MEETING SUMMARY

Methodologic Challenges in Intellectual and Developmental Disabilities Research Meeting Summary

March 15, 2021

Meeting Details and Materials

Overview

On March 15, 2021, PCORI's Methodology Committee held a public workshop to discuss methodologic issues encountered in research evaluating the effects of interventions for children and adults with intellectual and developmental disabilities (IDD). IDD is a new research priority for PCORI, which is responding to a congressional mandate in the legislation that reauthorized PCORI in 2019 for another 10 years. The purpose of this workshop was to offer an overview of IDD methodology issues.

The first session of the workshop addressed a broad range of measurement issues. Maureen Durkin, PhD, DrPH, University of Wisconsin, called for the use of social contract theory, which aims for the greatest benefit for the least advantaged members of a society, to study IDD. Dr. Durkin also described IDD definitions, types of outcomes (beyond biomedical ones) that IDD studies should measure, and categorization schemes for interventions. Tracy M. King, MD, MPH, of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), commented that more work is needed to identify which outcomes are most meaningful to persons with IDD and how best to measure these meaningful outcomes. She also discussed that IDD studies need to measure the many levels of individual exposures, interpersonal factors, and societal influences that affect outcomes in people with IDD, and emphasized the need to measure both positive and negative outcomes.

The second session focused on observational and interventional study designs. David Mandell, ScD, University of Pennsylvania, called for merging public and private healthcare claims data with special education data from the Department of Education. Combining these data and linking them to registry data could help answer important questions about children with IDD. Luther Kalb, PhD, MHS, Kennedy Krieger Institute (KKI), described the learning health system (LHS) model and its use to analyze the data collected during the delivery of services to children with IDD. Such a system can track changes over time, collect information from several informants, and facilitate recruitment for traditional efficacy studies.

The topic of the third session was heterogeneity. Sarabeth Broder-Fingert, MD, MPH, Boston University and Boston Medical Center, described the many differences among people with autism spectrum disorder (ASD) and their families. The experiences and characteristics of families that deliver interventions to children with IDD can affect how they implement these interventions and thus the outcomes in their children. Tawara Goode, MA, Georgetown University, called for greater recognition of the diversity of people with IDD in research by, for example, not treating all persons with IDD as a homogeneous group and using approaches that produce nuanced portraits of these individuals.

Introduction

Steven Goodman, MD, MHS, PhD, Associate Dean for Clinical and Translational Research, Professor of Epidemiology and Population Health, Professor of Medicine, Stanford University; Chair, PCORI Methodology Committee
Kara Ayers, PhD, Assistant Professor of Pediatrics, University of Cincinnati; Member, PCORI Board of Governors

The legislation that authorized PCORI mandated that the institute form a Methodology Committee to ensure that the science PCORI funds is as strong as possible. The legislation also required this committee to create methodology standards, which provide requirements for the conduct of scientifically valid patient-centered outcomes research. Other Methodology Committee activities include the following:

- Producing the PCORI Methodology Report (most recently revised in January 2019), which explains the context and rationale for the standards.
- Organizing workshops focused on methodology to inform the committee about issues in the field and to educate PCORI staff.
- Counseling PCORI on its methodology research portfolio, which is designed to improve the methods used in PCORI-funded research.

When Congress reauthorized PCORI in 2019 for another 10 years, the statute added IDD as a new research priority. This workshop would offer a big-picture overview of IDD methodology issues. Studies of people with IDD have a wide range of methodological challenges, including scientific paternalism or ableism (the temptation for researchers to speak for, rather than with, people with IDD).

The Methodology Committee might organize future workshops of this type on more narrowly defined IDD topics, develop methodology standards to address the issues discussed at this workshop, and identify topics for future PCORI-funded methodology research.

Topic 1: Measurement Issues

Moderator: Cynthia Girman, DrPH, President, CERobs Consulting, LLC; Member, PCORI Methodology Committee

Definition and Measurement Issues in IDD Research

Maureen Durkin, PhD, DrPH, Evan and Marion Helfaer Professor of Public Health and Chair, Department of Population Health Sciences, University of Wisconsin School of Medicine and Public Health

Dr. Durkin defines IDD as limitations in functioning that result from disorders or injuries that affect the developing nervous system. The manifestations of IDD, which begin early in life, are delays in reaching developmental milestones (e.g., walking, talking) or functional limitations in cognition, motor performance, vision, hearing, communication, speech, or behavior. Approximately 18 percent of US children have IDD. The heterogeneous etiologies and phenotypes of IDD include intellectual disability; cerebral palsy; epilepsy; ASD; attention deficit hyperactivity disorder (ADHD); and speech, language, vision, and hearing disabilities. Many children with IDD have more than one disability; for example, many children have IDD, cerebral palsy, and epilepsy or both ASD and IDD.

Two intellectual traditions have shaped population health policies and outcome measures relevant to IDD research. The first tradition, utilitarianism, aims for the greatest good for the greatest number of people. The focus of utilitarianism in this context is on allocating limited resources in a way that maximizes happiness and well-being for the population. According to this view, a society with high levels of inequality in which a minority, including people with disabilities, is suffering might be acceptable if this society maximizes benefits for the entire population. Outcomes of interest for this approach are disability- and quality-adjusted life years. In contrast, social contract theory aims for the greatest benefit for the least advantaged. The rationale is that under a veil of ignorance, people would choose policies that benefit those with disabilities and complex needs. According to this theory, a just society is one that rational, self-interested

individuals would choose to gain protection in exchange for some loss of freedom. Outcomes of interest for social contract theory are health equity; absence of disparities; and needed levels of functioning, participation, and supports.

