Global Genes®
Allies in Rare Disease

# Patient Identification, Inclusion & Engagement for Rare CNS Disorders (PIE4CNS)

## REPORT AND RECOMMENDATIONS FOR ACTION

March 2022

# 1 INTRODUCTION

## 1.1 Project Summary

Global Genes is a 501(c)(3) non-profit organization dedicated to eliminating the burdens and challenges of rare diseases for patients and families globally. In pursuit of its mission, Global Genes connects, empowers, and inspires the rare disease community, helping to spur innovation, meet essential needs, build capacity and knowledge, and drive progress within and across rare diseases. Global Genes serves more than 400 million people around the globe and nearly one in 10 Americans affected by rare diseases.

The Patient Identification, Inclusion, and Engagement for Rare CNS Disorders (PIE4CNS) initiative aims to highlight and address the challenges of patient engagement in and access to diagnosis, research, and drug development for rare CNS conditions. The PIE4CNS initiative is being conducted with support from Passage Bio, Alexion (AstraZeneca Rare Diseases), SIO Gene Therapies, Taysha Gene Therapies, and Praxis.

PIE4CNS brings together stakeholders from the rare disease ecosystem with a vested interest in improved, earlier, more inclusive patient identification and engagement to discuss and align on key obstacles and barriers, and to identify and collaborate on recommended solutions.

The recommendations contained in this report are based on several thoughtfully programmed and integrated activities, including a targeted pulse survey of clinicians, caregivers, and patients, workshops to explore challenges and potential actions specific to pediatric and adult rare CNS disorders, and a workshop on health equity related challenges in rare CNS disorders -- all guided by advice and inputs from an expert advisory panel (listed below).

| Members | Affiliations |
|---|---|
| Anna Bican, CCRP | Undiagnosed Diseases Network |
| Terry Jo Bichell, PhD, MPH | COMBINEDBrain |
| Wendy Erler | Alexion |
| Mark Forman, MD, PhD | Passage Bio |
| Vanessa Vogel-Farley | Dup15Q Alliance, RARE-X |
| Cindy Jackson, D.O., F.A.A.P | I-ACT for Children |
| Mary Anne Meskis | Dravet Syndrome Foundation |
| Matt Might, PhD | NGLY1 Foundation |
| Kris Pierce, RN, MHSc | SCN2A Australia |
| Tracy Dixon-Salazar, PhD | LGS Foundation |

The survey findings, insights derived from workshops, and resulting recommendations are designed to form the basis for a set of immediately actionable, collaborative initiatives to generate progress in addressing key challenges in 2022 and beyond.

A detailed record of the inputs from the survey, workshops, and advisory panel are all included in the Addenda to this report. While the specific initiatives and actions recommended as an output of the surveys and workshops are necessarily prioritized and limited, we have made a more complete record spanning a range of challenges and potential solutions available to provide context and perhaps inform other efforts or initiatives focused on driving progress or improving the diagnosis, care, and treatment of patients and families living with rare CNS conditions.

## Rare Diseases

There are more than 7,000 known rare diseases, which affect about 400 million people worldwide and 1 in 10 Americans (fda.gov). Fewer than 5% of rare conditions have an approved treatment, making rare diseases one of the most significant public health challenges and areas of collective unmet need and disease burden worldwide. Despite the collective reach of rare diseases, however, most affect fewer than 1,000 patients, and some are discovered in only a handful of people worldwide.


Rare diseases have significant impacts on patients and entire families. Of the total estimated population of rare disease patients, more than half are children. Tragically, a third of those patients will die by age 5 (Editorial-Lancet). Considering that it typically takes 7.3 years to get to a diagnosis (Blöß 2017), the diagnostic odyssey can quite literally last more than a lifetime for many children with rare diseases. Other rare conditions manifest in teenage years and even much later in life, often with rapidly debilitating and devastating effects. The collective unmet need and burden of rare diseases is among the most significant of any disease category worldwide.

## Gene-Based Diagnosis and Treatment

About 80% of rare diseases have a genetic basis (Jackson 2018), which makes potential diagnosis and patient identification leveraging genetic testing and the latest sequencing technologies increasingly possible. Providing coverage and affordable access to such tests, technologies, patient medical histories, and expert analysis must be readily available to diagnosing clinicians. Sadly this is not the case in many countries around the world, including the U.S. and other developed countries.

Fortunately, because the vast majority of rare conditions have a genetic basis, and 95% or more have no approved or competing treatment available, rare diseases have become an attractive area of exploration for drug developers and an ideal proving ground for promising platform technologies such as gene and cell therapies or gene editing. According to the Alliance for Regenerative Medicine, there are more than a hundred clinical trials for potential regenerative therapies for rare indications underway around the world.

## Patient Identification

This increased interest in developing treatments for rare conditions, while welcomed, also creates some distinct challenges: a) most of the current drug development activity is centered around more "common" rare conditions, which can mean that multiple active clinical trials within a single rare disease are all seeking to enroll qualified patients from a very small and diverse pool at the same time; or b) a rare disease has such a low number of patients, geographically scattered, that finding enough diagnosed and qualified patients to conduct a single trial can be challenging, potentially jeopardizing advancement of transformative treatments.

Failure to diagnose, find, and engage patients in research, treatment, and community activities can significantly hinder innovation, access to care, treatments, and support services and, ultimately, result in suboptimal outcomes for rare disease patients.

## Rare CNS Conditions

By some estimates, nearly half of all rare diseases are neurological and as many as 90% of pediatric onset rare diseases are associated with major neurological impacts–so addressing the challenges associated with diagnosing and driving drug development and access to treatments for rare neurological conditions represents a major challenge in the rare disease community.

It is often very challenging to diagnose CNS conditions accurately and early enough for treatments to have a significant effect. Some of these reasons include:

- Clinicians (even neurologists) may not be familiar with signs associated with rare and ultra-rare conditions or the best available diagnostic tools, and/or may confuse observable symptoms with more common CNS conditions, potentially leading to delayed diagnosis or misdiagnosis;
- Newborn screening panels and other tests don't identify all known rare conditions, don't always yield a conclusive diagnosis, and aren't consistently accessible to families and clinicians;

- Caregivers and family members often are pivotal to diagnosis of CNS conditions–yet they aren't trained to do so, are often unaware of what to look for, and can struggle to convey observations about what is going on with a patient in a way that is meaningful to their doctors; and,
- In pediatric rare diseases in particular, the patient is often not able to communicate what they are experiencing to support a diagnosis.

## 1.3 Objective and Approach

### 1.3.1 Objective

The PIE4CNS initiative seeks to identify and take action to overcome key challenges standing in the way of inclusive involvement of patient populations with rare CNS conditions in diagnosis, research, drug development, and access to care and treatments.

Factors contributing to these challenges include: reaching and engaging small, highly dispersed, and diverse patient populations; low awareness and familiarity among physicians, caregivers, and patients; inconsistent, lengthy paths to diagnosis and lack of access to appropriate diagnostic tools and expertise; low awareness of and inconsistent access to trials; and siloed patient data that further complicates and prevents inclusivity.

### 1.3.1 Approach

The Global Genes PIE4CNS Initiative is designed to highlight and address the challenge of inclusive patient diagnosis, identification, and engagement in research, drug development, and treatment by bringing together stakeholders from the rare disease ecosystem and building consensus and support for a series of actions prioritized by the community.

The initiative consists of surveys, workshops, and advice and discussions with an expert panel comprised of advocates, clinicians, researchers, patients, and caregivers. The recommended solutions contained herein will create the foundation for a set of initiatives and activities designed to address key challenges in 2022 and beyond.

## PIE4CNS Process

**Approach**

***Phase I: Identifying Needs, Barriers and Priorities for Action***

**Ask** (Panel, Surveys, Workshops)

Survey - September 2021, Pediatric/Adult Patients & Caregivers, Researchers & Clinicians
Workshop 1 - October 21st; Pediatric Rare CNS
Workshop 2 - November 4th; Adult Rare CNS
Workshop 3 - November 17th; Health Equity in Rare CNS

**Assess** (Report & Recommendations)

***Phase II: Acting on Recommendations***

**Act** (Collaborate Initiative)

## 1.4 Key Findings and Observations from Pulse Surveys and Workshops

### 1.4.1 Pulse Surveys

Global Genes commissioned an initial set of three pulse surveys, conducted by CE Outcomes, in September 2021. The pulse surveys included Pediatric Caregivers, Adolescent/Adult Patient and Caregivers, and Clinicians and Researchers, respectively. The survey guide was reviewed, and input was provided by the PIE4CNS Advisory Panel (identified above).

| | |
|---|---|
| **Pediatric Caregivers** | **52** |
| **Adolescent/Adult Patient/Caregivers** | **99** |
| **Clinicians/Researchers** | **53** |

The total numbers of vetted responders in each category are included above (note that hundreds of additional responses were received but where there were questions regarding the validity of profile information or profile information was incomplete, those responses were removed from the final survey cohort of caregivers, patients, clinicians, and researchers.

Data was collected from Patients/Caregivers related to the following topics of exploration:

- Diagnosis
- Testing
- Diagnostic Challenges
- Treatment Availability
- Clinical Trials
- Patient Advocacy Groups
- Patient Registries
- Clinical Trials

Data was collected from Clinicians and Researchers related to the following topics of exploration:

- Diagnosis
- Patient Identification
- Diagnostic Challenges
- Information Resources
- Clinical Trials
- Patient Resources on Clinical Trials

Key highlights from the surveys are included below and served as a basis for PIE4CNS workshop discussions and final recommendations.

**What is the diagnosis (if known) for patient?**

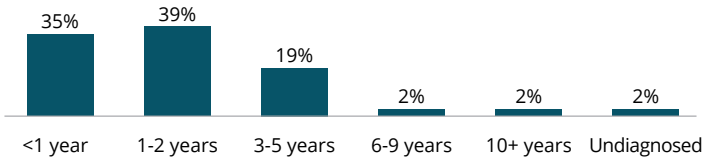
- 17p12 deletion, HNPP, Autonomic Dysfunction, epilepsy, gastroparesis, sensory processing disorder
- Angelman Syndrome (3)
- ASH1L related disorder
- Aicardi-Goutières Syndrome
- BBSOAS (mutation of the NR2F1 gene)
- BPAN (3)
- Cabezas Syndrome
- CACNA1A-related congenital ataxia
- Charcot Marie Tooth 2A
- Chromosome abnormalities
- CLN2 Batten disease
- Creatine Transporter Deficiency
- Dup15q (4)
- FOXG1 Syndrome
- Fragile X, and Lennox-Gastaut Syndrome
- GDD, no proper diagnosis has been made
- Generalized dystonia
- GRIN Disorder (2)
- KCNA2 Epileptic Encephalopathy
- Koolen-de Vries Syndrome
- Leigh Syndrome
- Lennox Gastaut Syndrome (2)
- Lessel-Kreienkamp (Ago2 gene), West syndrome
- longitudinally extensive transverse myelitis
- NEDAMSS/ IRF2BPL Disorder
- Nijmegen breakage syndrome
- Noonan Syndrome
- NTNG2 syndrome
- Rett Syndrome
- SCN2A related disorder (2), SCN8A-DEE
- Shwachman-Diamond Syndrome
- Skraban Deardorff Syndrome
- Smith Kingsmore Syndrome
- SMA
- SynGap encephalopathy
- Tethered cord syndrome, spina bifida, syringomyelia
- Tuba 1a pathogenic variant
- Unknown (2)
- Unspecified Leukodystrophy

