(the topic of a workshop in September 2019)

3. Include individuals with Down syndrome in existing and future clinical trials (the focus of the current workshop)

Thanks to congressional funding for research on Down syndrome, NIH funding has increased dramatically in recent years, from $24.3 million in 2016 to $86 million in 2019. Much of this increase was due to the

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Children with Down syndrome and leukemia respond well to AML therapy. However, their risk of toxicity might lead to physician bias against enrolling patients with Down syndrome and leukemia into clinical trials or to offer these patients other therapies. Guidelines for supportive care for patients with

Communication and Language Intervention

Ann P. Kaiser, Ph.D., Vanderbilt University

Language development and speech development are typically delayed in children with Down syndrome, resulting in challenges in productive syntax, comprehension of complex syntax, inferential language, and conversational pragmatics. However, these children have strengths in receptive vocabulary, social engagement, affect expression, and visuospatial skills. Almost all children with Down syndrome could benefit from early communication interventions and continuous support for language development.

Only a few randomized controlled treatment trials have included children with Down syndrome. Furthermore, the treatments studied were brief and targeted specific skills, and the studies did not measure the impact on long-term development. Children with Down syndrome do make gains with interventions for speech and language deficits. Phenotype-specific treatments might be more effective than standard treatments in these children.

Lori Leibold, Ph.D., Boys Town National Research Hospital

More than half of people with Down syndrome have hearing loss. In children with Down syndrome, chronic otitis media can lead to permanent hearing loss, which can result in less cumulative language exposure, language delays, difficulty hearing speech in noise, and reduced spatial hearing abilities. Other barriers to understanding speech in noisy environments for this population include impairments in executive functioning, weakness in receptive and expressive syntax, and weakness in verbal working memory.

Dr. Leibold is using a supplement to an R01 grant funded by the INCLUDE project to characterize speech-in-speech recognition in 60 children with Down syndrome, identify characteristics that affect speech-in-speech recognition, and identify factors that could improve speech-in-speech recognition in challenging environments.

Krista Wilkinson, Ph.D., Pennsylvania State University

Augmentative and alternative communication (AAC) is a set of tools and interventions that support communication in individuals whose speech does not meet their receptive or

collected from people with Down syndrome should give prominent credit to these people for their contributions. Members of the Down syndrome community can make a huge difference for themselves and the

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Michelle Palumbo, M.D., Massachusetts General Hospital

Regression in Down syndrome is typically characterized by a decline in functioning that often entails significant deterioration in or loss of skills of daily living, language, behavior, and motor function. In many cases, the onset of symptoms follows psychosocial precipitants, such as life events or medical problems.

Catatonia is defined as three of more of a long list of symptoms, including stupor, catalepsy, and mutism. First-line treatment typically consists of high doses of benzodiazepines, although electroconvulsive therapy can also be effective in patients who cannot tolerate lorazepam.

The available scientific literature consists of case reports, case series, and case-control studies that show variable regression symptoms, courses, and treatments. No treatment studies have been conducted in adults with Down syndrome.

Session 3 Q&A

Q:

objective is to evaluate the effects of Down syndrome and sleep disturbance measured with actigraphy on prefrontal neuro-efficiency during completion of a psychometrically sound executive function test battery.

tissues and lenses from Alzheimer's disease mouse models that recapitulate Down syndrome. The hope is to ultimately use the findings to treat cataracts with eye drops.

Clinical Trials Development (R61/R33) Grants

Daniel Combs, M.D., University of Arizona

In the R61 phase, this study will evaluate the short-term efficacy of high and low doses of atomoxetine and oxybutynin treatment for 4 weeks for OSA and the treatment's effect on health-related quality of life in 61 children with Down syndrome and OSA. The investigators hope to open this study for recruitment in June 2020. In the R33 phase, a 6-month, open-label clinical trial will evaluate the long-term efficacy of this treatment for OSA and its effects on both health-related quality of life and neurocognition.

Anna Esbensen, Ph.D., University of Cincinnati

The proportion of children with Down syndrome and ADHD who are treated with stimulant medication (the most effective ADHD treatment) is low. The reasons might include uncertainty about how to accurately diagnose ADHD in this population and the lack of clinical trials examining the safety and efficacy of stimulants in this population. Dr. Esbensen will conduct a triple-blinded clinical trial of methylphenidate in 30 children aged 6–17 years who have Down syndrome and ADHD to determine the optimal dose for the larger R33 clinical trial. The R61 trial will assess the short- and long-term safety and efficacy of methylphenidate treatment for remediating cognitive, behavioral, and functional impairments in children with Down syndrome and ADHD.

Joaquin Espinosa, Ph.D., University of Colorado, Denver

This Phase II, single-arm, open-label trial will evaluate treatment with tofacitinib, a JAK inhibitor, for 16 weeks, with 2-week follow-up, in adults aged 18–60 years with Down syndrome and an active autoimmune skin condition (alopecia areata, psoriasis, vitiligo, hidradenitis suppurativa, or atopic dermatitis). The trial will determine the treatment's safety profile and impact on immune dysregulation, immune skin conditions, cognition, and quality of life.

v

Michael S. Rafii, M.D., Ph.D., University of Southern California

This study is forming a trial-ready cohort of 120 adults (aged 35–55 years) with Down syndrome who do not have dementia. Participants will undergo longitudinal cognitive and clinical assessment, genetic and biomarker testing, imaging, and biospecimen collection. The study will analyze the relationships between cognitive measures and biomarkers of Alzheimer's disease to identify endpoints that best reflect progression of this disease for clinical trials in

operant learning, contingency management, motivational enhancement, and engagement strategies involving caregivers. In the R33 phase, the investigators will assess the effects of PAP adherence on quality of life, neurobehavioral outcomes, and health care utilization.