Having a disability does not mean that a person has poor health, but people with disabilities are more likely to have poor health than people without disabilities. Health inequalities or disparities are differences in the health status of groups that result from injustices (e.g., inequitable access to care or resources), risk factors, or stigma. According to some experts, people with IDD should be considered a health disparities population, and they can experience more than one type of health disparity. For example, the life expectancy of individuals with Down syndrome, at approximately 50 years, is much lower than that of the general population. However, the life expectancy of Black individuals with Down syndrome is half that of their White peers. Furthermore, the complex medical needs and illnesses of people with many IDD conditions are not necessarily attributable to injustices. Identifying health differences that might be preventable is challenging for IDD research.

International consensus has emerged on the International Classification of Functioning, Disability and Health (ICF), developed by the World Health Organization. This biopsychosocial model aligns well with social contract theory and a capabilities approach to disabilities. According to the ICF model, disabilities encompass limitations in bodily functions and structures, activities of daily living, and participation (e.g., in school or work). The relationship between impairments in bodily functions and structures and outcomes in the other domains is not necessarily linear, partly because of the modifying effects of social, physical, cultural, environmental, and personal behaviors.

Much clinical research in IDD outcomes focuses more on biomedical outcomes (i.e., body structures and functions in the ICF model) and not enough on real-life outcomes over the life course that matter most to those living with IDD and their families. Biomedical research is critical because advances in early treatments could help prevent IDD and improve outcomes. However, to improve outcomes for people with IDD, PCORI research needs to address all of the domains and determinants of IDD outcomes.

The ICF model includes different kinds of measures and outcomes as well as environmental factors and personal behaviors that can modify these outcomes. Not every study can include the broad array of outcome measures and address all determinants of IDD, but patient-centered IDD research should incorporate some aspects of these factors.

The World Health Organization is developing the International Classification of Health Interventions, currently available in beta format, to categorize health interventions into target domains of body systems and functions, activities and participation, environment, and health-related behaviors. This system can be used to classify IDD interventions tested in PCORI-funded research and monitor how well they cover the scope of interventions needed to improve outcomes for people with IDD.

Many new technologies could be used to monitor outcomes. For example, electronic health record (EHR) systems now include modules for social determinants of health and much more. A plethora of wearable devices can generate real-time data to monitor the full range of outcomes important in IDD research. Use of artificial intelligence is also promising for IDD research. However, these technologies must be used to advance IDD research without compromising participant privacy or exacerbating health disparities.

Methodological Issues in Studies of IDD

Tracy M. King, MD, MPH, Medical Officer, Intellectual and Developmental Disabilities Branch, NICHD

Dr. King discussed four key questions:

Key Question 1: What needs to be measured?

Risks, exposures, interventions, and outcomes all need to be measured in ways that are valid and reliable among persons with IDD. The IDD field often focuses on individual-level exposures (e.g., genes, behaviors, medical

comorbidities) and interpersonal factors (especially parent–child relationships). But many other levels of exposures influence individual outcomes, including organizational, community, and societal factors. Forces that drive health and health disparities at these levels can exacerbate or confound the effects of interventions but have been neglected in IDD research. These exposures also evolve over time, and better ways are needed to measure them at multiple levels and across time.

Intervention fidelity is also a critical parameter to measure but is often overlooked in IDD research. Factors that can reflect whether an intervention is delivered with fidelity include the level of exposure, adherence, engagement, and quality of intervention delivery.

Key Question 2: How do we measure it?

Many standard neuropsychological tests suffer from floor effects (where everyone whose results are below a certain threshold is assigned the same low score), diminishing the instruments' utility for individuals with IDD. Studies using certain instruments and approaches systematically exclude certain groups; for example, most studies of magnetic resonance imaging (MRI) end up excluding people who are very sensitive to loud noise or are unable to stay still or follow verbal instructions. These exclusions have major implications for the generalizability of study results to IDD populations.

Studies of people with IDD often use proxy reports, not first-person reports, and more research is needed to determine whether such proxy reports accurately capture the perspectives of persons with IDD. Some research has found, for example, that people with IDD rate their quality of life more highly than the parents or caregivers who provide proxy ratings.

The thresholds used to decide who is given the opportunity to report for themselves are often arbitrary. Many people with IDD are probably capable of providing self-reports. There is also a great deal of room to push current practices on who can provide their own consent to participate in research.

Many outcomes are compared with normative samples, but the definition of "normal" can introduce substantial and often unrecognized biases. For example, the definition of an abnormal finding in an MRI study is often based on the extent to which it deviates from a defined reference value, but the reference values used in different studies may vary widely. Furthermore, variations in "normal" values from different sources may be correlated with factors such as race or ethnicity. Therefore, the choice of reference values may introduce systematic bias into determining which results in a study are considered in or out of the normal range. This issue applies to many measures used in IDD research.

Personal preferences or cultural differences might affect the values placed on outcomes. For example, the value placed on spoken or sign language varies among individuals with hearing impairment, and these differences could affect studies that use spoken language as a primary outcome measure. A participant's condition or level of symptom control can also affect how that individual reports about certain outcomes. Some metabolic conditions, for example, can affect attention or memory much more than cognition during acute exacerbations, but these metabolic exacerbations can also affect the person's awareness of their own symptoms. These factors have implications for the tools, perspectives, and designs used in studies.

Key Question 3: How *well* do we measure outcomes?