## Patient Diagnosis History

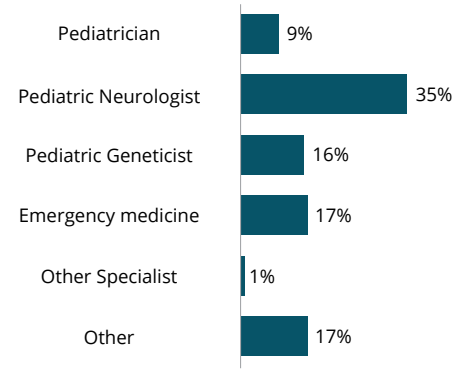
**Age at time of diagnosis (mean)**

**Pediatric**
**34 months**

**Please select the time period between the patient's onset of symptoms to their formal diagnosis.**



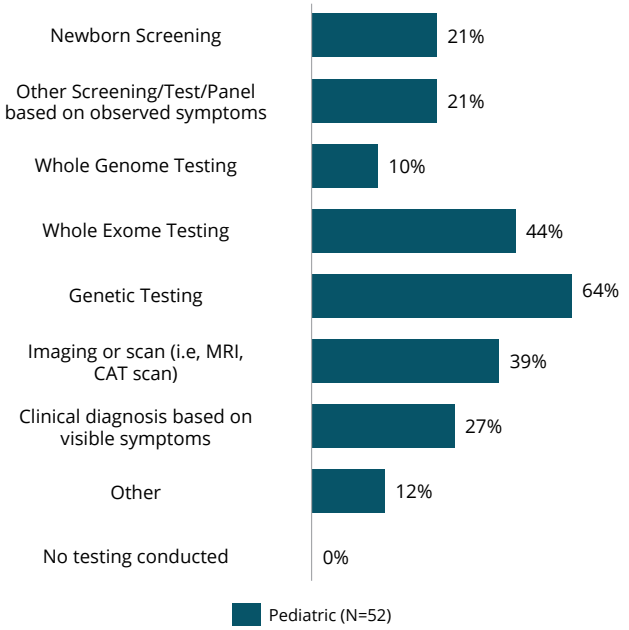

**What type of physician gave the patient their formal diagnosis?**



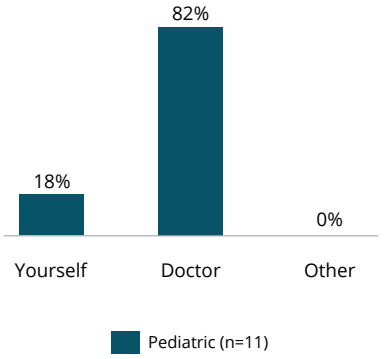
It's worth noting that among pediatric respondents the majority were diagnosed within a 2-year period (much sooner than the overall 7.3 years average). This may be attributable to the fact that the majority of these children were referred to pediatric neurologists and geneticists who were able to make a diagnosis. This highlights the need to get these patients to a referral quickly. Additionally, newborn screening, whole genome/exome sequencing, and other diagnostic tools and panels were accessible and utilized for diagnosis among most caregivers responding to this survey.

## Test Conducted for Diagnosis

**What types of testing were conducted to receive a diagnosis?**




**Who requested the screening/test/panel?**

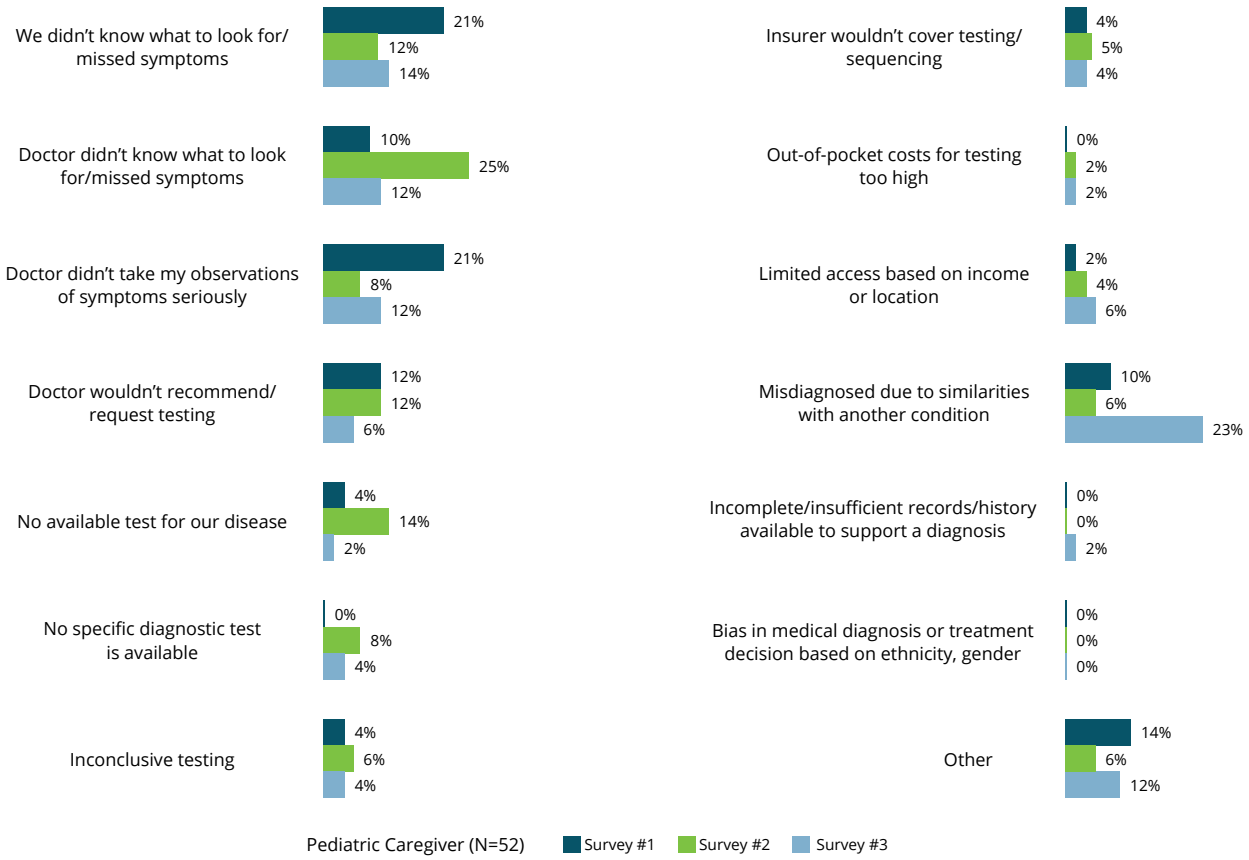



Note that among respondents the top reported challenges were that patients didn't know what to look for or missed symptoms, or their doctor did, and that a doctor didn't take the caregiver's observations of signs or symptoms (critical in CNS conditions) seriously–suggesting that the diagnosis could have been more precise and occurred earlier. Delays in diagnosis can often have significant and irreversible implications in many rare neurological disorders.

## Challenges in Pursuing a Diagnosis

**Pediatric/Caregiver**

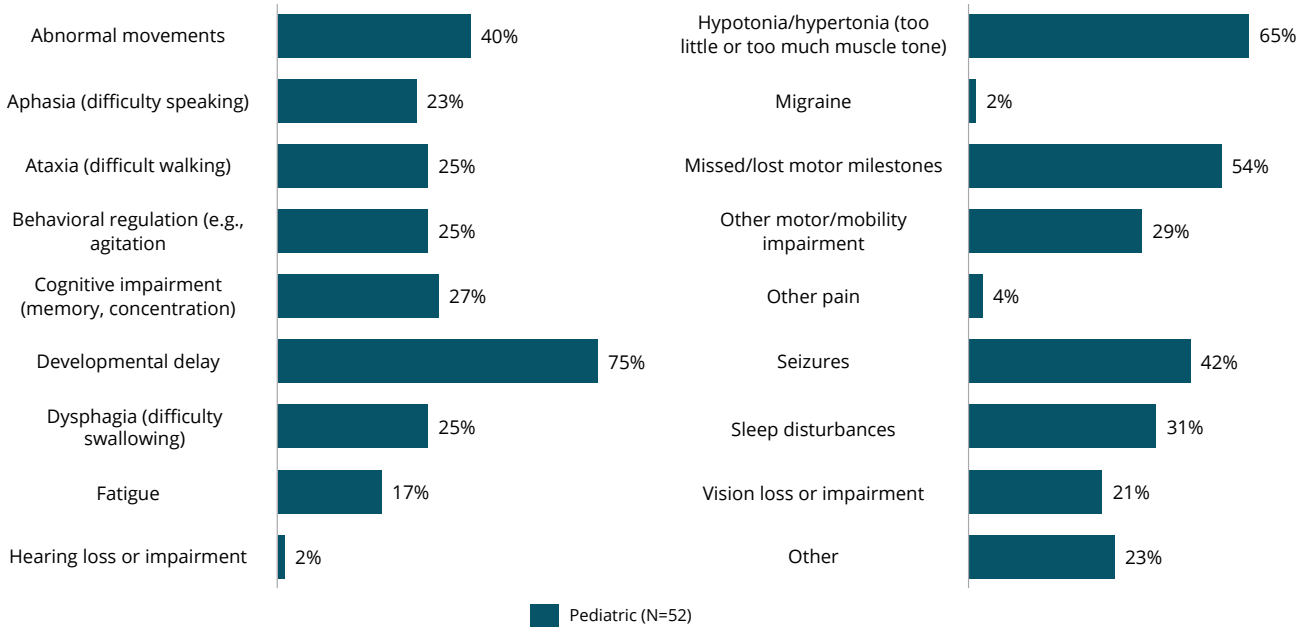
**What were the most significant challenges you experienced in pursuing a diagnosis?**



Many respondents reported a diagnosis based on developmental- and movement-related signs and symptoms, which speaks to the importance of clinicians and caregivers aligning around descriptions of symptoms, as the diagnosing physician must rely upon the observations of caregivers to identify potential manifestations of a condition that could lead to an earlier or more accurate diagnosis.

## Symptoms Leading to Diagnosis

**What were the patient's initial signs/symptoms that led to a diagnosis**




## Patient Diagnosis History

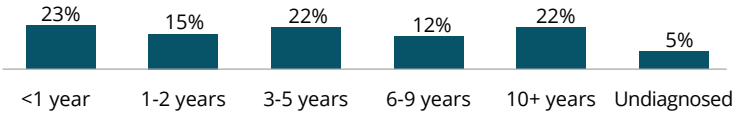
**What is the diagnosis (if known) of patient?**

- Angelman Syndrome (2)
- Addison Disease
- Anderson Twail Syndrome
- Ataxia Pancytopenia
- Arachnoiditis (3)
- Autism then MED13 mutation
- Bulbar ALS
- Cauda Equina Syndrome
- Cadasil (2)
- Central Pain Syndrome
- Demyelinating disease of the CNS
- Dravet syndrome (7)
- Dup15q Syndrome (5)
- Dystonia-27
- EEF1A2 gene mutation
- Epilepsy
- FAM177A1
- FOXP1 Syndrome
- Glut1 Deficiency
- Inclusion Body Myopathy
- Jouberts Syndrome and Congenital Central Hypoventilation Syndrome
- Kleine-Levin syndrome
- Lennox Gastaut Syndrome (2)
- Lessel-Kreienkamp syndrome
- Lgs, cp, cvi, non verbal
- Neuropatia
- NOMID
- Other (5)
- Phelan McDermid Syndrome (3)
- PMSF
- Rasmussen encephalitis
- Ring14 Syndrome - Ring Chromosome 14
- Sanfilippo Syndrome (MPSIIIB)
- SCn2A
- seizure disorder
- SMEI, exotic deletion 25-26
- Tarlov Cyst
- Unknown/undiagnosed (6)
- WHS, Lissencephaly, Agenesis of Corpus Collosum, Cerebral Palsy