Session 5: Clinical Trial Infrastructure

Moderator: Steve Abman, M.D., University of Colorado Denver

Down Syndrome Patient Registries

Steve Abman, M.D., University of Colorado Denver

The Pediatric Pulmonary Hypertension Network (PPHNet) is a multidisciplinary network of clinical pediatric pulmonary hypertension centers that has created a longitudinal database to determine the natural history of diseases, comorbidities, and benchmark approaches. Dr. Abman has analyzed data in the registry on 157 patients with Down syndrome. Of these children, 69% had pulmonary arterial hypertension and 21% had primary lung disease. This analysis offers an example of the lessons that can be learned from registries.

DS-Connect®: The Down Syndrome Registry

Sujata Bardhan, Ph.D., NICHD

NIH leads the Down Syndrome Consortium, which is made up of several NIH Institutes and Centers, professional societies, foundations, and advocacy organizations. The consortium's first activity was to create DS-Connect, the Down syndrome registry, to collect demographic and health information from self-advocates, family members, and providers. The resulting cohort can be used for natural history and biomarker studies.

Families can use the registry to store all of the patient's medical history in a single place. Families, researchers, providers, and others can view all of the survey questions and deidentified responses. The site also offers a list of health care providers who care for adults and children with Down syndrome as well as a set of health care guidelines. A new portal will provide information from ClinicalTrials.gov about NIH-funded clinical trials that are recruiting individuals with Down syndrome, and researchers can submit applications to use DS-Connect to recruit

Pediatric Heart Network (PHN)

Julie Miller,

New York State subsequently implemented the Willowbrook Permanent Injunction, which has been widely interpreted to apply to any New York State resident with intellectual or developmental disabilities. The standard only permits behavior modification, research, or hazardous or experimental treatment after approval from the resident, a caregiver, or a three-person special committee. The standard prohibits physically intrusive, chemical, or biomedical research or experimentation without a federally approved assurance of compliance with regulations for the protection of human subjects.

Until 2012, individuals with intellectual or developmental disabilities in New Jersey could not participate in any research without a court-appointed guardian ad litem. Currently, the

Dr. Handen: The types of information shared are determined by local institutional review board requirements. The University of Pittsburgh does not share positron emission tomography scan results because these scans are considered experimental and their meaning is not clear. However, investigators do inform participants and their primary care providers of significant magnetic resonance imaging (MRI) findings.
Dr. Krinsky-McHale: We also share MRI results but not neuropsychology findings unless participants or families ask for that information.

Reports from Breakout Sessions

The presentations in this session summarized two recent online breakout sessions.

Pediatric Issues and Considerations: Gaps and Opportunities in Clinical Trials in Children and Adolescents with Down syndrome

Steve Abman, M.D., University of Colorado Denver

Breakout session participants discussed the rationale for developing a multicenter clinical trial consortium for studies of children with Down syndrome. Such a consortium could address the limited understanding of disease mechanisms for many aspects of Down syndrome, the heterogeneity of comorbidities, the lack of multidisciplinary care beyond major centers, and the small number of patients at each center to provide the samples needed for multicenter trials.

Most current management strategies and preliminary data come from case reports or adult data, and clinical guidelines and age-relevant and disease-specific endpoints to assess clinical course and treatment response are lacking. Preliminary disease data on the disease mechanisms being targeted are needed. The network should bring together basic scientists, families, foundations, and companies.

A registry is needed to support better study designs and establish precise phenotypes and endotypes, natural history, and long-term outcomes. The database would characterize disease prevalence and support power analyses for clinical trials, and its data should be linked to a biorepository. In addition, training and experience conducting clinical research will be critical to help the next generation of clinical scientists develop strong clinical trial expertise in Down syndrome.

Adult Issues and Considerations: Gaps and Opportunities in Clinical Trials in Adults with Down syndrome

Annie Cohen, Ph.D., University of Pittsburgh, and Michael S. Rafii, M.D., Ph.D., University of Southern California

The topic that drew the most attention from this breakout group was recruitment. Recruitment challenges include the following:

- The legally authorized representatives of adults with Down syndrome often change, for example, from an aging parent to a sibling.
- Adults living in group homes might lack a legally authorized representative or informant who can consistently provide information on the study participant.
- Diverse populations sometimes do not have trust in research.

Recruitment opportunities include:

- Working with self-advocates to engage participants throughout the research process
- Using simple and accurate information that can be understood by individuals with Down syndrome and their families
- Leveraging the Down syndrome community's interest in Alzheimer's disease to recruit members of this community into Alzheimer's disease clinical trials

Leveraging adult Down syndrome clinics, which are often trusted sources of information

Logistical challenges include differences in state regulations and policies regarding informed consent and the need to minimize the number of clinic visits and burden of participating in clinical trials. The best methods to assess target engagement in adults with Down syndrome need to be identified, and whether the same measures can be used in adults with Down syndrome as in trials of typical adults must be determined. Measures that can detect cognitive decline at an early stage, are sensitive to change, and can be used in individuals with more severe intellectual disability are needed. Safety-related challenges include the need for experienced sites to promptly identify and manage adverse events in studies in which participant reporting of these events might not be straightforward. In addition, clarity is needed on a regulatory pathway for new drugs for this population.

Breakout Session Reports Q&A