Much more needs to be understood about the accuracy and precision of many measures in individuals of different ages, developmental levels, cultures, and communities. Some measures used in IDD populations have not been validated in these populations, and the heterogeneity of these populations might affect the accuracy and precision of certain measures. Cultural and community considerations are also important to consider, because the cultural features of a measure may, for example, impact its performance among specific groups.

Some technologies could be used to address certain measurement challenges, but they could also introduce new ones. For example, it needs to be determined whether mobile technologies have the same performance in populations with and without IDD. Artificial intelligence algorithms are increasingly being used for research in a broad range of settings, but these algorithms are trained on datasets that might not include people with IDD. Use of these technologies might therefore incorrectly flag results for people with IDD as outside of the normal range.

Key Question 4: Does it matter?

It has been challenging to define and measure which outcomes are most meaningful to people with IDD. Researchers must balance the ease of measurement with how meaningful the outcome being measured is to the research participant, because meaningful outcomes are often not easily captured by instruments that are easy to use.

Recommendations for many clinical interventions are based on their ability to reduce morbidity and mortality rates, which are negative outcomes. However, many interventions for people with IDD are designed to improve positive outcomes. These benefits can take many years to accrue, so studies need innovative designs. Furthermore, positive outcomes (e.g., improved well-being) have not been well defined or operationalized, especially in people with IDD.

Discussants

Marc J. Tassé, PhD, Director, Nisonger Center; Professor, Departments of Psychology and Psychiatry, Ohio State University

Ruth Luckasson, JD, Distinguished Professor, Chair, Department of Special Education, University of New Mexico

Dr. Tassé noted the importance of "caseness" and the need for IDD researchers to make clear whether they are studying people with intellectual disability, developmental disabilities, or both. Researchers also need to specify the definitions or diagnostic criteria they are using to characterize their sample and the criteria they use should be widely accepted by the professional community.

The American Association on Intellectual and Developmental Disabilities and the American Psychiatric Association (in the *Diagnostic and Statistical Manual of Mental Disorders*) define "intellectual disability" as significant limitations in intellectual functioning and adaptive behavior (conceptual, social, and practical skills) that originate during the developmental period (i.e., before age 22). The Developmental Disabilities Assistance and Bill of Rights Act (DD Act) uses a function-based (not categorical) definition of developmental disabilities as chronic, lifelong limitations in at least three of seven life areas that are similar to adaptive skills. The categorical definition given by Dr. Durkin is often used by the Centers for Disease Control and Prevention (CDC) and includes disorders or conditions (e.g., intellectual disability, ASD, cerebral palsy, ADHD, learning disability, epilepsy, visual impairment, hearing loss) that originate during development but are not necessarily associated with significant limitations in several life areas. The prevalence of these conditions as defined by CDC is approximately 16 percent to 18 percent in US children, but the prevalence based on the DD Act definition is closer to 2 percent or 3 percent.

PCORI should encourage use of patient-reported outcomes in research involving people with IDD, and these measures should be developed with people who have these disabilities. Neurophysiological and behavioral measures should focus not only on caregiver-reported outcomes but also on self-reported outcomes. Furthermore, people with IDD and their families should be involved in developing research ideas, designs, methods, analyses, and conclusions.

Professor Luckasson agreed that research would be stronger if researchers clarified their definitions and provided references to them. Researchers also need to indicate the basis of their subgrouping or classification system, which can consist of many factors (e.g., IQ, adaptive behavior, functioning, intensity of need for supports). In addition, assumptions about IDD should be specified, because they vary according to the conceptual framework used. Researchers should report any supports or accommodations used by people with IDD to provide their self-reports and which participants received them. More clarity is also needed on the assessments used to establish caseness, including the method used,

when it was used, and the qualifications of the person who conducted the assessment. Research results should be disseminated in ways that ensure that people with IDD understand what is being said about them and what has been learned from them.

Research could integrate several conceptual frameworks to study people with IDD, such as biomedical, psychoeducational, sociocultural, and justice frameworks, to yield a more complete picture of the lives of people with IDD, what they want, and what they need to reach their goals.

Discussion

Dr. Girman asked whether deficits vary by IDD etiology and whether measures need to be specific to etiologies. Dr. Durkin replied that many interventions do not target a particular diagnostic category or etiology and are instead tested in people with similar functional limitations. Etiology can help researchers identify effective variations, but it is not sufficient on its own.

A participant commented on the potential tension between individualized intervention fidelity and population heterogeneity. Dr. King said that the balance between heterogeneity and generalizability is a prime area of opportunity for PCORI research.

Another question was whether the National Core Indicators®, which use a set of life domains and associated indicators, are positive outcomes. Dr. Durkin said that these indicators capture contextual factors that influence positive outcomes, and more such measures are needed. Dr. Tassé added that the National Core Indicators require an interview with the person with IDD and a caregiver; obtaining two perspectives on outcomes is valuable. The indicators include both positive outcomes (e.g., quality of life) and other issues that are important to people with IDD.

A participant noted that altruism often motivates people to participate in research. However, people with IDD often drop out of a study when the intervention does not suit their preferences, and intention-to-treat approaches are probably not sufficient. Dr. Durkin questioned whether dropping out is more common among people with IDD than people without IDD.

A participant asked whether a unifying conceptual framework is better than measuring outcomes in different ways using different frameworks and then determining whether the outcomes align. Dr. Durkin and Dr. King favored the use of more frameworks. Dr. King added that each discipline brings its own frameworks and perspectives to IDD research, and aligning outcomes or themes can be powerful.