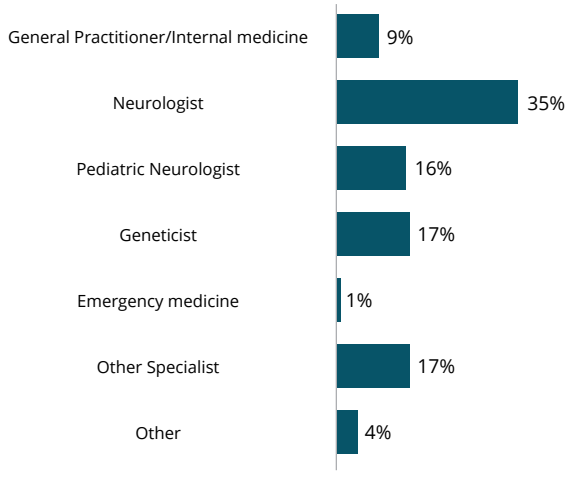
**Age at time of diagnosis (mean)**

**Adolescent/Adult 22 years**

**Please select the time period between the patient's onset of symptoms to their formal diagnosis.**



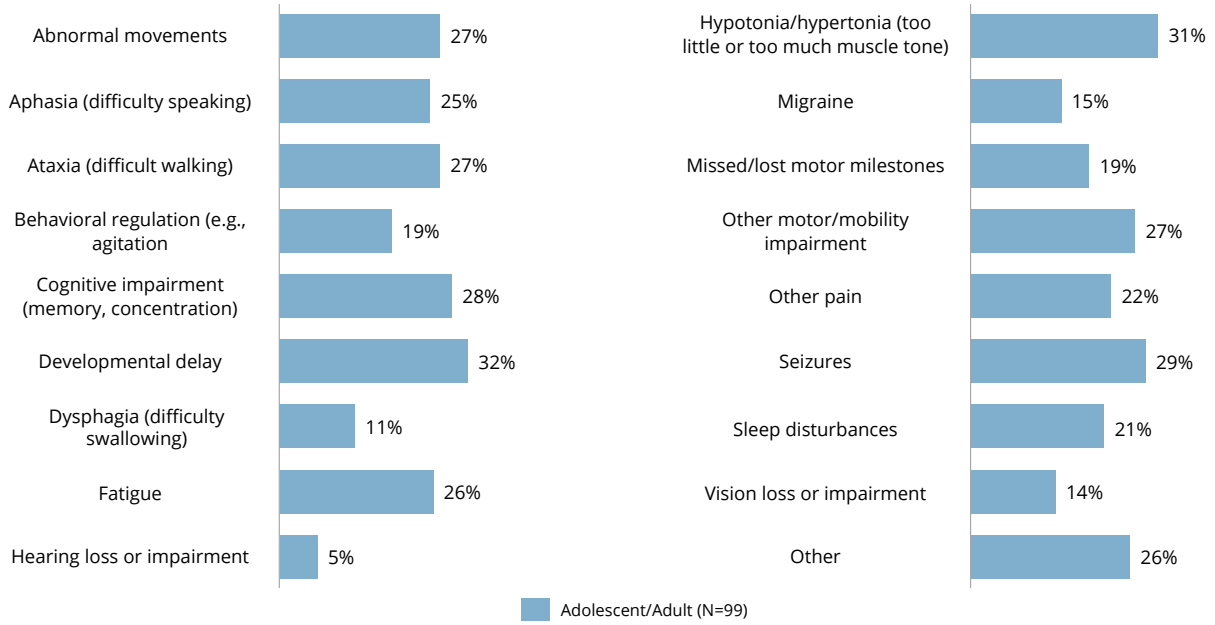

**What type of physician gave the patient their formal diagnosis?**



The time to diagnosis among responding adolescent/adult patients was noticeably longer, on average. The lengthy odysseys may reflect various challenges, including: lack of awareness among clinicians and more attention and diagnostic options available and applied to pediatric conditions; potential loss or missed signs from medical history and patient experience lost in transition from pediatric to adolescent/adult providers; and misdiagnosis or confusion with other more common conditions affecting adult populations.

## Symptoms Leading to Diagnosis

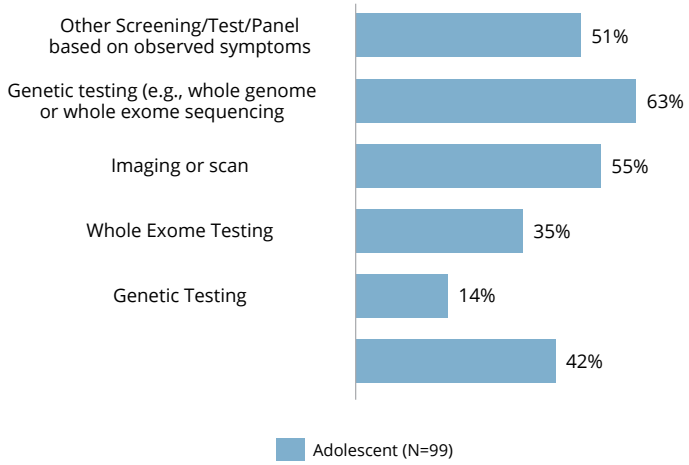
**What were the patient's initial signs/symptoms that led to a diagnosis**



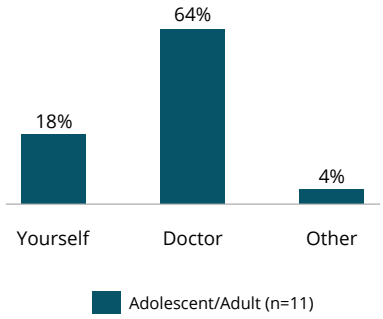

Symptoms that respondents indicated led a diagnosis of adolescent/adult-onset CNS conditions were more evenly spread than those associated with pediatric conditions (i.e., no telltale adult signs were reported by a majority of respondents) and a number of the symptoms could also be associated with more common conditions, which underscores some of the difficulties of accurately diagnosing adult/adolescent patients.

## Test Conducted for Diagnosis

**What types of testing were conducted to receive a diagnosis?**




**Who requested the screening/test/panel?**

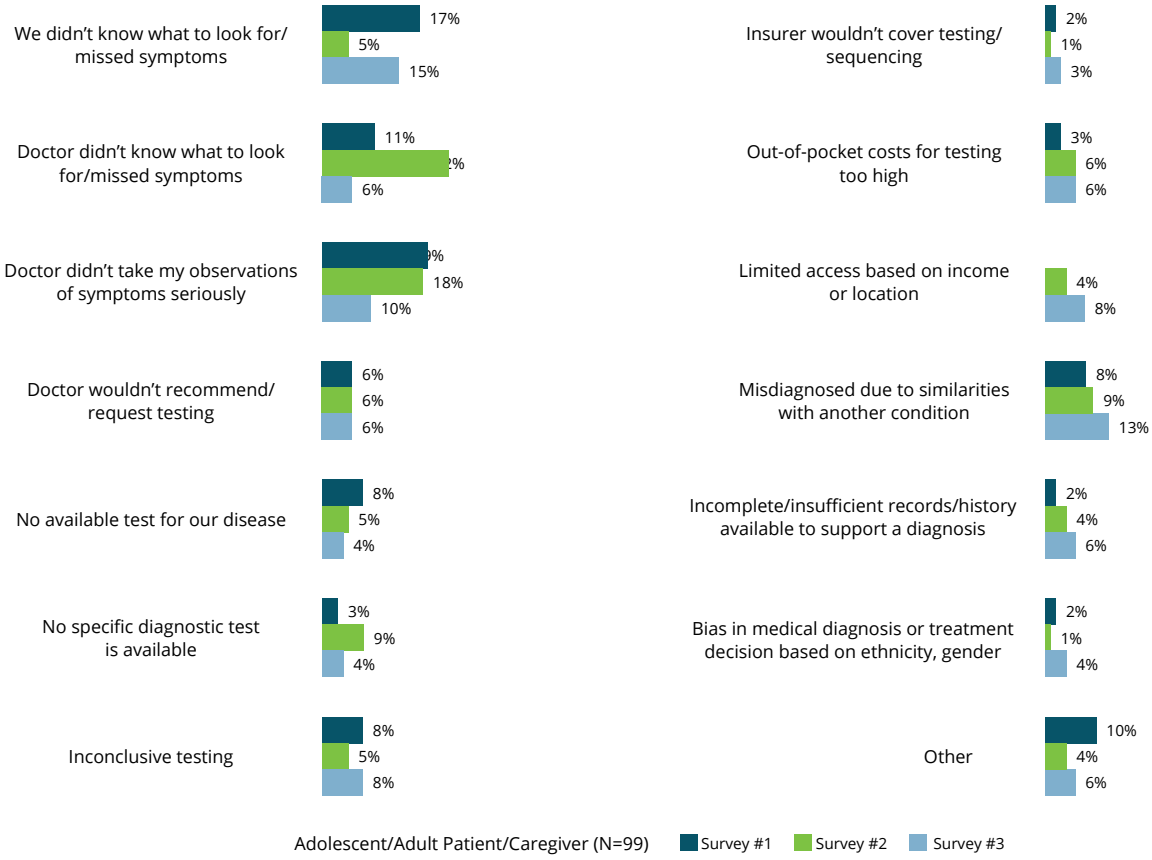



A relatively high percentage of respondents indicated that their diagnosis was hindered by a lack of familiarity with relevant symptoms among both patients and clinicians, and misdiagnosis due to similarities of some symptoms with those associated with other more common conditions.

## Challenges in Pursuing a Diagnosis

**Adolescent/Adult Patient/Caregiver**

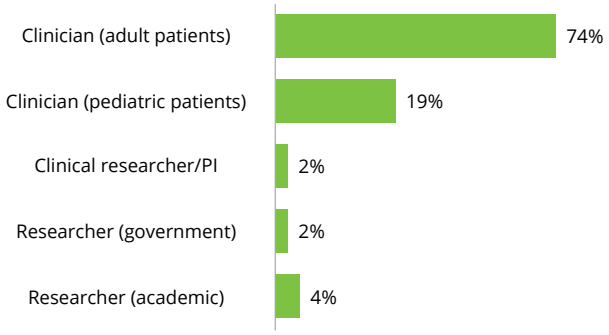
**What were the most significant challenges you experienced in pursuing a diagnosis?**



