed early in life in people with Down syndrome?** Both treated and untreated, how do mental health conditions impact outcomes for people with Down syndrome throughout life? Are there specific patterns of mental health conditions early on in children with Down syndrome that seem to map onto future mental health challenges throughout adulthood, much like in the typical population? How does mental health impact outcomes for people with Down syndrome such as overall quality of life, ability to have a job, future incidences of mental health conditions, medical health, including Alzheimer's Disease?
- d. **What are the most appropriate diagnostic(s)/screening tool(s) for each of these conditions for people with Down syndrome?** A better understanding of the broad behavioral phenotype in children and adults with Down syndrome is needed. How those behavioral phenotypes compare to the typical population might shed light on symptomology, which would impact screening tools used. There are screening tools such as the DMID-2 used to diagnose mental health conditions in adult with IDD. Is this appropriate for use in people with Down syndrome and what modifications might increase its validity for Down syndrome?
- e. **What are the best treatment modalities for these conditions?** Many of the most common treatment approaches for mental health conditions for the typical population (cognitive-behavioral, psychodynamic, etc.) are not validated or appropriate for use with people with Down syndrome, but what are the modifications that might make them more useful for people with Down syndrome? For example, how can visual cues which have been proven to be effective modification tools for people with Down syndrome, be incorporated? In addition, the medications commonly used to treat mental health conditions were also not tested on people with Down syndrome. More research is needed to inform doctors or psychologists when prescribing these medications for people with Down syndrome regarding dosage, interaction, and side effects. For the typical population, we know a combination of therapeutic interventions and psychopharmaceuticals together tend to have best results, but we do not have the evidence to say this is the case for people with Down syndrome. As mentioned above, given the high rate of trauma via abuse many people with Down syndrome statistically experience, a specific focus should be on treatments for post-traumatic stress validated in people with Down syndrome.
- f. **What are the mechanisms by which trisomy 21 increases the risk and/or severity of neurological and psychological conditions?** Although this topic has been the topic of much research in the field, the genes and mechanisms affecting neurological health in Down syndrome still await elucidation. We believe that special emphasis should be placed in understanding how dysregulation of innate immunity impacts brain function in Down syndrome. The fact that interferon signaling is consistently dysregulated in all brain regions studied at all developmental stages studied in mouse models of Down syndrome highlights the importance of this research avenue (Aziz et al., 2018). Furthermore, the fact that inhibitors of the interferon-activated protein kinase R (PKR), a key enzyme in the integrated stress response (ISR), was found to reverse behavioral and neurophysiological abnormalities in a mouse model of Down syndrome (Zhu et al., 2019) further supports this line of inquiry. Special attention should be paid to mechanisms by which immune dysregulation may impact brain function through changes in neurotransmitter metabolism. For example, the recent discovery that trisomy 21 activates the kynurenine pathway of tryptophan catabolism could lead to imbalances in serotonin- and glutamate-mediated neural pathways (Powers et al., 2019). Furthermore, activation of the kynurenine pathway leads to production of quinolinic acid,

a known convulsant involved in the etiology of seizure disorders in the typical population (Guillemin, 2012).

- g. Infantile Spasms in Children with Down syndrome.** The Pediatric Epilepsy Research Consortium (PERC) is a national collaboration of over 40 pediatric epilepsy centers in the United States and is funded by various local nonprofit development centers. PERC developed the National Infantile Spasms Consortium (NISC) database, which collects data on the general pediatric population with infantile spasms through a multicenter prospective database enrolling infants with a new diagnosis of infantile spasms from approximately 23 medical centers. It is important to include a large and well-defined cohort (gender, race, ethnicity, etc.) of infants with Down syndrome. NINDS, a participant in INCLUDE, is a funder of PERC.
- h. What is mental health and what is behavioral?** We need to have criteria, rubric and testing for specific diagnoses for both. We need to measure the efficacy of treatment interventions in longitudinal studies engaging multiple medical centers, harmonizing protocols and sharing data. We need funding related to characterization and diagnosis and research for existing treatments as well as translating basic science into new treatments. Special attention should be paid to age, gender, race, ethnicity and co-occurring conditions.

**3) Addressing Research Challenges & Opportunities for individuals with Down syndrome.**

How might a treatment for mental health conditions be best modified for implementation in a group living environment (nursing home, group home, host home, etc.)? What is the percentage of individuals with Down syndrome who have access to a Down syndrome mental health specialist and what are the largest barriers to mental health care for this population? How does obtaining a formal mental health diagnosis benefit a person with Down syndrome and their family? How does a family's perception of behavior/mental health impact the mental health of the person with Down syndrome?

What are the exclusion criteria that most often indirectly result in the exclusion of people with Down syndrome from participation in psychopharmaceutical trials and how could that exclusion criteria be modified to include people with Down syndrome?

How does having a social worker or resource coordinator embedded in a clinic impact the delivery of services/ wrap around care for families? What are the ways in which a dual diagnosis (Down syndrome and autism) might increase access to services or therapies? Are families with dual diagnosis more likely to engage with the autism community, the Down syndrome community and how might this change how researchers reach this population? What are the barriers to soft tissue, especially brain, donations for individuals with Down syndrome and their families? What are the key motivating factors for families who complete brain bank donation?

### III. Heart, Lung and Blood

#### 1) Cardiovascular disease in Down syndrome.

Although there is strong epidemiological data for some cardiovascular conditions in the population with Down syndrome (e.g. congenital heart disease, CHD), definitive data is lacking for most other conditions in this category. Even for CHD, existing epidemiological data does not address potential protective and risk factors during pregnancy, or variations by ethnicity, geography, or other potential modifying factors.