A participant noted that an emerging theme in the literature is the importance of attitudes of researchers, healthcare professionals, and society. Bias can affect topic selection, tools, and expectations in studies of people with IDD. When asked how to approach this concern, Dr. Tassé said that in participatory action research, people with lived experience help inform researchers about the research questions, study design, and measurement approaches.

Dr. Durkin explained that the language in PCORI's reauthorization does not clearly define IDD, and this term has been used in many ways in the literature.

Dr. Girman asked whether any valid, reliable, and responsive measures of outcomes that are important to people with IDD are available. Dr. Durkin replied that many measures have been validated in IDD populations, and researchers are constantly developing new ones. Dr. King said that some instruments have been validated, but only for small subsets of people with IDD, such as for individuals with a given diagnosis. Whether these measures are appropriate for a broader range of people with IDD is not known.

A participant asked how to engage people with IDD in research. Professor Luckasson replied that people with IDD need to be included in every aspect of research, including identifying research questions, determining caseness, and choosing

interventions to study and outcomes to measure. Dr. Tassé added that ongoing relationships with people with IDD are necessary to engage them in research. Simply bringing them in for a study is not enough; they need to be true partners. Dr. Girman noted the challenge of ensuring that people with IDD feel that they are part of the research and that they understand team discussions. Dr. King emphasized the importance of including people with IDD who are diverse (e.g., have different levels of cognitive functioning, are of different races and ethnicities, live in rural and urban communities, have different socioeconomic statuses).

The final comment in this session was a suggestion for PCORI to fund research on public policies that might benefit people with IDD. Dr. King noted that PCORI can fill the need for participant-initiated research that might not be suitable for National Institutes of Health (NIH) funding.

Topic 2: Issues in Observational and Interventional Designs

Moderator: Brian Mittman, PhD, Research Scientist, Division of Health Services Research and Implementation Science, Kaiser Permanente Department of Research and Evaluation; Member, PCORI Methodology Committee

Using Administrative Data to Study Outcomes in Observational and Pragmatic Trials

David Mandell, ScD, Professor and Director, Center for Mental Health, University of Pennsylvania School of Medicine

One of the primary sources of data that Dr. Mandell uses, especially for studies of children with IDD, comes from the special education system. In 2020, 7.1 million US children received special education services, and most probably met the criteria for IDD. The National Center for Education Statistics (NCES) at the Department of Education makes a wealth of data publicly available, including survey results, disciplinary actions, proportion of time spent in general education settings, and graduation rates for these students. Several datasets provide information on subpopulations of students with IDD. However, none of the data from NCES provides information on individualized education plans or services delivered.

Health insurance claims data from Medicaid and private insurance companies are available for millions more children with IDD, and researchers are increasingly gaining access to these data. As with education data, the outcomes that can be measured with claims data are limited. The data include medications, hospitalizations, emergency department visits, and outpatient services. The Healthcare Effectiveness Data and Information Set measures, created by the Centers for Medicare & Medicaid Services from claims data, can provide a sense of the quality of care and some outcomes, but none are specific to IDD. These data have been used to measure receipt of depression screening and diabetes care, for example, but researchers have not used them to study people with IDD.

Dr. Mandell proposed “a radical agenda” to advance pragmatic trials on the education and healthcare experiences of children with IDD on a large scale by merging education and healthcare claims data. Determining whether services are effective requires collecting data on the education services delivered and developing quality and outcome measures that are specific to IDD and are consistent with those used in pragmatic trials. Outcome measures currently available are too burdensome and do not support research on the effects of different interventions on a large scale.

Healthcare data and education data are governed by different sets of regulations: the Health Insurance Portability and Accountability Act (HIPAA) for use of healthcare data and the Family Educational Rights and Privacy Act (FERPA) for use of education data. HIPAA is much more conducive to research than FERPA, which makes use of education data challenging for understanding the experiences and outcomes of students with IDD. Changes to these regulations could enable more research on interventions and outcomes.

Other recommendations were to do the following:

- Link data from registries to data from education and healthcare datasets to show the treatments and services received by children with IDD and their associations with outcomes. The Individuals with Disabilities Education Act could be changed to require the collection of data on services delivered.
- Work with NCES to enrich its existing surveys for children with IDD or develop separate surveys for this population.
- Create a small network of large school districts to leverage their size for fielding interventions and studying outcomes in experimental and quasi-experimental ways that could more quickly lead to meaningful changes in practice.

Advancing a Learning Healthcare System in IDD through Clinical Informatics

Luther Kalb, PhD, MHS, Director of Informatics, Center for Autism and Related Disorders, Department of Neuropsychology, KKI; Assistant Professor, Department of Mental Health, Johns Hopkins Bloomberg School of Public Health

People with IDD have experienced a cascade of disparities throughout history, and they have a higher risk of medical and psychiatric conditions that can reduce their quality of life and lead to earlier mortality. The LHS model can address the need for measures and evidence-based interventions for this population. The LHS concept is designed to seamlessly integrate research into practice with the goal of integrating patient values, clinical acumen, research methodology, and information to drive discovery as a natural outgrowth of patient care. At KKI and Johns Hopkins University, the data generated during delivery of care to people with IDD are used for research.

LHS offers opportunities to reduce disparities in three ways:

- Enable people with IDD to choose outcomes that are important to them.
- Drive innovation to reduce inefficiencies by delivering better care.
- Produce generalizable findings by collecting real-world data and avoiding selection bias.