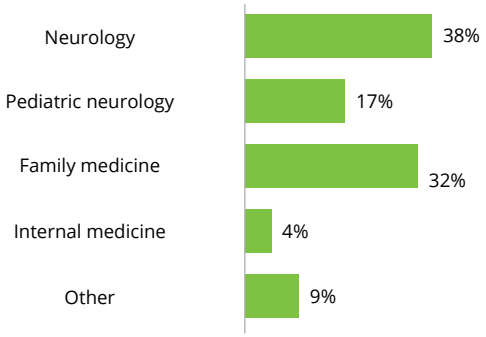

## Clinician/Researcher Demographics

**Years in practice**
**22 years (mean)**

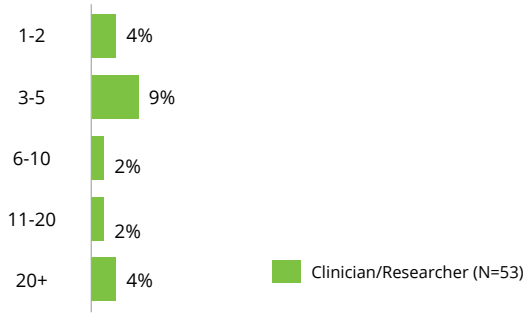
**Role**



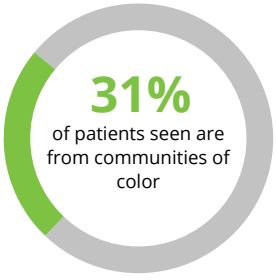

**Specialty**




**# of patients with rare neurologic conditions managed**



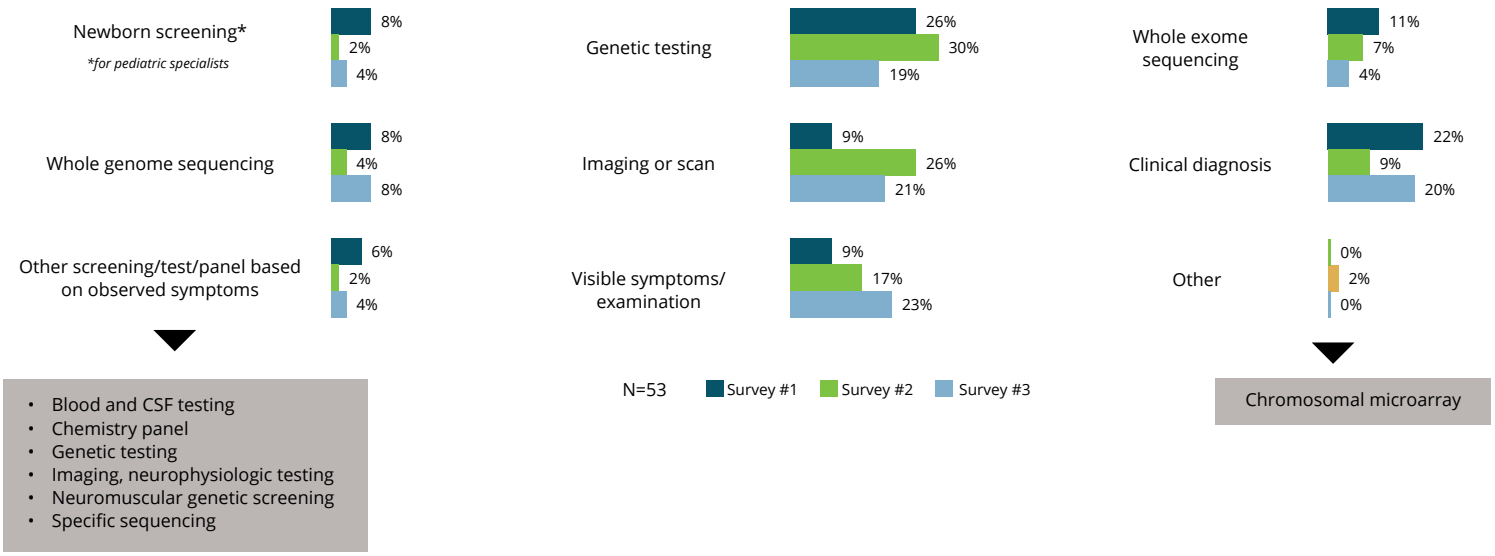

**% of patients with rare disease that you manage are from communities of color**




Responding clinicians and researchers reported that genome and exome sequencing and genetic testing were common methods of conclusive diagnosis. Respondents also indicated, however, that imaging/scans, visible clinical signs, and their own assessments were also major drivers of conclusive diagnosis, perhaps indicative of the demographic composition (74% identified as treating adult patients) of the clinician/researcher cohort. The composition of the group may also explain why newborn screening and other screening panels were reported as a minor contributor to diagnosis.

# Most common methods to conclusive diagnosis

**What are the most common method(s) of conclusive diagnosis for your patients with rare diseases?**

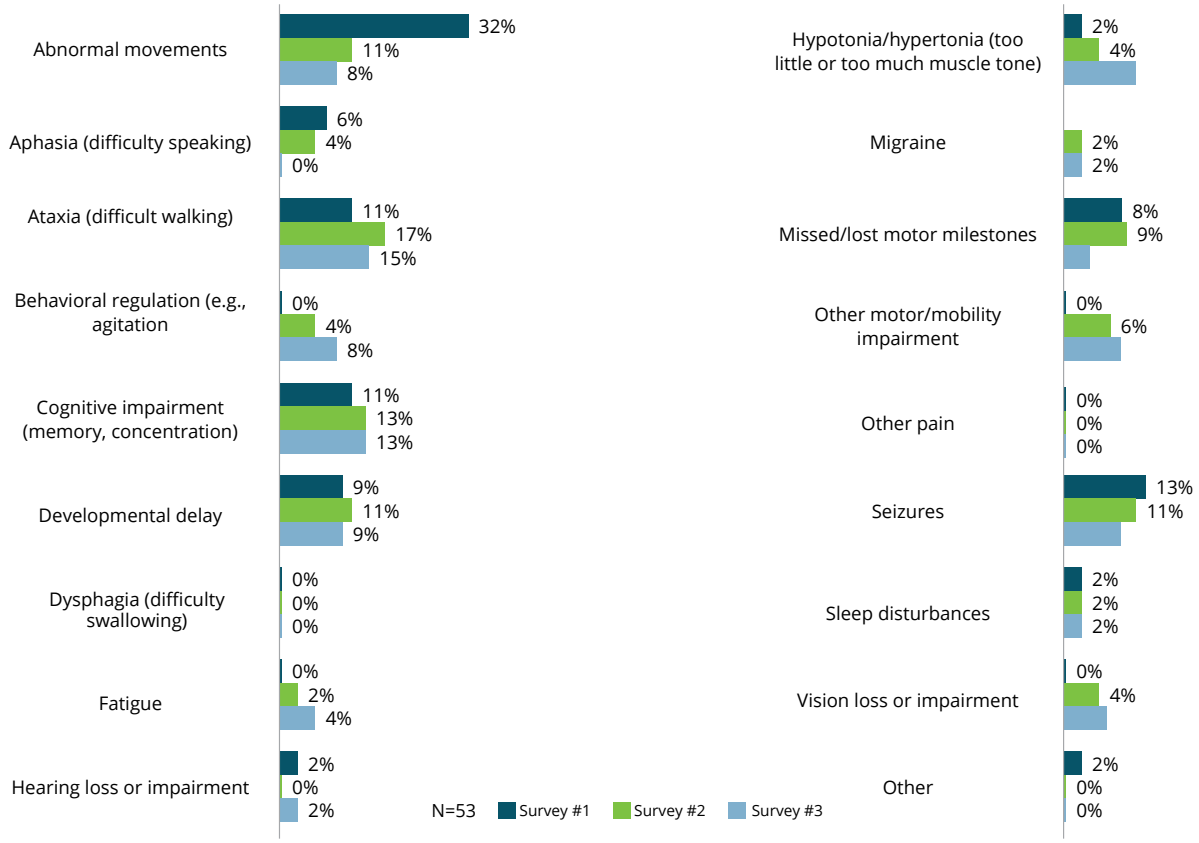



- Blood and CSF testing
- Chemistry panel
- Genetic testing
- Imaging, neurophysiologic testing
- Neuromuscular genetic screening
- Specific sequencing

Chromosomal microarray

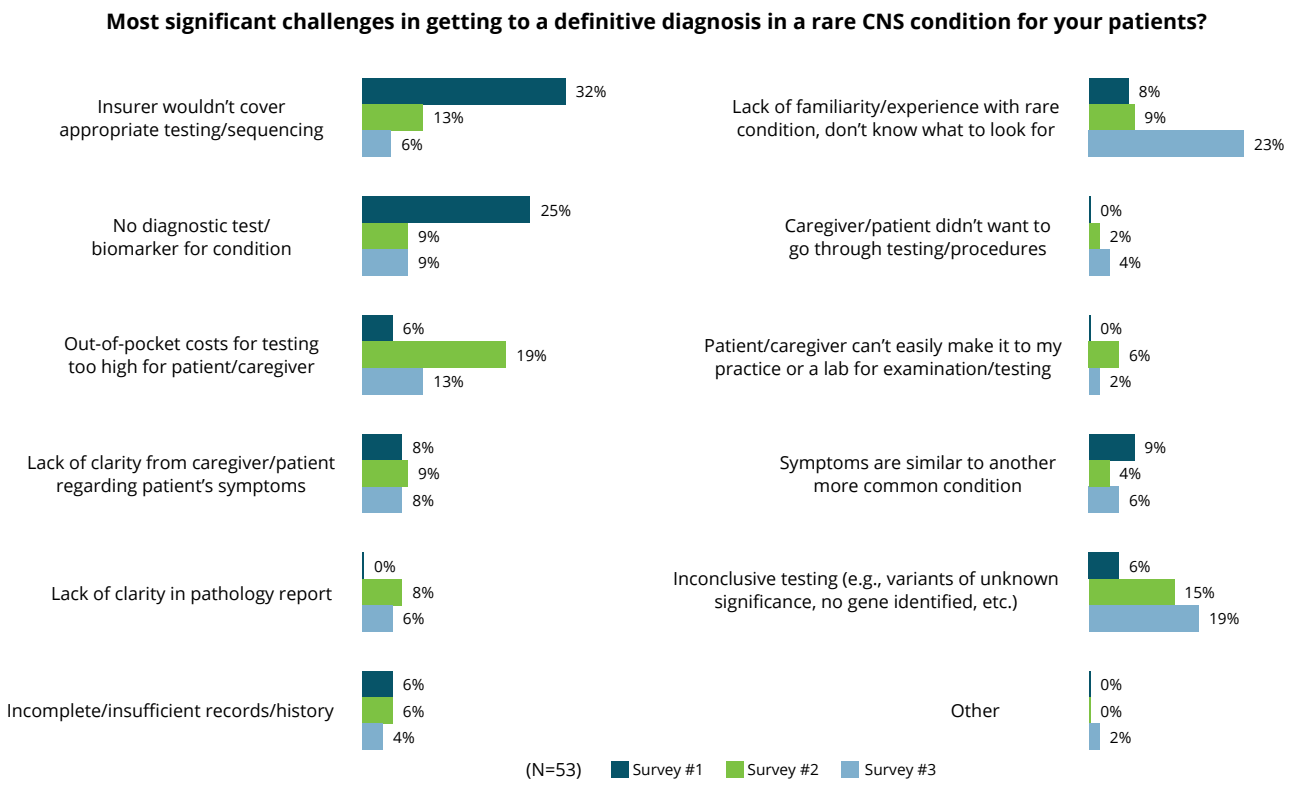
# Signs and symptoms leading to diagnosis

**Signs/symptoms most likely to lead to diagnosis/additional testing in your patients with rare diseases?**




Similarly, respondents indicated that abnormal movements were by far the most common symptom that led to a diagnosis or request for additional testing (whereas developmental delays, missed milestones and seizures–as might be expected among a clinician group predominantly treating children–were reported as relatively minor contributors to diagnosis). Clinicians and researchers also cited lack of insurance coverage for testing/sequencing (32%) and no diagnostic test or biomarker for conditions as significant barriers to definitive diagnosis for their patients.

# Most significant challenges in getting to a definitive diagnosis




### 1.4.2 Workshops

In addition to the pulse surveys, Global Genes developed and conducted three facilitated workshops:

- Workshop 1 - October 21st, 2021; Pediatric Rare CNS
- Workshop 2 - November 4th, 2021; Adult Rare CNS
- Workshop 3 - November 17th, 2021; Health Equity in Rare CNS

| Workshop | Attendees | Participants |
|---|---|---|
| 1 | 30 | Advocates, Clinicians, Researchers, Patients, Caregivers |
| 2 | 23 | Advocates, Clinicians, Researchers, Patients, Caregivers |
| 3 | 30 | Advocates, Clinicians, Researchers, Patients, Caregivers |

The workshops were facilitated by Paul Cooper, CPF, of Face to Face Strategies, an experienced facilitator with a history working with groups focused on CNS disorders and with Global Genes. Workshop participants shared perspectives on patient identification, engagement, and inclusiveness across rare CNS conditions. The activities were designed to explore, assess, and elevate challenges, and pursue and prioritize opportunities to address issues that were most meaningful to participants.