##### a. What is the prevalence of the following conditions in people with Down syndrome?

Congenital heart disease (any type)  
Heart arrhythmias/dysrhythmia  
Hypertension  
Cardiomyopathy  
Elevated cholesterol  
Peripheral artery disease  
Myocardial infarction

b. What are the protective and risk factors for the aforementioned conditions and how do they compare to those identified in the typical population? For example, do dietary or pharmacological interventions to lower circulating cholesterol levels have the same effect in people with Down syndrome?

c. What is the long-term impact of the aforementioned conditions on overall development and other health outcomes in Down syndrome? For example, this is the first time in history that sizable population of individuals with Down syndrome that underwent perinatal heart surgery reaches adulthood. Are there differences in the adult population between those with surgically repaired CHD versus those who did not have a CHD diagnosis?

d. What are the most appropriate diagnostic(s)/screening tool(s) for the aforementioned conditions in people with Down syndrome? For example, do blood-based biomarkers have the same prognostic values in people with Down syndrome relative to the typical population (e.g. HDL, LDL)?

e. What are the most appropriate therapeutic approaches for the aforementioned conditions in people with Down syndrome? Are there important differences that should be taken into account when applying these interventions in individuals with trisomy 21? For example, do statins work similarly in individuals with Down syndrome to lower cholesterol, or should they be employed in a tailored fashion?

f. What are the mechanisms by which trisomy 21 modifies the risk and/or severity of the aforementioned conditions? Although advances have been made in mouse models to narrow down the genes on chromosome 21 that may contribute to the CHD phenotype, the genetic versus non-genetic factors contributing to CHD risk in Down syndrome remain to be identified. What are the specific genes on chromosome 21 and downstream signaling pathways that contribute to this comorbidity in Down syndrome? Research in this area may lead to novel diagnostics and therapeutic approaches for CHD in DS. The same inquiry applies to cardiovascular conditions that seem to be less frequent in the population with Down syndrome, such as atherosclerosis and myocardial infarction. Identifying the genes on chromosome 21 and downstream pathways driving this protective effect could have broad impacts in our understanding of a leading cause of death in the typical population.

#### 2) Pulmonary disease

a. What is the prevalence of the following conditions in people with Down syndrome across the lifespan? Are there differences by age, sex, race/ethnicity differences or geography?

Asthma

- b. What are the protective and risk factors for the aforementioned conditions in people with Down syndrome?** Members of our team have published the most comprehensive assessment of risk factors of pulmonary hypertension in children with Down syndrome to date (Bush et al., 2018), but even larger in-depth studies are needed for further identification of protective and risk factors, as well as the elucidation of actionable biomarkers of clinical value. Given the finding that individuals with Down syndrome seem protected from allergic sensitization (Eijsvoogel et al., 2017), what is the true definition and clinical presentation of asthma in people with Down syndrome? Is it truly asthma or a different pulmonary condition of similar presentation?
- c. What is the long-term impact of the aforementioned pulmonary conditions in people with Down syndrome?** For example, what are the lifelong impacts of recurrent pulmonary hypertension on other developmental and health outcomes?
- d. What are the most appropriate diagnostic(s)/screening tool(s) for these conditions in people with Down syndrome and how do they vary relative to the approaches employed in the general population?** For example, how should diagnostic criteria for asthma be applied to individuals with Down syndrome?
- e. What are the molecular and cellular mechanisms by which trisomy 21 modifies the risk of these pulmonary conditions?** For example, it is well established that some subtypes of pulmonary hypertension are associated with an inflammatory phenomenon (Florentin et al., 2018; Savale et al., 2016; Stenmark et al., 2015), and that interferon hyperactivity can drive pulmonary hypertension (Savale et al., 2016). Given that people with Down syndrome display signs of chronic autoinflammation and interferon hyperactivity (Araya et al., 2019; Powers et al., 2019; Sullivan et al., 2017; Sullivan et al., 2016; Waugh et al., 2019), what is the role of genes on chromosome 21 (e.g. interferon receptors) in the observed autoinflammation and increased risk of pulmonary hypertension in this population? If epidemiological studies confirm that individuals with Down syndrome are less prone to allergic sensitization, which may lead to lower rates of asthma, what are then the mechanisms driving this protective effect? For example, our team reported clear depletion of immunoglobulin E in the circulation of individuals with Down syndrome (Sullivan et al., 2017), which could be linked to lower allergic sensitization. Therefore, what are the mechanisms by which the extra chromosome leads to loss of IgE production and what are the consequences of this phenomenon?

### 3) Leukemias and other hematological disorders.

Although there is strong epidemiological data defining the increased rates of various leukemias in the population with Down syndrome (Buitenkamp et al., 2014; Maloney et al., 2015; Whitlock et al., 2005), a much stronger epidemiological assessment is needed to identify protective and risk factors, as well as potential variations by race, geography, and other variables.

- a. What is the prevalence of the following conditions in people with Down syndrome across the lifespan? Are there differences by age, sex, race/ethnicity, and geography?**

Acute T-cell lymphoid leukemia (T-cell ALL)  
Acute B-cell lymphoid leukemia (B-precursor ALL)  
Acute myeloid leukemia (AML or AMKL)  
Chronic lymphocytic leukemia (CLL)  
Chronic myeloid leukemia (CML)  
Leukemoid reaction  
Transient myeloproliferative disorder (TMD)

- b. What are the genetic versus non-genetic risk factors for diverse leukemias and hematological disorders in people with Down syndrome?** For example, earlier research identified that TMD is a risk factor for AML (Maloney et al., 2015), but, what are the risk factors for perinatal TMD? Are there genetic variants that modulate the impact of leukemogenic genes encoded on chromosome 21 to

define the risk of developing these diverse hematological disorders? Are there protective or risk factors during pregnancy that could modulate the incidence of perinatal TMD?