In 2012, KKI had several separate outpatient data-collection efforts, and most used the institution's custom EHR. Acquiring the Epic EHR system in 2018 allowed KKI to harmonize and standardize its institutional records. KKI's EHRs now collect data on more than 400 psychometric measures, including cognitive and other outcomes data. KKI investigators have access to deidentified data to evaluate the care delivered and recruit study participants.

KKI collects data from patients starting before they arrive and lasting until after the appointment. For example, KKI sends surveys to families to collect demographic and contact information when they schedule an appointment. KKI then collects standardized data from the visit, including the reason for the visit, the patient's diagnostic history, which provider the patient saw, and billing diagnoses. From the notes, the EHR captures the results of psychometric measures and standardized information. After the patient leaves, the system captures patient-reported outcomes and satisfaction measures.

Strengths of the KKI LHS include its low cost and the access it provides to data from high-quality assessments for a large, generalizable sample. The system can track changes over time, collect information from several informants (e.g., caregivers, clinicians, teachers) regarding social determinants of health and health equity, and facilitate recruitment to traditional efficacy studies. Challenges include the need for a common IDD data model and data harmonization, ways to monitor treatment fidelity and overcome barriers to LHS implementation, long-term follow-up after patients complete their care, and creation of control groups.

Discussants

Margaret Daniele Fallin, PhD, Sylvia and Harold Halpert Professor and Chair, Department of Mental Health, Johns Hopkins Bloomberg School of Public Health

Danny van Leeuwen, MPH, RN, Founder, Health Hats; Member, PCORI Board of Governors

Dr. Fallin said that bringing health and education data together is not new but is radical, and now is the time to do so. The challenges that the presenters had discussed related to data standardization in the LHS model and the types of healthcare and education data available for research need to be overcome. Dr. Fallin supported the suggestion to develop a registry, because it could be controlled, but HIPAA and other regulations would have to be navigated.

Both speakers had mentioned the connections among mixed-methods research and implementation science but had not discussed ways to use qualitative data to shed light on the quantitative data they were describing. Information from LHS and medical claims data can best be understood by using qualitative methods, such as focus groups, to ask the people whose data are being collected for their perspectives. KKI could, for example, use its EHR system to choose people for focus groups that could offer information on qualitative aspects of the quantitative data collected.

Dr. Fallin offered the following recommendations for IDD research using the resources described in this session:

- Develop collaborations among providers, analysts, and consumers to identify the outcomes that are important.
- Identify the types of data on these outcomes that can be captured and used in analyses. For example, what do providers in the LHS model need to know?
- Choose standardized instruments and identify formats that make data shareable.
- Identify appropriate uses of data beyond research, such as clinical improvement or sharing information with patients and the public.

Mr. van Leeuwen described a concern, using an analogy of researchers who are searching for their keys under a streetlight, even though they lost those keys in a dark alley. Interactions between people with IDD and their clinicians are not at the center of the IDD universe, and methodologies for research on IDD need to reflect the lives of people with IDD beyond what occurs during acute care management. By working with people with IDD, researchers could learn how to conduct this research more effectively.

Family caregivers are important sources of information on people with IDD, and caregivers have their own health and lifestyle challenges that affect the health, well-being, and agency of people with IDD. Methodologies are needed to understand the experiences of family caregivers. For anyone with a chronic condition, including IDD, building abilities is a lifelong experiment with a sample of one person. Everyone learns from experience about what does and does not work, but people who are designing IDD research studies often lack the benefit of knowing what has and has not worked for the people they are studying. When developing their methodologies, researchers need to give more weight to what does and does not work.

Research almost always ends when the funded study is completed, but research participants want to use what has been learned in their own lives. Research methodologies should be designed to continue to collect data to determine, for example, whether an intervention is still effective and what other populations might benefit from it.

Discussion

Dr. Mandell confirmed that health service claims data could be used for IDD research; for example, he has used claims data to show that children with ASD receive more intensive outpatient services in states with ASD insurance coverage mandates, and rates of polypharmacy, emergency department visits, and hospitalizations in these children have declined. One challenge in evaluating mental health services for IDD is that the focus is more commonly on the presence or absence of less-desired outcomes than on that of positive outcomes. Evaluating positive outcomes requires linkages to EHRs. Dr. Mandell also clarified that he did not mean to imply that all special education students have a developmental disability, but many of these students do.

Dr. Kalb explained that KKI conducts mixed-methods research by, for example, using parent reports of ASD symptoms, and these data can be collected and stored in the informatics framework. Opportunities are available to standardize the fields created to store these data. The LHS model supports partnerships (e.g., having people with IDD serve on the KKI board) and offers opportunities to continue research after the funding ends. In efficacy studies, for example, KKI can find out what happens in the community. Dr. Kalb called for the creation of best-practice models and dissemination of tools.

Dr. Mandell argued against drive-by research, in which researchers do not meaningfully collaborate with community members to ensure that interventions are sustained or determine which groups benefit from the interventions. The IDD scientific community also needs to learn from what does not work as expected.

When asked how to conduct patient-centered research on IDD in rural areas that lack the healthcare delivery, research, and data infrastructure of many large cities, Dr. Mandell said that researchers have shown during the COVID-19 pandemic that they can conduct their studies remotely. He hopes that remote research does not end when facilities reopen and that lessons learned from the pandemic will be used for studies in remote areas. Solutions will be needed to ensure that health insurance plans cover the costs of remote care. Dr. Kalb added that informatics approaches can be extended to rural healthcare systems. Rural systems would not need to use the same EHR platforms as systems in large cities, but they would need to use a common data model that allows data sharing. Partnerships and financial support are needed to make such collaborations work. Extending the reach of the types of research conducted by academic medical centers, typically on the east coast, needs to be a priority.