## Exploration of Critical Issues and Barriers

The workshops included opening discussions among workshop participants of what they viewed as the most significant key supporting factors and barriers to effective patient Identification, Inclusion, and Engagement specific to rare pediatric and adult CNS conditions, and to health equity, informed by survey results but also drawing on participants' distinct experiences and perspectives.

Participants were asked to share thoughts on what specific factors or influences from their perspectives were important to either supporting or inhibiting Identification, Engagement, and/or Inclusion in diagnosis, research, and access to treatments and trials in rare CNS disorders.

Responses during the workshops, which were conducted virtually (with exception of the health equity focused workshop, which included in-person attendees in advance of Global Genes' Health Equity Summit in Philadelphia, PA), were captured in real-time (via miro) and are shared below.


# Meeting 1

## Pediatric CNS Disorders


# Meeting 2

## Adult CNS Disorders


# Meeting 3

## Pediatric CNS Disorders

*Note: The relative size of the text above is due to formatting, not reflective of frequency of response. A more detailed summary of the Workshops is included in Addendum B, Section 2 of this report.*

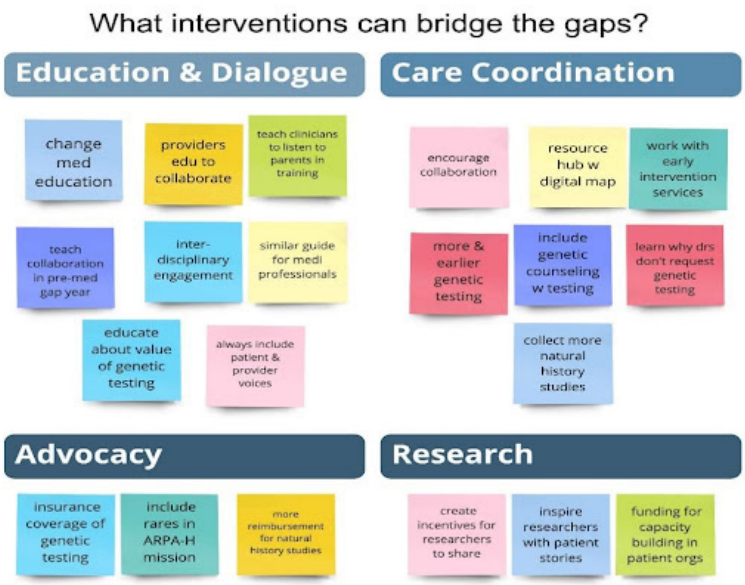
### Exploration of Potential Actionable Interventions

Following the initial discussions of challenges and issues, the participants self-selected to participate in two consecutive break-out groups called "Intervention Cafés" around four potential areas of intervention: ***Education & Dialogue, Care Coordinatio, Advocacy, and Research***, with the opportunity for groups to identify an additional category if one arose during the discussion of challenges.

During the breakouts participants focused on interventions that could help bridge the gap between where they are and where they aspire to be with respect to patient identification, inclusion and engagement, and what potential solutions could be applied in the four intervention areas.

After the breakout sessions the participants reviewed the results from the sessions to find areas of alignment and to pinpoint which interventions resonated most with them. The topline results from the exercise are detailed on the next page.

## Workshop 1: Pediatric CNS Disorders



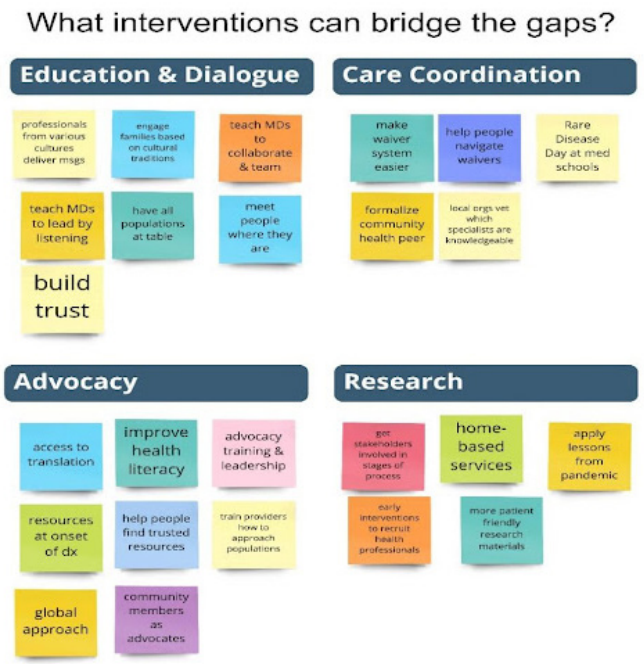

Participants in **Workshop 1 (pediatric)** placed particular emphasis on the need to engage and educate medical professionals, particularly in the earlier stages of their careers and as students, about the experiences of rare disease patients, the challenges and importance of early diagnosis and the value of genetic testing, and to keep them informed of the latest available diagnostic tools. In addition, participants urged more inter-departmental/ disciplinary engagement and coordination, and for the voice of the patient to be more central as a component of diagnostic, research and clinical trial design, and treatment decisions.

There was also consensus around the need for more and earlier genetic testing accompanied by genetic counseling, early intervention services, and the importance of collecting information that can inform and be contributed to natural history studies, with a related objective of incentivizing and reducing barriers that prevent researchers from sharing data. Lastly, there was strong support for multi-stakeholder advocacy to increase coverage of genetic testing and investment in ground-breaking and translational research via initiatives like ARPA-H.

## Workshop 2: Adult CNS Disorders


Participants in **Workshop 2 (adult)** also emphasized the importance of educating medical students and professionals about rare diseases and the experiences of patients and families, and greater coordination and collaboration across medical teams and specialties. There was also a compelling sense among the group of the need to make genetic testing, tools, and expertise more readily accessible and widely available in order to accelerate diagnosis, and for more collaborative research and data-sharing to accelerate progress in disease understanding, diagnosis, and drug development.

### Workshop 3: Health Equity




The participants in **Workshop 3 (health equity)** stressed the importance of recruiting and involving medical professionals from a variety of cultures, backgrounds and communities to engage with patients in diagnosis, research, trial design, and participation; the need to translate and convey educational material and information via trusted sources and channels; to "meet patients where they are" e.g., via community leaders and institutions, and to think more globally about addressing health disparities; and to build cultural competency among medical professions.

The following section provides topline recommendations for action based on the collective input from Pulse Surveys, Workshops and the PIE4CNS Advisory Panel.

## 1.5 Recommendations

The following recommendations are organized according to the categories used to identify and explore potential interventions as part of the Workshops, recognizing that there is some overlap of interventions across categories. Wherever possible, we've also identified existing Global Genes or partner initiatives that could serve as a foundation for immediate progress and collaboration, as the PIE4CNS was specifically designed to stress actionable recommendations that can achieve rapid and meaningful impact.

### 1.5.1 Education & Dialogue

Education & Dialogue was a major topic of discussion across workshops, with an emphasis on helping to get patients/caregivers and clinicians/researchers on the same page in terms of identification and reporting of relevant signs and symptoms, understanding the patient experience (from diverse perspectives), understanding the latest science and importance of genetic testing, providing resources for genetic testing and genetic counseling, working across care teams, and navigating access and coverage.

#### Key Interventions & Recommended Actions:

- **Conduct Annual PIE4CNS Summit or Symposium**. Potentially in conjunction with a neurological professional society (e.g. CNS, AAN) or scientific meeting (rotating annually) that brings together multi-disciplinary professionals and researchers with patient/caregivers and advocates to discuss key topics including:
  - » **Experience Matters**: understanding how unique aspects of the rare disease experience can influence diagnosis, identification, and inclusion in research and care
  - » **Finding a Common Language**: Working together to develop a lexicon of symptom descriptions and other tools to help ensure consistency and relevance to diagnosis
  - » **Functioning in a Rare Disease Care Team**: learning to work with other professionals is critical to improving rare disease diagnosis, care, and outcomes
  - » **Advanced Science, Tools, and Applications**: exploring the latest diagnostic tools and analytic capabilities to support rare CNS condition diagnosis

- **Adapt/Develop/Launch Experiential Medical Education Programs**, bringing medical students together with rare disease patients/families to improve awareness of the rare disease experience and related diagnostic and access challenges, potentially including:
    - » **Adapt and expand Global Genes' Rare Compassion program**, which pairs rare disease families with medical students to build understanding and attract students to rare disease focused careers, and incorporate into curricula, CME/CPD.
    - » **Develop Virtual Grand Rounds initiative**, in partnership with professional societies and/or leading centers of excellence, to share diagnostic odysseys and case histories of participating patients and families w/various health care agencies.
    - » **Work with the Rare Disease Diversity Coalition and other organizations** and families/ clinicians/ researchers from diverse backgrounds to emphasize unique challenges of minoritized populations and patients from various regions globally, and to engage HBCUs and medical centers and clinics representing diverse communities.

- **Create, Launch, and Amplify a Multi-Channel Storytelling Initiative**, leveraging stories generated from experiential education (including the above) and other ongoing content generated by patients, clinicians, and researchers, to illustrate challenges, experiences, and learnings from rare CNS conditions, with elements including:
    - » Leverage Global Genes' RAREly Told Stories short film-making partnership with the Disorder Channel and other partner initiatives and content to create, translate, and expand a base of content to be disseminated via social channels and/or partner websites to support awareness and education. (Note: RAREly Told Stories 3-5 minute films were developed by participants in Global Genes' Rare Compassion Program in 2021 as part of a pilot initiative, along with instructional film-making content available through our Resource Hub.)
    - » Adapt and disseminate content to be generated as part of a pilot Family Health History initiative in conjunction with the Rare Disease Diversity Coalition to emphasize unique challenges in diagnosis, identification, and inclusion of rare disease patients from communities of color based on lack of documentation of relevant medical histories in families, and hesitancy to participate in genetic testing and/or broader implications associated with bias or mistrust of medical systems.
    - » Launch a distinctive TikTok or other social platform/influencer-driven initiative specifically designed to reach adolescent and young adult patients and to address distinct disparities or challenges faced in getting to a diagnosis, access to testing, etc., to support both advocacy and educational efforts through patient advocacy organizations.

### 1.5.2 Care Coordination

Care Coordination was also an area of considerable discussion and frustration among participants, including with the lack of case management/navigation/genetic counseling resources, difficulty in accessing, collecting, managing, and sharing relevant medical information with care teams, lack of access to and clear explanations of genetic testing, whole genome/exome sequencing or other diagnostic options, and difficulties in finding and getting to or seen by relevant specialists. Also noted were the challenges of transition from pediatric to adolescent/adult care.

#### Key Interventions

- **Provide easily accessible navigation services** for patients and caregivers to guide users to resources (supported or made available via PIE4CNS partners), based on priority needs identified through the PIE4CNS initiative, where they are in their rare disease journey, etc.
    - » Enhance/expand/scale Global Genes' existing RARE Concierge service and partner with other service and support providers to provide navigation and access to case management, genetic counseling, and other critical services, globally where possible .