- c. What is the long-term impact of hematological disorders and their treatments in people with Down syndrome?** For example, even though most cases of TMD resolve without treatment, are there lifelong impacts on hematopoiesis, myeloid cell function, and immune control for those who experienced TMD in the first few months of life? For cases of TMD that required treatment, what are the lifelong impacts of those treatments (e.g. methotrexate) on the development and health outcomes of individuals with Down syndrome? How do these impacts compare to those in typical people? For example, it is well established that some chemotherapy regimens used in leukemia treatment cause more undesirable side effects in individuals with Down syndrome (Garre et al., 1987; Maloney et al., 2010; Maloney et al., 2015; Rabin et al., 2012; Shah et al., 2009; Whitlock et al., 2005). Therefore, are there long-term effects that are also more pronounced in leukemia survivors with trisomy 21?
- d. What are the most appropriate diagnostic(s)/screening tool(s) for hematological disorders in people with Down syndrome?** Given that some genetic perturbations are more common in hematological disorders in Down syndrome (e.g. GATA1 mutations in DS-AMKL) (Crispino, 2005; Hertzberg et al., 2010; Maloney et al., 2010; Stankiewicz and Crispino, 2009), how should this knowledge be applied for customized screening, diagnostics, and treatment in Down syndrome?
- e. What are the best therapeutic approaches for leukemias in Down syndrome and how should approaches employed in the typical population be modified for individuals with trisomy 21?** For example, it is well established that treatment of B-ALL is more difficult in Down syndrome, mostly due to a higher burden of undesired side effects in response to chemotherapy, leading to modified dosing protocols (Arico et al., 2008; Garre et al., 1987; Maloney et al., 2010; Shah et al., 2009; Whitlock et al., 2005). What are the best chemotherapy protocols for diverse leukemias in Down syndrome? With the advent of non-chemotherapy approaches to treat blood malignancies in the typical population (e.g. chimeric antigen receptor T cells, CARTs), how would these approaches function in individuals with Down syndrome? For example, given the obvious dysregulation of T cell lineages in people with Down syndrome (Araya et al., 2019), research is needed to understand how trisomy 21 would affect the generation and use of CARTs.
- f. What are the mechanisms by which trisomy 21 increases the risk, development, and outcome to therapy for diverse leukemias?** Although several genes with leukemogenic properties encoded on chromosome 21 have been identified (e.g. interferon receptors, CHAF1B, HMGN1) (Cupples and Tan, 1977; Lane et al., 2014; Malinge et al., 2012; Thompson et al., 2015; Volk et al., 2018), their relative contributions to leukemogenesis, mechanisms of action and therapeutic value remain to be defined. How do these and other genes on chromosome 21 disrupt hematopoiesis and bone marrow homeostasis toward a leukemic-prone state? What are the signaling and metabolic pathways modulated by these genes? Do these dysregulated pathways offer unexpected genetic or pharmacological liabilities that could be exploited in novel therapeutic strategies?

#### **4) Addressing Research Challenges & Opportunities for individuals with Down syndrome.**

What are the harms versus the benefits, and costs of screening asymptomatic children with Down syndrome for TMD and leukemia? Are the non-chemotherapy approaches to treat blood malignancies in the typical population (e.g. chimeric antigen receptor T cells, CARTs) as effective as chemotherapy approaches in people with Down syndrome? What are the costs (social, economic, developmental) of leukemia for families with Down syndrome and how might those costs be offset with supports such as food vouchers, housing, or transportation? Are there opportunities for better clinician education related to leukemia and the side effects of treatment on people with Down syndrome? For example, are families preparing to undergo treatment for leukemia made aware of the additionally intense adverse side effects in people with Down syndrome or not?

## IV. Eyes and Vision

Although it is well accepted that visual impairment is very frequent in people with Down syndrome, a definitive epidemiological assessment is missing.

**a. What is the prevalence of the following conditions in people with Down syndrome across the lifespan? Are there differences by age, sex, race/ethnicity, and geography?**

Amblyopia  
Astigmatism  
Cataracts  
Glaucoma  
Hyperopia  
Keratoconus  
Myopia  
Nystagmus  
Strabismus (esotropia)  
Blocked nasolacrimal duct

**b. What are the genetic and non-genetic risk factors for modulating the manifestation of these conditions in people with Down syndrome? Are there protective or predisposing risk factors during pregnancy or during the first few months of life?**

**c. What is the long-term impact of various forms of visual impairment in people with Down syndrome? How do these conditions affect the development of children with Down syndrome and how should this knowledge be applied toward improved developmental stimulation and pedagogic strategies?**

**d. What are the most appropriate diagnostic(s)/screening tool(s) for these condition for people with Down syndrome and how should traditional approaches be adapted for screening in this population?**

**e. What are *the* mechanisms by which trisomy 21 increases the risk and/or severity of these eye conditions? Are there any specific genes on chromosome or signaling pathways that contribute to these comorbidities in Down syndrome? For example, the crystallin alpha A gene (CRYAA), which encodes for a major lens protein, is encoded on chromosome 21. What is the impact of CRYAA increased gene dosage on lens development, visual impairment, and risk of cataracts in this population?**

**Addressing Research Challenges & Opportunities for individuals with Down syndrome.**

What is the rate of compliance across pediatric Down syndrome clinics nationally with vision screenings set forth in the 2011 AAP Guidelines? What are the barriers for families completing vision screenings?

What are the harms versus benefit, and costs associated with screening asymptomatic adults with Down syndrome for keratoconus?

What are the incentives for research participation commonly used by researchers for the general population and are those incentives equally motivating for people with Down syndrome? For their families?

What percentage of research recruitment materials for the Down syndrome community does not use people-first language and how might that be updated to increase participation from families?

What are the modifications beyond visuals (commonly understood to be a strength for people with Down syndrome), that would be most accessible to people with Down syndrome with visual impairments?

## V. Ear, Nose, Throat

ENT comorbidities are very common in this population and a major cause medical care costs, hospitalization, and morbidity. Additional basic and clinical research is needed to decrease the burden of these comorbidities through better diagnosis and treatment. Obstructive sleep apnea (OSA) in particular is a major comorbidity likely to have multidimensional detrimental impacts on the development and health outcomes of individuals with Down syndrome.

1) **What is the prevalence of the following ENT conditions in people with Down syndrome across the lifespan?** Are there any differences by age, sex, race/ethnicity, and geography?

Eustachian tube dysfunction  
Laryngomalacia  
Chronic rhinitis  
Hearing loss  
Obstructive Sleep Apnea

a. **What is the long-term impact of these ENT conditions in people with Down syndrome?** For example, in typical people, OSA is known to cause dysregulation of important physiological processes, such as disruption of the leptin hormonal circuitry controlling appetite control and metabolism (Harsch et al., 2003; Kelesidis et al., 2010; Magge et al., 2008). Additionally, hypoxemia associated with OSA is also known to cause inflammation (Eltzschig and Carmeliet, 2011). Therefore, what is the interplay between OSA, metabolism and inflammation in Down syndrome?

b. **What are the most appropriate diagnostic(s)/screening tool(s) for these conditions for people with Down syndrome and how should canonical approaches be adapted for this population?** For example, definitive OSA diagnosis requires sleep studies at hospitals or medical care facilities that most often are ill adapted to accommodate people with Down syndrome. This most likely leads to massive under-diagnosis of OSA in Down syndrome. Therefore, what is the value of ‘at-home’ sleep studies for diagnosis of OSA? What is the value of wearable monitors, oximeters and other less disruptive technologies to assess OSA in this population?

c. **What are the most appropriate treatment modalities for ENT comorbidities in Down syndrome?** For example, what is the benefit of treating OSA with CPAP/BiPAP, tonsillectomy, adenoidectomy, tongue reduction surgery, oxygen supplementation, dental appliance, hypoglossal stimulation, and weight loss in people with Down syndrome? In another example, what are the demonstrated benefits of different hearing aids in children and adults with Down syndrome?