In response to a question about the use of single-case study designs, Dr. Kalb said that single case studies are more common in the education literature than the healthcare literature and are helpful for understanding heterogeneity, but what works in these studies might only work for one individual. Dr. Mandell does conduct N-of-1 studies to determine which education and healthcare approaches do and do not work for an individual, but these are not case studies. A type of case study that might be useful is to treat an organization as a case and study what that organization needs to do to develop an LHS; lessons learned from this experience could be applied to another health system. Case study methods might be most useful for this type of research.

A participant commented on the difficulty of obtaining funding for high-quality research in rural settings for researchers who do not interact directly with patients or students and who cannot guarantee treatment fidelity. Dr. Mandell replied that in implementation science, the practitioner, not the patient, is the unit of analysis. Measuring fidelity in traditional ways requires careful coding and approaches that are difficult to scale up. Therefore, fidelity measures that can be scaled up and used remotely are needed. Dr. Kalb added that researchers in rural areas could study the use of remote approaches to deliver new interventions or administer cognitive assessments.

The final request in this session was for the presenters to discuss the IDD research questions they have studied using comparative-effectiveness, patient-centered approaches. Dr. Kalb said that he has been monitoring the frequency of physical activity of children who are recovering from concussion. Some experts have suggested that these children avoid physical activity, but other evidence suggests that non-contact physical activity can reduce time to recovery. Much of Dr. Kalb's research has been observational, and he has not conducted pragmatic randomized trials. Dr. Mandell has conducted three pragmatic or comparative effectiveness trials evaluating behavioral strategies for classrooms or behavioral interventions for young children. In one case, a local school district wanted to change its early intervention practices. Dr. Mandell and colleagues identified outcomes of interest and interventions that might produce the desired outcomes. The school district chose the intervention, and Dr. Mandell's team compared the intervention to other approaches being used, including what schools were doing before. He would like to conduct more studies where the partner identifies the intervention to study. Dr. Mandell is also working with the local school district, the mayor's office, and the department of behavioral health to study the outcomes of mental health interventions for elementary and middle school students. For these studies, he merges administrative data with observational data, and the results show

that young children with IDD who receive early interventions are more likely to be placed in a general education kindergarten class.

Topic 3: Heterogeneity

Moderator: Naomi Aronson, PhD, Executive Director of Clinical Evaluation, Innovation, and Policy, Blue Cross and Blue Shield Association; Member, PCORI Methodology Committee

Heterogeneity and Autism Research: Challenge or Opportunity?

Sarabeth Broder-Fingert, MD, MPH, Associate Professor of Pediatrics, Boston University School of Medicine and Boston Medical Center

ASDs are heterogeneous, and the federal government is spending almost $200 million on research to better understand ASD subtypes, but heterogeneity in ASD extends far beyond subtypes. The families of people with ASD experience heterogeneous stressors and have diverse types and levels of social support, engagement, income, knowledge, attitudes, and time. Support for families is important in patient-centered approaches to health care, and family profiles probably affect the outcomes of people with ASD. For example, a recent study showed that family factors (parental buy-in, involvement, and actions) predict more of the variance in outcomes than whether the person with ASD was assigned to the intervention group. Supporting families more effectively and mitigating this variance could improve outcomes for children with ASD and their families.

Many ASD treatments rely on parental involvement, so heterogeneity in families' ability to provide treatment leads to heterogeneity in treatment. Families might not understand the intervention materials if, for example, they do not speak English and the materials are not available in their language, and they might not implement all of the intervention components if they do not understand the explanations provided by an English-speaking trainer. In this example, structural racism could lead to poorer outcomes.

Dr. Broder-Fingert offered additional examples of sources and effects of the heterogeneity of families of children with ASD:

- Nearly twice as many pediatricians experience challenges in identifying ASD among Spanish-speaking families as among English-speaking White families. Pediatricians might therefore support different families differently, leading to profound disparities.
- In Michigan, the interventions provided to children with ASD are heterogeneous, which can create challenges for pragmatic trials that use a usual-care control group. Standardizing the treatments used would provide a major opportunity to improve outcomes.
- The prevalence of ASD appears to vary widely by state, but these differences are probably a result of variations in identification of children with ASD and do not reflect true prevalence differences. In addition, state spending on services for children with ASD varies widely, which can lead to heterogeneous outcomes.
- Differences in outpatient services received are greatly influenced by race and geography. For example, some of the differences in outpatient services received by Black and White children with ASD are accounted for by differences in the distribution of urban and rural counties of residence of these two groups.

Recognizing and Responding to Diversity Among Persons with IDD in Research

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The number of people with IDD in the United States is difficult to determine. Although several researchers have published estimates, no consistent mechanism is available to provide this information. According to one estimate based

on IDD prevalence rates in 1994–1995 in children and adults from the National Health Interview Survey, 2016 US Census data, and 2016 data on people in congregate settings, 7.27 million children and adults were living with IDD in 2016. According to another estimate, 17 percent of children ages 3 to 17 have at least one developmental disability.