*Note: RARE Concierge was established in 2016 and has partnered with GARD and others, receiving referrals from a number of institutions, and is in the process of investing in new platform technology to increase our ability to efficiently capture process and triage requests, and is exploring several partnerships to add offerings around financial support, genetic counseling, and other support services.*

  - » Build partnerships with major health plans, health systems, testing labs, and other non-profits that provide financial assistance or other forms of support to further expand offerings

- **Increase access to digital tools** for rare disease caregivers and patients that can address some of the unique challenges associated with coordinating care for rare CNS disorders, capturing symptoms and experiences, sharing cohesive information relevant to diagnosis with care teams, and contributing data to natural history studies or registries, with translation to address language barriers and obstacles in conveying information to clinicians.
  - » Adapt/Launch PHI tool (in development) with capabilities to capture relevant information on CNS disorder signs and symptoms using consistent terminology and allowing for video capture and translation, experiences, medical history, etc. (in a GDPR/HIPPA compliant manner), providing patients/caregivers the ability to capture and share information with their care teams, feed data into diagnostic decision support/ analytics tools, and/or (with their full control and consent) to contribute data to support natural history studies, registries, or other research efforts
  - » Provide educational content and sessions at Global Genes and partner events and through our RARE Portal for caregivers/patients, clinicians, and researchers to learn about PHI, data governance and privacy, and discuss information and data needs relevant to earlier and more accurate diagnosis of rare CNS conditions

- **Provide broader, more inclusive access to testing, genetic counseling, and related services** globally, tied to educational efforts described above and with the ability to transfer/include analysis and testing results to a personal health information management tool (e.g., as described above) and with proper consent to contribute data to support research efforts with their rare disease community or across rare diseases (e.g., via the RARE-X collaboration described below).
  - » **Launch pilot program** (in development) **to provide testing/ sequencing** and related education and genetic counseling to patients, at no or very low cost to them across a select range of global markets.
  - » **Create a consortium to expand access to affordable or free testing and sequencing** tying into partners' initiatives where possible (e.g., CNF's efforts with illumina) to avoid duplication and allow for more rapid scaling up of efforts and reach around the world, with agreements for data to be contributed back to the effort and to patient communities for research purposes.
  - » **Provide educational content and sessions at Global Genes and partner events** and through our RARE Portal for caregivers/patients, clinicians, and researchers to learn about genetic testing and relevance to diagnosis, advancements in gene-based diagnostics and therapies, coverage and access to testing/ sequencing and other relevant topics.

### 1.5.3 Advocacy

Global Genes' primary focus is on supporting individual patients and caregivers to take positive next steps toward diagnosis, support, or treatment and build advocates' and patient communities' knowledge and capacity to drive innovation and progress in rare disease. We work collaboratively with other non-profits focused in advocacy to bring the patient perspective to the forefront in policy discussions and help educate policymakers and influencers on the experience of rare disease patients and the potential implications of policy on innovation and access to treatment. As a result, we approach advocacy interventions with an eye toward where we can best play a supportive role to other organizations.

### Key Interventions

- **Continue to support and equip rare disease patients, families and advocates to participate in efforts to inform policymakers** about the unique needs of the rare disease community and the urgency and importance of continued innovation and broader access to testing and treatment
    - » **Adapt and provide stories, data, and content** from PIE4CNS efforts described above to support partners' advocacy efforts in support of rare disease-relevant policies and government initiatives (e.g., ARPA-H, Cures 2.0 in the U.S.)
    - » **Invite policymakers and influencers to participate in an annual PIE4CNS Summit** (described above) and/or other partner or Global Genes events to ensure the patient voice is consistently heard and considered as policies are developed
- **Elevate needs of minoritized populations in rare disease,** drawing on Global Genes' partnership with the Rare Disease Diversity Coalition in the U.S. and other advocacy groups and patient communities globally
    - » **Develop content, data and evidence to share with policymakers** that more specifically illuminates the unique challenges for patients and caregivers from diverse and underserved communities seeking or facing a rare disease diagnosis or access to testing, trials, or treatment (drawing on initiatives described above as well as other partners' EDI programs)

#### 1.5.4 Research

As an organization representing patients, caregivers, and advocates spanning more than 8,000 rare diseases, Global Genes focuses on efforts that can empower and equip more communities to drive and participate in research leading toward improved and accelerated diagnosis and development of treatments.

Increasingly, we see patients asserting themselves as partners in driving innovation–empowered by increased knowledge of advancing science and technologies, new pathways for collaborative drug development, and improved capacity and expertise as data stewards. These new approaches and capabilities are particularly relevant and vital to advance progress in diagnosis and treatment of rare CNS disorders, as the insights above and recommended interventions from PIE4CNS outlined below reflect.

### Key Interventions

- **Expand development of/access to resources for collaborative research and data sharing,** with the understanding that lack of access to patient data and medical histories is a major barrier to more effective and early diagnosis, as well as drug discovery and development for rare CNS disorders
    - » **Form a Rare CNS Open Research Working Group or Network** that would help to build consensus around data standards, registry and trial design, and inform development of collaborative, cross-disease data collection, sharing, and analysis for rare CNS disorders
    - » **Drive increased and inclusive participation in patient-directed, non-profit, open data collection, analysis, and sharing platforms** (e.g., RARE-X) by educating potential users, lowering barriers to access for underserved communities, build awareness, and enlisting large numbers from diverse patient communities to participate and contribute data from efforts described above

*Note that Global Genes has formed a partnership with RARE-X to provide the more than 800 rare disease groups that are part of our Global Advocacy Alliance with education and equitable access to the platform for data collection or to analyze existing registry data alongside other relevant data sets, and is working with the IT provider that developed the RARE-X Data Collection Portal platform to develop our PHI tool (helping to ensure that symptom descriptions and other data elements are consistent and contributed data can be better used to support research when contributed by participating patients).*

### 1.6 Next Steps Toward Phase II (Taking Action) of PIE4CNS

1. Reconvene Advisory Panel to review findings and recommendations and agree on proposed areas of focus and action (February)
2. Approach potential partners and funders for Phase II (February)
3. Convene PIE4CNS stakeholders at WORLD (assuming in-person) to network, discuss and build support for Phase II initiatives (February 9)
4. Secure partners and funding for Phase II (February-March)
5. Confirm Advisory Panel members for Phase II (March)
6. Conduct Phase II multi-stakeholder kick-off meeting (April)
7. Initiate Phase II programs (April)

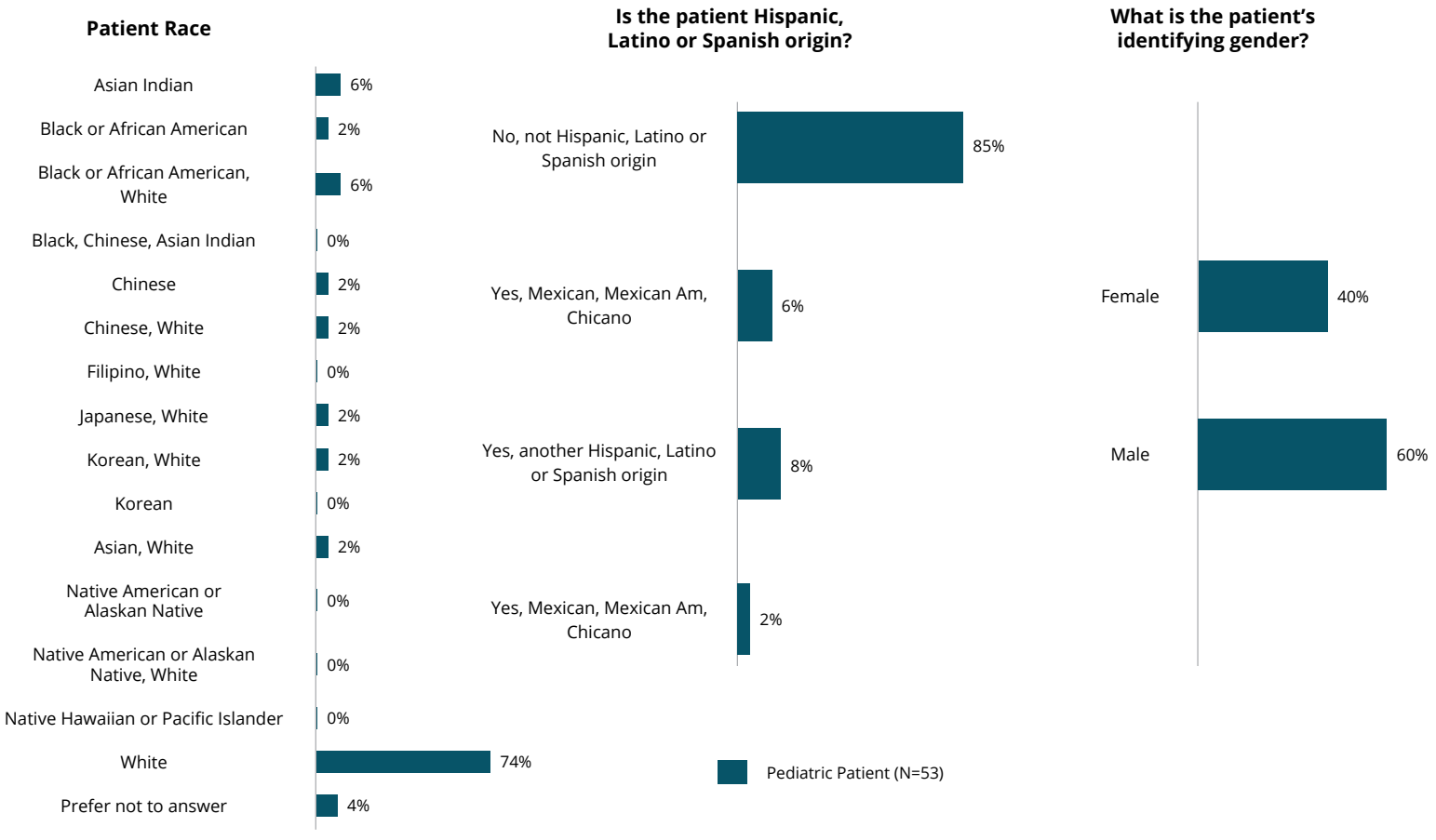
# Addendum A: PIE4CNS Survey Findings

## 2. Survey Background

Global Genes Patient Identification, Inclusion & Engagement for Rare Central Nervous System Conditions (PIE4CNS) initiative led to the dissemination of a pulse survey in September 2021 to patients, caregivers, and clinicians. The survey data was collected to inform this multi-stakeholder initiative, being led by Global Genes and other partners to identify and take action on critical needs. The survey results include insights from patients/caregivers and clinicians about the most critical issues affecting inclusive, timely, and accurate diagnosis and identification of patients with rare CNS conditions, and their involvement in research and care. Summarized here are key findings from the pediatric and adult focused surveys of patient caregivers, clinicians, and researchers.