d. **What are the mechanisms by which trisomy 21 increases the risk and/or severity of ENT comorbidities?** Are there any specific genes on chromosome or signaling pathways that contribute to these class of comorbidities? Importantly, little is known about the occurrence of these comorbidities in animal models of Down syndrome. For example, pioneer studies by scientists at the Crnic Institute documented disruption of ERM sleep in the Dp16 mouse model (Levenga et al., 2018), which open up a plethora of opportunities for mechanistic investigations.

e. **OSA Research and Clinical Trials. Sleep Apnea.** OSA has such a high prevalence in the pediatric Down syndrome population and yet there is little known about testing and treatment as compared to the typical population, and even less known about OSA in adults with Down syndrome. We need detailed, thorough natural history and endocrinology studies across the lifespan and a better understanding of how aerodigestive clinics can contribute to this research and how OSA may lead to early mortality.

2) **Addressing Research Challenges & Opportunities for individuals with Down syndrome.** Are “at-home” sleep studies as valid of a diagnostic tool compared to in-hospital sleep studies, and how might “at-home” sleep studies reduce the burden of the test/how might they be modified to be more appropriate for people with Down syndrome ? What are the most effective means of supporting CPAP/BIPAP compliance for people with Down syndrome? What are the harms versus benefits of tonsillectomy in childhood without formal OSA diagnosis confirmed by test?

## VI. Endocrine System, Diabetes & Metabolism

Individuals with Down syndrome show widespread dysregulation of endocrine systems, most prominently among them thyroid dysfunction, estimated to affect more than half of adults with Down syndrome. Diabetes is another endocrine condition disproportionately affecting those with Down syndrome. Altogether, these conditions impose significant metabolic dysregulation, which in turn could be linked to the higher rates of obesity among those with Down syndrome. Additional research is needed to understand the etiology of these disorders as well as their long-term impact in people with Down syndrome, which could in turn lead to innovative diagnostics and therapeutic strategies.

### 1) Thyroid dysfunction

#### a. What is the prevalence of the following thyroid disorders in people with Down syndrome across the lifespan? Are there variations by age, sex, race/ethnicity, or geography?

Remarkably, although thyroid dysfunction affects preferentially females in the typical population, this sex bias is not observed in Down syndrome (Amr, 2018):

Hypothyroidism  
Hyperthyroidism  
Grave's disease  
Hashimoto's disease

Importantly, although all four conditions mentioned above are more prevalent in this population and often associated with the presence of auto-antibodies targeting the thyroid gland, auto-antibody testing is not commonly employed, which prevents a full assessment of autoimmune thyroid disease (AITD) in Down syndrome. Furthermore, the full spectrum of auto-antibodies targeting the thyroid gland in Down syndrome remains to be defined, and there may be important differences with those antibodies identified in the typical population.

#### b. What are the long terms impact of these various thyroid disorders in Down syndrome?

In the typical population, it is well established that autoimmune disorders tend to show 'clinical clustering', whereby appearance of one autoimmune condition predisposes to other autoimmune conditions. Is this true in Down syndrome as well? If so, what is the 'autoimmunity sequence' in Down syndrome? Given that immune dysregulation, inflammation, and autoantibodies have been involve in myriad neurological disorders, and that neuroinflammation is prevalent in Down syndrome (Heneka et al., 2015; Ohja et al., 2018; Wilcock, 2012; Wilcock and Griffin, 2013), is there a long term neurological impact of AITD in Down syndrome (e.g. progression of Alzheimer's disease?).

#### c. What are the genetic and non-genetic risk factors for thyroid disease in Down syndrome?

GWAS studies have identified SNPs associated with high risk of AITD in the typical population, but the prognostic value of these gene variants in Down syndrome remain to be identified (Wellcome Trust Case Control et al., 2007). Similar GWAS studies should be performed for the population with Down syndrome, and we applaud the collaboration between the INCLUDE Project and the Gabriella Miller Kids First project leading to the sequencing of >2,000 genomes of individuals with trisomy 21, which should provide a strong foundation for the necessary GWAS studies. Given the important role of autoreactive T cells in the development of AITD and other autoimmune conditions, more research is needed to understand T cell dysregulation in Down syndrome. Individuals with trisomy 21 show clear dysregulation of T cell lineages toward autoimmunity-prone states (Araya et al., 2019; Waugh et al., 2019), including clear impairment in Treg function (Araya et al., 2019). Further research is needed to understand how genetic and non-genetic risk factors may impact T cell biology. For example, it is well known that the microbiome can shape the immune cell repertoire in autoimmunity (Markle et al., 2013), but definitive studies of the microbiome in individuals with Down syndrome are lacking.

#### d. What other treatment modalities could be effective to treat these disorders beyond thyroid hormone management?

Although hypothyroidism is clinically managed with hormone replacement, targeting the underlying autoinflammation and autoimmunity could potentially have broader



benefits. For example, if AITD predisposes to other autoimmune conditions common in DS, such as celiac disease and various autoimmune skin disorders, could immune-modulatory strategies be developed to lower the burden of autoimmunity more broadly? One example is the recently launched clinical trial for JAK inhibition in Down syndrome funded by the INCLUDE Project (NCT04246372) (Rachubinski et al., 2019), but many other strategies could be explored in the field of immune modulation, including natural compounds currently being studied at NICHD, such as apigenin (Guedj et al., 2016).

- e. **What are the mechanisms by which trisomy 21 increases the risk and/or severity of these thyroid diseases?** Again, assuming the main underlying cause is an autoimmune reaction targeting the thyroid gland, much research is needed to understand the genetic, molecular, and cellular basis of autoimmunity in Down syndrome. The renewed interest in the clear interferon hyperactivity observed in people with Down syndrome is an obvious area of further research (Araya et al., 2019; Drasner et al., 1979; Epstein et al., 1987; Epstein and Epstein, 1976; Hallam et al., 2000; Hallam and Maroun, 1998; Maroun, 1980, 1995, 1996; Powers et al., 2019; Sullivan et al., 2017; Sullivan et al., 2016; Tan et al., 1974; Waugh et al., 2019), and the INCLUDE Project is already funding in this area, but more research is needed in both humans and animal models. Given that interferon hyperactivity is a known driver of AITD (Nair Kesavachandran et al., 2013; Oppenheim et al., 2004), definitive cause-effect experiments could be performed in mouse models of Down syndrome. Additionally, a deep mapping of autoantibodies targeting the thyroid gland is warranted, along with studies of B cell dysregulation. Beyond the observed disruption T cell lineages mentioned above, trisomy 21 also causes clear dysregulation of B cell differentiation and function (Carsetti et al., 2015; MacLean et al., 2018; Waugh et al., 2019), which in turn could impact on production of autoantibodies targeting the thyroid gland and others tissues. Additional research into B cell function is also likely to advance other areas of importance, such as response to vaccines, predisposition to infectious diseases, and increased risk of B cell-ALL.