About 5 percent of Americans are of some race other than the typical categories, and about 3.4 percent are of more than one race. People within these categories are typically not well represented in research. Furthermore, 13.4 percent of US persons speak Spanish, 2.7 percent speak Indo-European languages, 3.5 percent speak Asian and Pacific Islander languages, and 1.1 percent speak other languages. In 4.3 percent of US households, no one over age 14 speaks English or speaks it well. Many people with IDD and their families speak languages other than English, and these groups are probably rarely included in IDD research. Equity in IDD research requires addressing linguistic diversity. Professor Goode and colleagues have created a tool to promote linguistic competence in research to include populations that are underserved by research.

The US Census provides some information on individuals with certain types of disabilities by race, ethnicity, and age, but the disability categories do not include some types of IDD. The data show great diversity in races, ethnicities, and ages of individuals with disabilities.

The term “cultural diversity” is used to describe differences in ethnic or racial classification and self-identification, tribal or clan affiliation, nationality, language, age, gender, sexual orientation, gender identity or expression, socioeconomic status, education, religion, spirituality, physical and intellectual abilities, personal appearance, and other factors that distinguish one group or individual from another. These characteristics are important for understanding who someone is beyond whether they have IDD.

The literature tends to categorize people according to the cultural group with which they identify most. Some researchers consider compartmentalization, which refers to the maintenance of several separate cultural identities and is particularly common in families that have felt marginalized or had other experiences that make them uncomfortable sharing information because they do not know whether that information might be used against them. Another set of studies uses integration, in which people link their cultural identities and are forthcoming about these identities.

The concept of intersectionality was introduced by Kimberlé Crenshaw, a lawyer and civil rights advocate, in 1991 to refer to Black women who, because of their membership in certain social groups, experience discrimination, oppression, and marginalization. This term is sometimes used incorrectly to refer to having several cultural identities without the important defining factors of discrimination, marginalization, and oppression because of the person’s identity. Research is needed on the impact of intersectionality on people with IDD and its implications for research conduct.

Recognizing and responding to the diversity of people with IDD requires research methodologies that:

- Avoid treating all people with IDD as members of a homogenous group.
- Employ approaches, including mixed methods, that produce nuanced portraits of people with IDD.
- Describe research participants in ways that account for their diversity.
- Collect, analyze, and report data in ways that reflect social identities and memberships in addition to neurodevelopmental disabilities.

Questions for researchers to address include how the family and community respond to the child’s disability; available supports; and the impact of socioeconomic, political, and environmental factors. Other factors that can affect people with IDD include the healthcare, transportation, mental healthcare, disability and finance, and educational systems, which might have different languages, cultures, and rules. A family member of a child with IDD must enter a different culture every time they begin interacting with a different service. This framework is useful for examining the data gathered during the COVID-19 pandemic on the experiences of young adults who have IDD with mental health services.

People with IDD experience disparities in the availability, accessibility, acceptability, quality, and use of various services and supports (e.g., health care, housing, childcare, recreation, education, employment). In some cases, for example, services are available, but they are not acceptable to the person with IDD because they are not tailored to their sociocultural context or are not available in a language that the person understands. Public policies and resources affect the meaningful, respectful inclusion of people with IDD in every aspect of community life.

Suggestions for researchers to recognize and respond to diversity among people with IDD include the following:

- Recognize the historical experiences of people with IDD across all racial, ethnic, and cultural groups in research.
- Be cognizant of the power differentials between research institutions and vulnerable and marginalized communities.
- Address the power dynamics between researchers and people with disabilities across cultural groups.
- Admit and examine researchers' own biases.
- Revisit and revise the terminology and tenor used to describe people with IDD.
- Use methodologies that recognize, respect, and address the multiple cultural identities of people with IDD.
- Consider how the experiences of people with IDD vary by sociocultural context.
- Use measures and instruments that are appropriate for the diverse racial, ethnic, and cultural groups of people with IDD, their families, and their communities.
- Use study designs that foster meaningful partnerships with people with IDD who belong to different cultural groups.
- Embed cultural and linguistic competence in study methodologies.
- Increase the capacity to include people with IDD who speak languages other than English and their families in research.

Discussants

Elizabeth Stuart, PhD, Associate Dean for Education and Professor, Department of Mental Health, Department of Biostatistics, and Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health; Former Chair, PCORI Advisory Panel on Clinical Trials

Bradley L. Schlaggar, MD, PhD, President, CEO, and Zanvyl Krieger Endowed Chair, KKI

Melissa A. Parisi, MD, PhD, Chief, Intellectual & Developmental Disabilities Branch, DS-Connect® Registry Coordinator, NICHD

Dr. Stuart focused her remarks on themes from throughout this meeting. One such theme was the complexity of people with IDD and their contexts. Traditional study designs, such as randomized controlled trials, may not always be appropriate for this type of research, so researchers must be creative and flexible in choosing designs that make sense.

Researchers in epidemiology and statistics have been discussing external validity more formally than in the past, and these issues are important for IDD research and for PCORI. Researchers must be aware of whom they are enrolling and how to describe these individuals to ensure that their study is relevant to the target population.

Dr. Stuart praised PCORI for its focus on methods since its beginning. PCORI is one of the few funders that sets aside funding for methodology research. This meeting had highlighted methodological needs, including how to account for the heterogeneity of people with IDD and whether interventions might be differentially effective. The previous panel had emphasized the importance of mixed-methods research and possibly using the learning health system to identify participants for focus groups. Creative approaches can be used to triangulate large datasets.

Some of the issues discussed during this meeting—including population heterogeneity and the availability of data systems for research—apply to many areas of PCORI-funded research. Dr. Stuart approved of the recommendation to

merge healthcare and education data, which is important to understand the experiences of children and adolescents with IDD who receive services from both systems. Researchers need to be creative in bringing together datasets that provide information on the different contexts that affect people with IDD every day.