### 2.1 Survey Key Findings and Insights - Pediatric Patient Caregiver

Respondent: Pediatric Patient Caregiver n=53, approximately 40 unique diagnoses represented, (patient demographics = 74% white, 85% not of Hispanic, Latino or Spanish Origin, 60% male/40% female)



- Physicians who gave the diagnosis were usually a Pediatric Neurologist (45%) or a Pediatric Geneticist (43%), and less often, another doctor (10%), or the Pediatrician (2%).
- Average patient age at time of diagnosis is 35 months.
- Time period between patient's onset of symptoms and time of diagnosis: 1-2 years (38%), <1 year (36%), 3-5 years (19%), 6-9 yrs (2%), 10+ yrs (2%); undiagnosed (4%).
    - » Majority indicated 2 years or less (74%) with 4% indicating undiagnosed.
- Commonly reported initial signs/symptoms that led to the diagnosis: Developmental Delay (76%), Hypotonia/ hypertonia (66%), Seizures (42%), abnormal Movements (42%), Cognitive Impairment (26%), Missed/lost motor milestones (55%), Sleep disturbance (30%), Other motor/mobility impairments (28%), Dysphagia/difficulty swallowing (25%), Behavioral Regulation (25%), Ataxia/difficulty walking (25%), Other (23%), Aphasia/difficulty speaking (23%), Vision loss or impairment (21%), Fatigue (17%), Other Pain (4%), Hearing Loss or Impairment (2%), and Migraine (2%)

**What is the diagnosis (if known) of patient?**

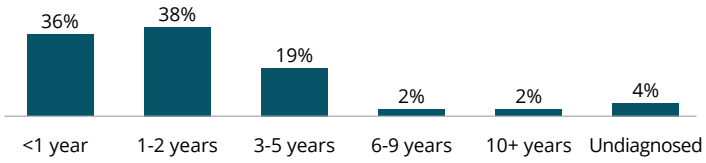
- 17p12 deletion, HNPP, Autonomic Dysfunction, epilepsy, gastroparesis, sensory processing disorder
- Angelman Syndrome (3)
- ASH1L related disorder
- Aicardi-Goutières Syndrome
- BBSOAS (mutation of the NR2F1 gene)
- BPAN (3)
- Cabezas Syndrome
- CACNA1A-related congenital ataxia
- Charcot Marie Tooth 2A
- Chromosome abnormalities
- CLN2 Batten disease
- Creatine Transporter Deficiency
- Dup15q (4)
- FOXG1 Syndrome
- Fragile X, and Lennox-Gastaut Syndrome
- GDD, no proper diagnosis has been made
- Generalized dystonia
- GRIN Disorder (2)
- KCNA2 Epileptic Encephalopathy
- Koolen-de Vries Syndrome
- Leigh Syndrome
- Lennox Gastaut Syndrome (2)
- Lessel-Kreienkamp (Ago2 gene), West syndrome
- longitudinally extensive transverse myelitis
- NEDAMSS/ IRF2BPL Disorder
- Nijmegen breakage syndrome
- Noonan Syndrome
- NTNG2 syndrome
- Rett Syndrome
- SCN2A related disorder (2), SCN8A-DEE
- Shwachman-Diamond Syndrome
- Skraban Deardorff Syndrome
- Smith Kingsmore Syndrome
- SMA
- SynGap encephalopathy
- Tethered cord syndrome, spina bifida, syringomyelia
- Tuba 1a pathogenic variant
- Unknown (2)
- Unspecified Leukodystrophy

## Patient Diagnosis History

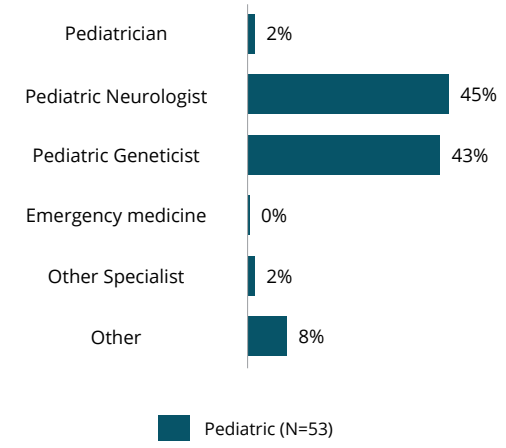
**Age at time of diagnosis (mean)**

**Pediatric 35 months**

**Please select the time period between the patient's onset of symptoms to their formal diagnosis.**



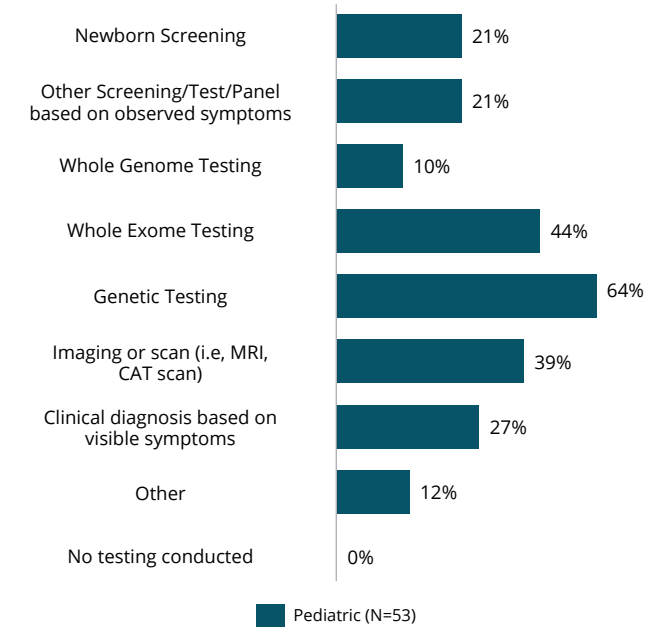

**What type of physician gave the patient their formal diagnosis?**



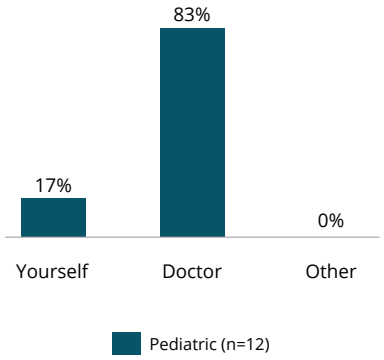

### Testing (n=11)

- Tests that were conducted to receive a diagnosis include: genetic testing, whole exome testing, imaging/scan, clinical diagnosis based on visible symptoms, newborn screening, and other screening tests/panels
- 83% reported that the doctor requested the screening/test/ or panel, and 17% requested it themselves (on behalf of the patient).

**What types of testing were conducted to receive a diagnosis?**




**Who requested the screening/test/panel?**

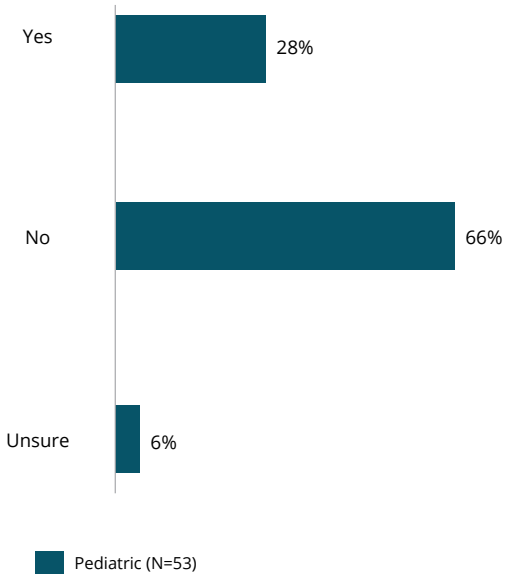



### Additional Testing (n=52)

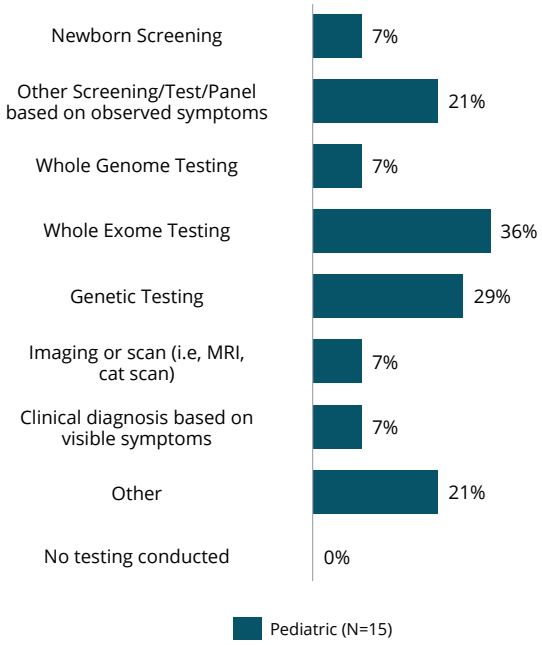
- 28% reported that additional testing was needed for a conclusive diagnosis (66% said no, and 6% were unsure).
  - » Of the 28% (n=15) that indicated additional testing was required, testing included: whole genome testing, whole exome testing, genetic testing, imaging/scans, and other

## Additional testing for a conclusive diagnosis

**Was there additional testing needed for a conclusive diagnosis?**

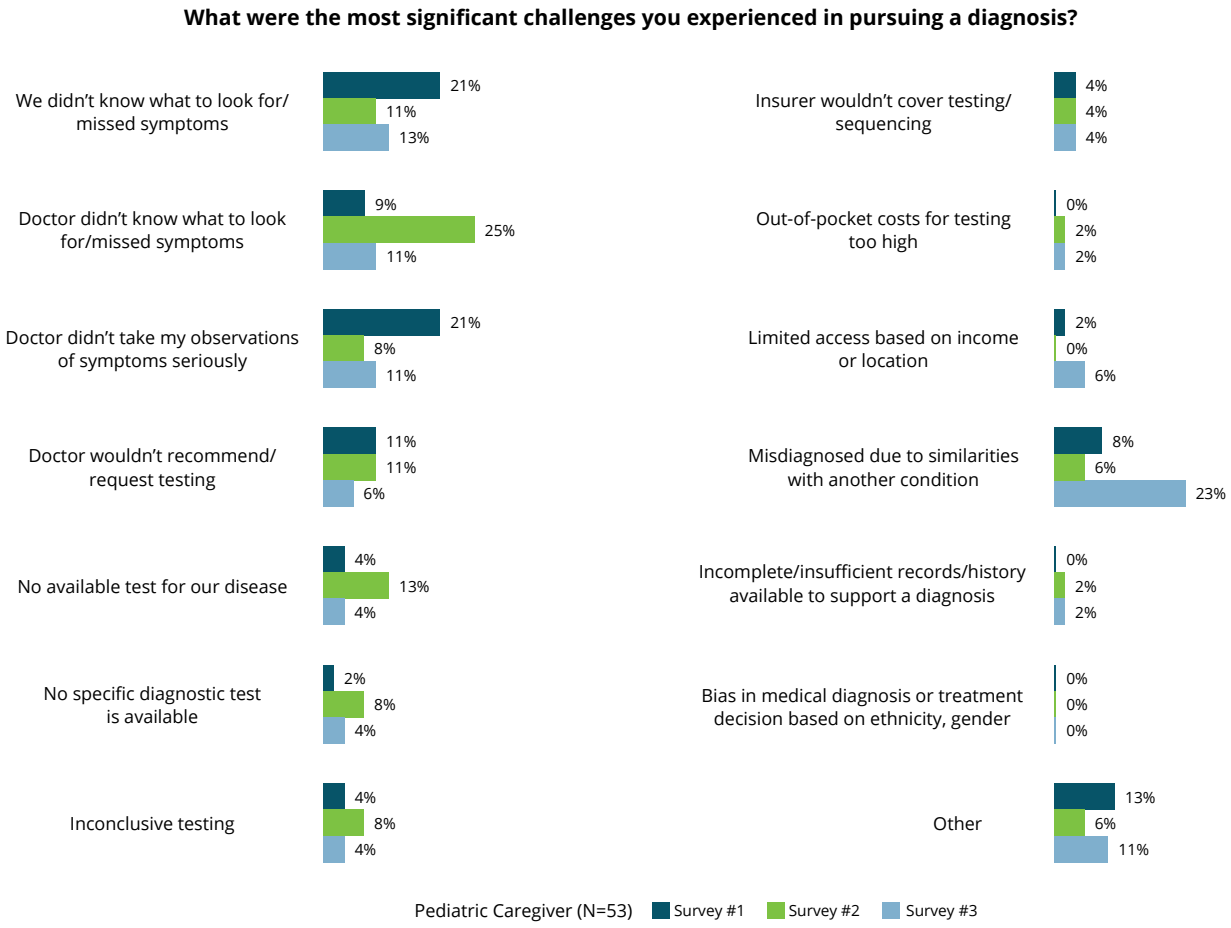



**What types of testing were conducted to receive a diagnosis?**



**Diagnostic Challenges (n=52)**

- Pediatric caregivers noted challenges experienced in pursuing a diagnosis: including not knowing what to look for/ missed symptoms, the doctor not knowing what to look for, doctor not taking patient's observations of symptoms seriously, doctor not recommending testing, no available tests for the disease, limited access based on income/ location, inconclusive testing, lack of coverage from insurer, or misdiagnosis due to similarities with another condition. Other reasons include conditions recently discovered, lengthy procedures, and disease not yet included in a panel.