## 2) Diabetes.

Although it is appreciated that both Type I and Type II diabetes are more common in people with Down syndrome, definitive epidemiological studies are lacking, and little if anything is known about the molecular and cellular mechanisms by which the extra chromosome may predispose to these conditions. Additionally, scarce knowledge on metabolic differences in those with trisomy 21 further prevents a better understanding and management of these conditions in the clinic.

- a. **What is the prevalence of the following types of diabetes in the population with Down syndrome across the lifespan? Are there differences by age, sex, race/ethnicity, or geography?**

Congenital/infant

Type 1

Type 2

Pre-diabetes

Some studies have revealed a remarkable increase in Type 1 diabetes (T1D) and islet autoimmunity in neonates and infants with Down syndrome (Aitken et al., 2013; Gillespie et al., 2006; Johnson et al., 2019), but more comprehensive epidemiological studies are needed to determine the prevalence of T1D across the lifespan. Obesity, Type 2 Diabetes and insulin resistance are also more common in Down syndrome (Real de Asua et al., 2014; Samur San-Matin et al., 2016), but again, definitive epidemiology is lacking, which prevents a thorough understanding of potential protective and risk factors specific to this population.

- b. **What is the long-term impact of various forms of diabetes in people with Down syndrome?** As explained above for AITD, a diagnosis of T1D early in life could indicate an increased risk of developing other autoimmune conditions later in life. Is this true in Down syndrome? If so, what is the autoimmunity sequence after T1D diagnosis? The long-term impacts of T1D and T2DM on health outcomes and quality of life is well characterized for the typical population, but not so for the population

with Down syndrome, with clear potential for important interactions with other comorbidities. For example, given the known interplay between brain glucose metabolism and Alzheimer's disease (Mosconi, 2005), what is the impact of T1D and T2DM in the progression of Alzheimer's in Down syndrome? If there is an impact, what are its mechanistic basis?

- c. **What are the best diagnostics tools for various types of diabetes in people with Down syndrome?** For example, studies of T1D in Down syndrome concluded that trisomy 21 creates a risk factor independent of the presence of HLA risk alleles (Aitken et al., 2013; Johnson et al., 2019), thus decreasing the utility of HLA testing for T1D diagnosis, a limitation that would likely apply for HLA testing for celiac disease and other autoimmune conditions. Also, what is the clinical presentation of diabetes in Down syndrome and how does it vary relative to the symptomatology of diabetes in typical people? Additional research in this area is necessary to develop screening protocols tailored to individuals with Down syndrome.
  - d. **What are the most appropriate treatment modalities for different types of diabetes in Down syndrome and how do they differ from canonical approaches?** For example, little is known about the efficacy of diverse dietary interventions in Down syndrome and how their efficacy may be modulated by other physiological and metabolic processes dysregulated in Down syndrome. The possibilities for interplays with other common comorbidities are many. For example, it is known that OSA disrupts leptin homeostasis in typical people (Harsch et al., 2003), often leading to dysregulation of appetite control and weight gain. Therefore, what is the interplay of OSA and diabetes in Down syndrome? Would management of sleep disorders contribute to the management of diabetes in this population? Likewise for thyroid dysfunction, which is also known to impact leptin circuitry and body weight control (Flier et al., 2000). A deeper understanding of metabolic dysregulation in Down syndrome, especially potential impacts on central carbon and energy metabolism is also likely to contribute to our understanding of diabetes management in Down syndrome.
  - e. **What are the mechanisms by which trisomy 21 increases the risk for different types of diabetes? Are there any specific genes on chromosome 21 and downstream signaling pathways that contribute to this comorbidity in Down syndrome?** As for other autoimmune conditions more common in Down syndrome, further investigation of the role of interferon hyperactivity is warranted. Type I interferon hyperactivity is a key trigger for T1D in typical people (Lombardi et al., 2018). The interplay between interferon hyperactivity and T cell dysregulation in T1D in Down syndrome should also be investigated, as dysregulation of CD8+ T cells and Tregs is associated with T1D development in typical people (Coppieters et al., 2012; Ihtola et al., 2018; Lawson et al., 2008; Roep and Peakman, 2011; Tsai et al., 2008). Also, variations in the gut microbiome have been associated with T1D development in the general population (Alkanani et al., 2015), which further emphasizes the importance of microbiome studies in Down syndrome. Therefore, additional animal and human research is necessary to elucidate the mechanistic basis for increased risk of diabetes in Down syndrome. Beyond interferon hyperactivity, which is likely driven by the triplication of four interferon receptor genes (IFNRs) encoded on chromosome 21, other triplicated genes could be involved in the development of T1D, such as AIRE and UBASH3A. AIRE (autoimmune regulator), which is also encoded on chromosome 21, is a known regulator of T cell maturation and elimination of self-reactive T cells in the developing thymus (Finnish-German, 1997). Given that mutations and SNPs in AIRE are consistently involved in development of autoimmune disorders (Finnish-German, 1997), the impact of AIRE triplication in the development of autoimmune disorders in Down syndrome warrants investigation. UBASH3A is another important regulator of T cell function encoded on chromosome 21 that has been linked to development of autoimmune disorders, including T1D (Ge et al., 2017).
- 3) **Obesity.** The majority of children and adults with Down syndrome are obese. What are the long-term effects on this population? Studies show that despite a diagnosis of T2D, lipids in patients with Down syndrome are rarely abnormal. What we could learn about obesity in patients with Down syndrome that could help them and possibly the typical population? In addition, the few studies on exercise interventions have resulted in poor outcomes. There should be a special emphasis on sex,

socioeconomic, cultural, race and ethnicity for this research. Anecdotally, clinicians are finding their pediatric patients with Down syndrome are gaining 15 to 17 pounds on average from March to June during the COVID-19 pandemic.