Dr. Schlaggar noted that the etiologies of the nervous system disorders that result in IDD, including the interactions with cultural, social, and other factors, are complex. Some phenotypes might appear to have similar etiologies, but the symptoms and their severity are disparate. The rules for manuscript publication and grants push researchers toward univariate and central tendency–directed heuristics. Clinical investigations seem to focus more on treatments than on patients, and a shift is needed toward a more patient-centered approach.

Dr. Parisi has conducted research in children and adults with IDD, and many of these individuals also had rare diseases. She therefore focused some of her remarks on the heterogeneity of rare diseases, which collectively have a major impact on the health and well-being of the US population. Many individuals with rare diseases are children, and their diseases often have neurological, psychiatric, and behavioral manifestations. The heterogeneity of rare diseases has much in common with that of IDD.

Major challenges for rare disease research include finding enough people with a rare disease to study and combining groups of patients with rare diseases of the same or similar etiology for meaningful studies. A new genomic era is beginning, and researchers are using whole-exome and whole-genome sequencing methods that enhance the ability to diagnose rare diseases. Families of people with rare diseases are using crowdsourcing to find one another. These advances are enhancing the ability to understand natural history, which is challenging in people with IDD who have rare diseases. NICHD has supported some natural history research, which can identify wide ranges of experiences, assess interventions, and identify meaningful outcomes.

Outcome measures for these heterogeneous disorders are important. NICHD has supported studies to develop validated outcome measures that can be used as benchmarks for interventions to improve quality of life. Functional measures are also important; some might be specific to certain types of IDD, but others might apply to several conditions.

In this new era of gene-directed therapies and targeted interventions that might need to be evaluated in N-of-1 studies, researchers need to consider individualized approaches. The use of such approaches appears inconsistent with calls in this workshop for more epidemiologic and population-based focuses.

Dr. Parisi described some NIH programs that are relevant to the themes of this workshop. The NIH UNITE initiative is identifying and addressing structural racism within the NIH-supported and greater scientific community. In addition, the trans-NIH INCLUDE (INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndromE) Project is investigating conditions that affect individuals with Down syndrome and the general population, such as Alzheimer's disease or dementia, ASD, cataracts, celiac disease, congenital heart disease, and diabetes.

People with IDD, including Down syndrome, have the same co-occurring conditions as the general population, but they are often excluded from clinical studies for invalid reasons. Minor modifications to consent processes and adjustments to study designs can make it possible to include more people with IDD in clinical studies.

Discussion

Dr. Goodman asked how to reconcile the need to study groups for the development of interventions that benefit everyone in a group with the recognition of each person's individuality. Professor Goode said that these factors are not mutually exclusive. By viewing people with IDD as a homogenous group, researchers can miss important factors. They need to consider other characteristics and collect both qualitative and quantitative data to develop a more nuanced understanding of each study participant. Dr. Schlaggar agreed that individual characteristics and research in groups are complementary. Studies need to be designed to determine not only whether an intervention is effective for a group but

also for whom the intervention is and is not effective. This knowledge can help avoid the use of treatments that are not effective for certain people or that could produce adverse effects. Investigators need to determine not only global effects but also how to apply a given intervention to a given person in a way that increases the likelihood of success and reduces the risk of adverse effects.

A participant asked about study designs and informed-consent approaches that can increase the number of people with IDD who participate in clinical trials. Dr. Broder-Fingert replied that some basic principles are useful for working with institutional review boards (IRBs) to develop policies and procedures for engaging people with IDD in clinical research. Traditional consent or assent approaches might not be appropriate for some people with IDD. Some IRBs have experience addressing these issues. Partnerships with communities can be helpful for recruiting community members. Strategies for studies that are testing interventions in the general population might be different from those that test interventions in people with IDD. However, clinical trials sometimes require additional funding to include people with IDD to cover the costs, for example, of assistive communication devices to collect informed consent or of additional time required for individuals to complete the informed consent process. Researchers need to include these factors in their study plans and account for these differences, if they affect outcomes, in their analyses.

When asked about just-in-time adaptive intervention studies, Dr. Broder-Fingert said that these and N-of-1 studies have a great deal of potential. Dr. Stuart cautioned, however, that to use these trial designs well, researchers must identify the characteristics of individuals for whom the intervention is being adapted, which requires appropriate measurement tools to determine which participants need help and what types of adaptations should be made. A great deal of formative work is needed before adaptive interventions can be used, but this approach seems promising.

A participant asked how to assess or stratify negative outcomes in IDD research in relation to underlying characteristics, such as gender, socioeconomic status, or genetic variation. Dr. Stuart said that this question is related to effect heterogeneity. Clinicians want to know which intervention will be effective for a given patient, and PCORI is seeking projects to develop methods that can be used to answer these questions. This research needs to be done in groups that are large enough to be heterogeneous and use a combination of randomized trial and nonexperimental evidence.

Professor Goode said that a given intervention's lack of effectiveness in a subgroup is not a negative outcome but is a fact that can be used to guide practice. Researchers need to examine their biases, including their cultural biases, and consider perspectives that are different from their own. Dr. Schlaggar said that this approach requires principles of inclusiveness in study design and a willingness to collect a great deal of data. Not every study can have the statistical power to assess one or two preidentified outcomes. Researchers need to change some of their standard approaches to answer the types of questions raised during this session.