



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.