**4) Addressing Research Challenges & Opportunities for individuals with Down syndrome.**

What are the harms versus the benefits of screening asymptomatic children and adults with Down syndrome for diabetes? How can diabetes management be supported through technology to increase independence and self-management for people with Down syndrome? Are there additional educational opportunities around vitamin supplementation for families of people with Down syndrome regarding the lack of evidence-based results?

## VII. Skin, Muscles and Bones

Individuals with Down syndrome show an elevated risk of developing a range of musculoskeletal and ectodermal conditions, but the true incidence of these conditions across the lifespan remains to be defined. Furthermore, little is known about the mechanism by which the extra chromosome affects the onset and development of these conditions.

### 1) Skin

a. **What is the prevalence of the following skin conditions in people with Down syndrome across the lifespan? Are there differences by age, sex, race/ethnicity difference or geography?**

Acne  
Alopecia areata  
Athlete's foot  
Atopic dermatitis/eczema  
Boils/ Hidradenitis suppurativa/ Folliculitis  
Cellulitis  
Psoriasis  
Rosacea  
Seborrheic Dermatitis/Eczema  
Tinea Capitis  
Toenail Fungus  
Vitiligo  
Xerosis

b. **What are the risk factors for these skin conditions in people with Down syndrome?** Among the conditions mentioned above, many are autoimmune conditions (alopecia areata, atopic dermatitis, hidradenitis suppurativa, vitiligo, psoriasis), which merits an investigation of immune-related risk factors, both genetic (e.g. HLA alleles) and non-genetic (e.g. microbiome) in the onset and development of these conditions. Interestingly, celiac disease, which is more common in Down syndrome, often present with dermatological manifestations. Therefore, what are the dermatological manifestations of celiac disease in Down syndrome?

c. **What is the long-term impact of these skin conditions if left untreated?** Untreated skin conditions could greatly diminish the quality of life in affected individuals, including potential psychological and social interaction issues (e.g. alopecia, vitiligo). In the case of autoimmune skin conditions, their appearance could indicate the start of an 'autoimmune sequence' leading to high risk of other autoimmune or immune driven conditions. For example, in the general population, an 'atopic march' has been identified, whereas the appearance of atopic dermatitis signals the beginning of a sequence that could progress to IgE-mediated food allergy (FA), asthma, and allergic rhinitis (AR). Is there an atopic march in the population with Down syndrome? Although atopic dermatitis is more common in this population, the fact that they display depletion of circulating IgE (Sullivan et al., 2017) and decreased allergic sensitization (Eijvoogel et al., 2017) could indicate that atopic dermatitis has a different etiology and course in Down syndrome. Another example is psoriasis, which can often progress into psoriatic arthritis in the typical population. Is there a relationship between psoriasis and the appearance of the so called arthropathy of Down syndrome?

d. **What are the most appropriate diagnostic(s)/screening tool(s) for these skin conditions in people with Down syndrome?** Our experience is that skin conditions are usually underdiagnosed or mis-diagnosed in Down syndrome, and we believe that greater literacy is needed in this area, both for professionals and families. For example, our studies within the Crnic Institute's Human Trisome Project have revealed that ~25% of adults with Down syndrome have been diagnosed with one or more autoimmune skin conditions, but this knowledge is not vox populi.

- e. **What are the best treatment modalities for skin conditions in Down syndrome?** Many of the skin conditions more prevalent in Down syndrome lack effective standard of care. For autoimmune skin conditions, we believe that targeting the underlying autoinflammation may address many of these conditions at once. In this regard, we look forward to the results of the INCLUDE/NIAMS-funded clinical trial for a JAK inhibitor for adults with Down syndrome affected by autoimmune skin conditions. We believe that other common mechanisms could be underlying other skin conditions, such as potential dysregulation or keratin or collagen metabolism by genes on chromosome 21.
- f. **What are the mechanisms by which trisomy 21 increases the risk and/or severity of skin conditions? Are there any specific genes on chromosome or signaling pathways that contribute to this comorbidity in Down syndrome?** In the case of the autoimmune skin conditions mentioned above, once again we emphasize the importance of studies on the origins and consequences of autoimmunity in Down syndrome (see above chapter I. Immunity). For all skin conditions, more research is needed in animal models of Down syndrome. Do mice carrying triplication of regions syntenic to human chromosome 21 display any signs of skin disease, improper barrier function or other dermatological manifestations? Of note, these studies should probably include scenarios where mice are challenge with topical immune stimuli or commensal microbes.

## 2) Musculoskeletal

Although it is well recognized that individuals with Down syndrome are more likely to be affected by a number of musculoskeletal conditions, a definitive understanding of the epidemiology, natural history and underlying mechanisms of these conditions is lacking.

- a. **What is the prevalence of the following musculoskeletal conditions in people with Down syndrome across the lifespan? Are there any differences by age, sex, race/ethnicity or geography?**

Arthropathy  
 Hypotonia  
 Atlantoaxial instability  
 Cervical spine degeneration  
 Osteopenia  
 Osteoporosis  
 Fractures  
 Osteoarthritis  
 Scoliosis or spine curvature

More specifically, what is the co-occurrence of these conditions? Is there a pattern of musculoskeletal conditions that cluster in Down syndrome? Given the well-established sex-specific bias for some of these conditions in the typical population (e.g. osteoporosis), are there any sex differences in Down syndrome? Also, defining the occurrence of these conditions across different age groups will be key to develop customized screening strategies. For example, given that some of these conditions are associated with age in the typical population, and given that some aspects of Down syndrome could be associated with accelerated aging, do any of these conditions present earlier in life relative to the typical population?

- b. **What are the risk and protective factors for these conditions in people with Down syndrome?** Given the importance of metabolism on the homeostatic control of bone and muscle development and function, are there specific metabolic pathways dysregulated by trisomy 21 that could modulate the onset and severity of these conditions? For example, are there differences in calcium metabolism and deposition that could predispose to skeletal conditions? Are there differences in mitochondrial metabolism that could impact conditions of the muscle? If so, what is the impact of diet on these conditions?
- c. **What are the long-term impacts of these conditions in people with Down syndrome?** The importance of this question cannot be overstated. Chronic hypotonia from an early age could have

massive detrimental impacts, not only on developmental milestones that required proper muscle function (e.g. speech), but also on development of other comorbidities, such as obstructive sleep apnea or dysphagia, which in turn can predispose to yet other comorbidities. Therefore, a deeper understanding of the natural history of hypotonia and other conditions in this category is warranted.

- d. **What are the most appropriate diagnostic(s)/screening tool(s) for each of these conditions in people with Down syndrome?** This question is of utmost importance for the arthropathy of Down syndrome, a condition that we believe is vastly underdiagnosed in this population, and whose presentation and biomarkers seem to be different from those used to diagnose rheumatoid arthritis, juvenile idiopathic arthritis, and other inflammatory joint diseases (Foley et al., 2019).
- e. **What are the best treatment modalities for these conditions in Down syndrome?** Even for those conditions in this class where treatments have been developed in the typical population (osteoporosis), the question is still valid for the population with Down syndrome, as the pathological mechanisms may be different and not modulated by the same drug targets.
- f. **What are the mechanisms by which trisomy 21 increases the risk and/or severity of these conditions? Are there any specific genes on chromosome or signaling pathways that contribute to this class of comorbidity in Down syndrome?** As for many other conditions for which the etiology in Down syndrome remains to be elucidated, this question could be answered with a synergistic portfolio of research activities in Components 1 and 2 of the INCLUDE Project. Basic science approaches using iPSC-derived cell types of interest and studies in animal models are warranted. Cohort studies in Component 2 could not only provide definitive epidemiological data, but also identify endotype signatures associated with these comorbidities that could aid in the understanding of mechanisms of disease, diagnostics and therapeutics. A detailed study of these conditions in animal models is warranted, as many of these phenotypes may not be fully penetrant, appearing in only a fraction of animals.

### **3) Addressing Research Challenges & Opportunities for individuals with Down syndrome.**

What supports can be put in place to help adults with Down syndrome better manage skin conditions independently and which treatments are better suited for more self-management? Are these treatments as effective as other treatments?

What are the social impacts of skin conditions on people with Down syndrome's ability to find employment? What are the harms versus the benefits of limiting physical activity for asymptomatic people with Down syndrome as a way to prevent possible future musculoskeletal injury?

## VIII. Gut, Kidney, Liver and Bladder

We believe this is an area with many knowledge gaps, and one where the significant expansion in the life expectancy of individuals with Down syndrome may reveal previously unanticipated issues with these key organs. For example, the recent realization that children with Down syndrome are more prone to display Nonalcoholic fatty liver disease (NAFLD) (Valentini et al., 2017) opens up a clear research avenue to understand how liver dysfunction may contribute to many of the clinical hallmarks of Down syndrome across the lifespan.

### 1) **What is the prevalence of the following conditions in people with Down syndrome across the lifespan? Are there any differences by age, sex, race/ethnicity, or geography?**

Gastroesophageal reflux (GERD, acid reflux)

Chronic constipation

Chronic diarrhea

Dysphagia

Celiac disease

Hirschsprung disease

Pyloric stenosis

Irritable bowel syndrome

Inflammatory bowel disease (IBD)

Peptic ulcers

Gallstones

Hemorrhoids

Diverticulitis

Duodenal stenosis or web

Anal stenosis or atresia

Esophageal atresia

Dysuria

Voiding dysfunction

Kidney disease

Cystic dysplastic kidney

Hydronephrosis

Hydroureter

Posterior or anterior urethral valves

Renal agenesis

Vesicoureteral

Nonalcoholic fatty liver disease (NAFLD)

#### a. **What are the risk and protective factors for these conditions in people with Down syndrome?**

We believe this is one of the areas where studies of the impact of diet and the microbiome could pay the biggest dividends. As explained above for celiac disease, identification of genetic and non-genetic risk factors could aid in earlier diagnosis, even perhaps prenatal diagnosis, such as in the case of Hirschsprung's disease. Beyond celiac disease, many of the conditions in this category have been found to be modulated by immune related factors, alone or in interplay with the gut microbiome, in the typical population, such as GERD, diarrhea, constipation, and IBD.

#### b. **What is the long-term impact of these conditions in people with Down syndrome?**

This question is of utmost importance for those conditions in the list that could induce chronic, lifelong dysregulation in nutrient absorption and metabolism (e.g. celiac disease, NAFLD). Even strong neurological impacts could be anticipated for some of these conditions, especially those that could dysregulate the so called gut-brain axis, leading in turn to higher risk of conditions such as autism, depression and anxiety disorders (Mayer et al., 2014; O'Mahony et al., 2015).

- c. **What are the most appropriate diagnostic(s)/screening tool(s) for each of these conditions in people with Down syndrome?** This question is of particular relevance for conditions in this list for which definitive biomarkers are not available, and which usually involve time and resource consuming imaging-based diagnostics (e.g. NAFLD, various urogenital problems).
- d. **What are the best treatment modalities for these conditions in people with Down syndrome?** Beyond pharmacological approaches, we believe this is one of the areas where studies of diet-based interventions could produce the most benefits. Definitive studies of the impact of gluten-free diet in Down syndrome are long overdue, but many other conditions on this list could be modulated by diet-based interventions, such as IBD, GERD and NFALD.
- e. **What are the mechanisms by which trisomy 21 increases the risk and/or severity of this class of comorbidities? Are there any specific genes on chromosome or signaling pathways that contribute to this comorbidity in Down syndrome?** The conditions in this class are many and their underlying pathophysiology could be very diverse. However, we believe that emphasis should be placed on defining the impact of core dysregulated biological processes and pathways that could be involved in many of these conditions at once. One obvious candidate is immune dysregulation. To what degree are the conditions above modulated by the clear autoinflammation observed in Down syndrome (e.g. celiac, IBD, NAFLD)? Another key area is epithelial biology. How does trisomy 21 impact the development and function of different epithelial tissues involved in the conditions in this class? As for other classes of comorbidities, this question deserves greater investment in studies of both iPSC-derived cell *types* and mouse models.
- f. **Dysphagia.** Given the large number of children with Down syndrome who suffer from dysphagia and the gaps in our knowledge, there is a pressing need for a longitudinal multi-site cohort study, where infants with Down syndrome would be followed from birth until age 5. The overarching question would be whether there are profiles of health or development that can help us 1) predict whether the child would have dysphagia and 2) what their dysphagia outcomes might be (for example continuation versus resolution of the problem). Developmental and medical outcomes via non-invasive means at regular intervals in areas such as feeding/swallowing, motor skills, cognitive development, speech/language development, medical comorbidities (with a focus on pulmonary outcomes) and hospitalizations would be collected. It is also important to assess what treatments are successful and identify biomarkers *associated* for chronic issues.

## 2) **Addressing Research Challenges & Opportunities for individuals with Down syndrome.**

Is a gluten-free diet financially feasible for the average family with a child with Down syndrome? What is the annual cost of a gluten free diet and how can we make the financial burden less for families pursuing this option?



## GLOBAL DOWN SYNDROME FOUNDATION DOWN SYNDROME RESEARCH COMMUNITY SURVEY

After we drafted our final NIH INCLUDE/Down syndrome research RFI, GLOBAL organized a survey that was sent to our constituents highlighting the specific areas of importance from our RFI. Respondents were given 2 ½ days to fill in the simple survey (see Survey Outline on the following page).

1,082 constituents from 45 states, 5 Canadian territories, and 12 countries responded to our survey. 97% of respondents ranked research as “extremely important” (82%) or “very important” (15%).

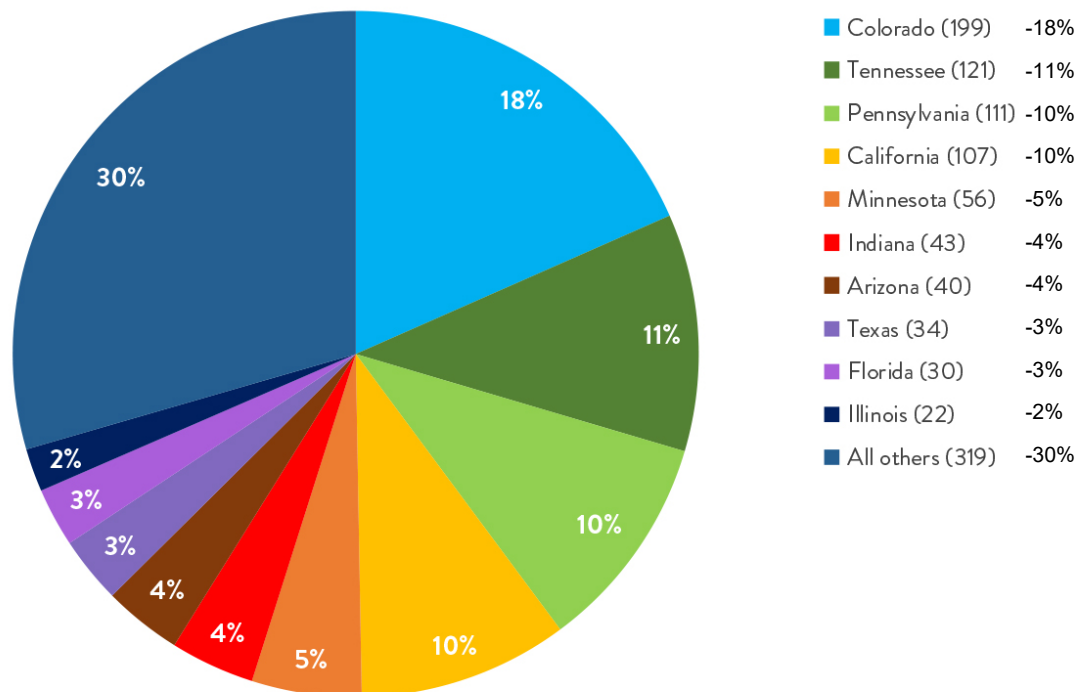
Of the 1,082 respondents, 12 identified as a self-advocate with Down syndrome, 852 (or 79%) identified as parents of an individual with Down syndrome, 101 as “other relative,” 35 as medical professionals, and 73 as “other.”

Nearly 400 respondents checked all eleven areas of research as being directly important to them. Nearly everyone (96%) checked “Development, Brain & Mind” research as important, 82% checked “Immune System Dysregulation” research, and 75% checked “Ears, Nose, & Throat” research. Over 70% chose more than half the research areas.

Respondents represented 45 of 50 states and included territories in Canada and 12 countries. Colorado, Tennessee, Pennsylvania, and California had over 100 respondents each.

### GLOBAL Down Syndrome Research Survey Responses

*by U.S. State (July 17, 2020)*



1,082 people in 45 out of 50 U.S. states, 5 Canadian territories, and 12 countries responded to the survey. This chart highlights the top ten states, which represent 70% (763) of the total responses. The other 30% include people in the remaining 35 states, plus international and those who chose not to disclose their location.

## **SURVEY OUTLINE**

GLOBAL's 5-Min Survey – Make Our Voices Count NOW!

1. Name & Contact Information
2. Relationship to Down syndrome
3. How important is Down syndrome research to you (five-point scale)
4. "GLOBAL and the Crnic Institute plan to highlight the following important research areas to inform the NIH next seven-year plan that should benefit people with Down syndrome. Please check all the areas you believe are important. (You can check more than one/all of them).
  - Development, Brain & Mind Research (including Alzheimer's disease, dementia/memory loss, speech/language delays, fine/gross motor delays, stroke, moyamoya syndrome, autism, ADD/ADHD, depression, OCD and more)
  - Immune System Dysregulation Research (includes autoimmune disorders such as celiac disease, thyroid disease, alopecia areata, eczema, Hashimoto's disease, inflammation, infections leading to croup/pneumonia/respiratory issues, and more)
  - Heart, Lung & Blood Research (includes cardiovascular disease, pulmonary hypertension, lung disease, leukemias and more)
  - Endocrine System Research (includes thyroid dysfunction, Type 1 and Type 2 diabetes, vitamin/mineral deficiencies and more)
  - Gut, Kidney and Bladder Research (includes reflux, chronic constipation, diarrhea, swallowing issues, ulcers, celiac disease, kidney disease, and more)
  - Skin, Muscles & Bone Research (includes alopecia areata, vitiligo, boils, atlantoaxial instability, hypotonia, osteoporosis and more)
  - Ear, Nose & Throat Research (includes obstructive sleep apnea, hearing loss, laryngomalacia and more)
  - Eyes & Vision Research (includes astigmatism, cataracts, glaucoma, myopia and more)
  - Research for Medical Care Guidelines for Adults with Down Syndrome
  - Creation and Funding of Medical Care Centers of Excellence for Down Syndrome across the United States
  - Research that reveals health outcome differences between genders, age, ethnicity and race, geography, and types of Down syndrome (including Mosaicism)
5. Please list any other areas of research you believe are important and why (open ended)

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