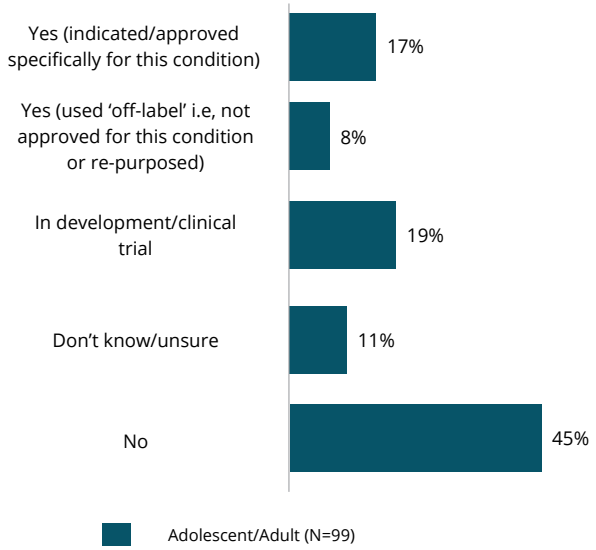



**Treatment Availability (n=53)**

- While 17% indicated that there are one or more available treatments for the disease/condition, 45% indicated there are no available treatments, 19% in development/clinical trial stage, 11% don't know/unsure, 8% used off-label or repurposed drugs.
- Of the 17% who indicated that there are one or more available treatments for the disease/condition, 62% (n=13) of these available treatments are to manage symptoms (supportive care) and 38% to treat the condition

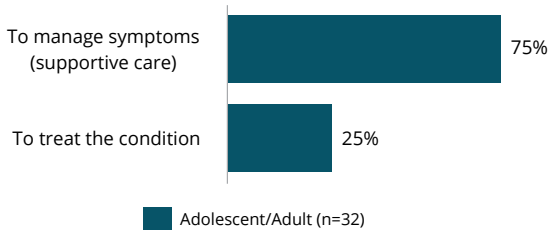
# Treatment Availability

**Was there additional testing needed for a conclusive diagnosis?**




- Off label treatments, and surgeries typically cause more harm than good.
- Eat Chinese traditional medicine
- Lithium but very dangerous side affects and doesn't work with over 60% of Kleine-Levin syndrome patients
- Deep brain stimulation
- Jak-inhibitors

**What types of testing were conducted to receive a diagnosis?**




**What is/are the available treatment(s) for?**

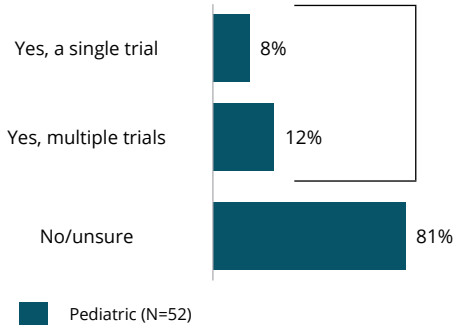
- Surgical revascularization
- Solaris, Uplinza
- Pediatric Neurologist
- Neurology
- Medication, implantable devices, neurosurgery
- Ketogenic diet
- Hormone therapy
- Glucocorticoid
- Fintepla, Epidiolex stiripentol
- Epidiolex
- Decompression and laminectomy surgery
- Brain bypass surgery
- Beta blockers, calcium channel blockers, diuretics, ICD/pacemaker
- Anticonvulsive
- Anakinra (kineret)

**Clinical Trials (n=53)**

- 11% have multiple active clinical trials available, 8% have a single trial, and 81% have no trial or are unsure.
  - » Of those who were not aware of an active trial or unsure, most searched for clinical trial information on Google/Facebook/social media, or clinicaltrials.gov, asking the hospital or doctor, or looking to a rare foundation.
- Select clinical trial experience feedback from pediatric caregivers includes:
  - » benefits:
    - fast treatment
    - good service
  - » barriers/challenges:
    - patient is too far past onset for inclusion criteria
    - patient is not of age and trial is not yet recruiting
    - our son was not eligible for this clinical trial when it opened in 2013

# Clinical Trials for Disease

**Is there an active clinical trial or multiple trials in your disease area?**




**Describe the area of study/study details**

Pediatric Caregiver

- The trial is for a type of gene therapy
- Neurology
- Mice study on all variant of the gene mutation, but mainly only on circadian issue.
- New SCN8A specific sodium channel blocker; trials now just for ages 12-21

**Are you/did you participate in the trial?**

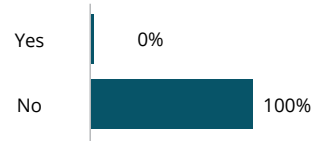

**Is it a gene therapy trial?**


**Do you know who is sponsoring the trial?**


Pediatric Caregiver

- CAPTURE
- BioMarin – ERT
- UTexasSouthwestern

**Did you have access to this trial**




Pediatric Caregiver

- Time past onset/too far progressed (2)
- Did not meet study criteria due to age (2)

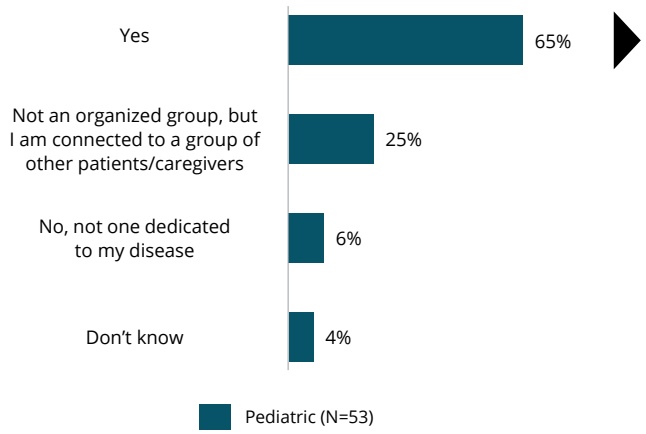
Pediatric (N=8)

## Patient Advocacy Groups (n=52)

- 66% noted that there is a patient advocacy/support group in their disease community, 24% did not have an organized group but were connected to groups of other patients/caregivers, 6% noted there is not one dedicated to their disease, and 4% did not know if there is one
  - » Of the 66% who have a patient advocacy group, 91% shared that they were actively involved with the group
    - Support groups helped pediatric caregivers with the doctor/specialist (59%), available treatment (35%), clinical trials (27%), and none of the above (32%)
  - » Of the 24% who do not have an organized group but are in contact with other patients/caregivers, Facebook and social media were listed as ways they are connected

# Patient Advocacy Groups

**Is there a patient advocacy/support group/ groups in your disease community?**




**Please list the patient/support group/groups that you are aware of in your disease community.**

**Pediatric Caregiver**

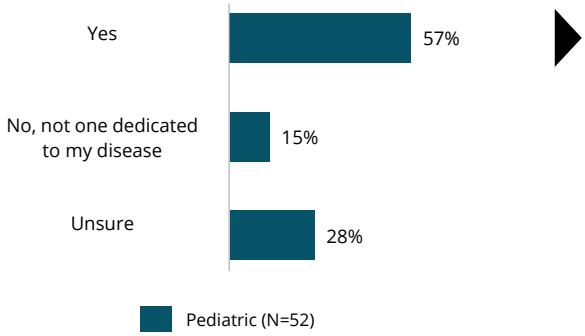
- There is a big Facebook support group (used to be impartial but now is strongly biased toward one particular organization, and so I don't feel welcome)
- Siegel Rare Neuroimmune Association
- NR2F1 Foundation, BBSOAS parent only fb group
- Noah's Hope-Hope 4 Bridget (ours), BDSRA, BDFA, BDSRA Australia
- LGS private Facebook
- LGS Foundation
- Koolen-de Vries Syndrome Foundation
- KCNA2 Epilepsy Inc.
- HNF, CMTRF
- GRIN2B Foundation, Cure GRIN Foundation
- Generic Leukodystrophy FB groups, Cerebral Palsy FB Groups, United Leukodystrophy Foundation
- FOXG1Foundation, International FOXG1 Foundation
- FAST, ASF
- FamilieSCN2A Foundation
- Dup15q Alliance (3)
- CureGRIN Foundation, GRIN2B Foundation
- Cure SMA, Fight for Kaiden Foundation, Gwendolyn Strong Foundation
- Cure Mito Foundation, Cure SURF1 Foundation
- Cabezas Syndrome Family group on FB
- BPAN Warriors, Autour DuBPAN, BPAN France, NBIA Alliance, NBIA Disorders Association, Don't Forget Morgan
- Angelman Syndrome Foundation
- AGO2 Association
- IRF2BPL Foundation, StandbyEli, IRF2BPL FB group
- Smith Kingsmore Syndrome Foundation
- International SCN8A Alliance; Wishes for Elliott - Advancing SCN8A Research, Shay Emma Hammer Research Foundation
- CACNA1A Foundation -Care4ASH1L
- SynGap Research Fund

**Patient Registry (n=53)**

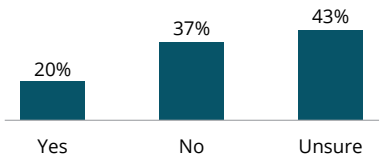
- 57% stated there is a patient registry available for their disease/condition, 28% are unsure, and 15% said there is not one dedicated to their disease.
  - » Of the 57% that stated that there is a patient registry available for their disease/condition, the group managing/recruiting for the registry includes: nonprofit organization (57%), academic institution/ primary investigator (33%), Other (7%), and NIH or government sponsored (3%)
    - Pediatric caregivers were asked if their involvement in the registry was helpful in getting them involved in the clinical trial: Yes (20%), No (37%), and Unsure (43%)
  - » Of the 15% who indicated there is not a patient registry dedicated to their disease, 25% indicated there is a broader registry they are participating in (75% - no)

# Patient Registry

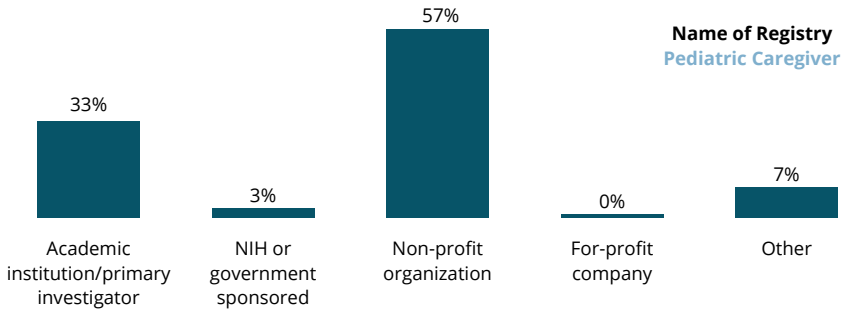
**Is there a patient registry in your disease/condition?**




**Was your involvement in the registry helpful in getting you involved in a clinical trial?**




**Who is managing/recruiting for the registry?**




**Name of Registry**

**Pediatric Caregiver**

- Uniform Batten Disease Registry and DEM-Child
- The Global FOXG1 Patient Registry
- SRNA Registry
- SCN2A Clinical Trial Readiness Study
- NBS registry
- LADDER DATABASE
- It's in progress with Matrix
- International SCN8A Registry
- GRIN Variant Patient Registry (2)
- Genida
- CreatineInfo Patient Registry
- Ciitizen SynGap registry
- CACNA1A Natural History Study through the Chung Lab
- NBIA Alliance/TIRCON NBIA International Registry, BPAN Warriors BPAN Digital NHS/ Registry, RARE-X
- BPAN Ready (3)
- AllStripes and CoRDS

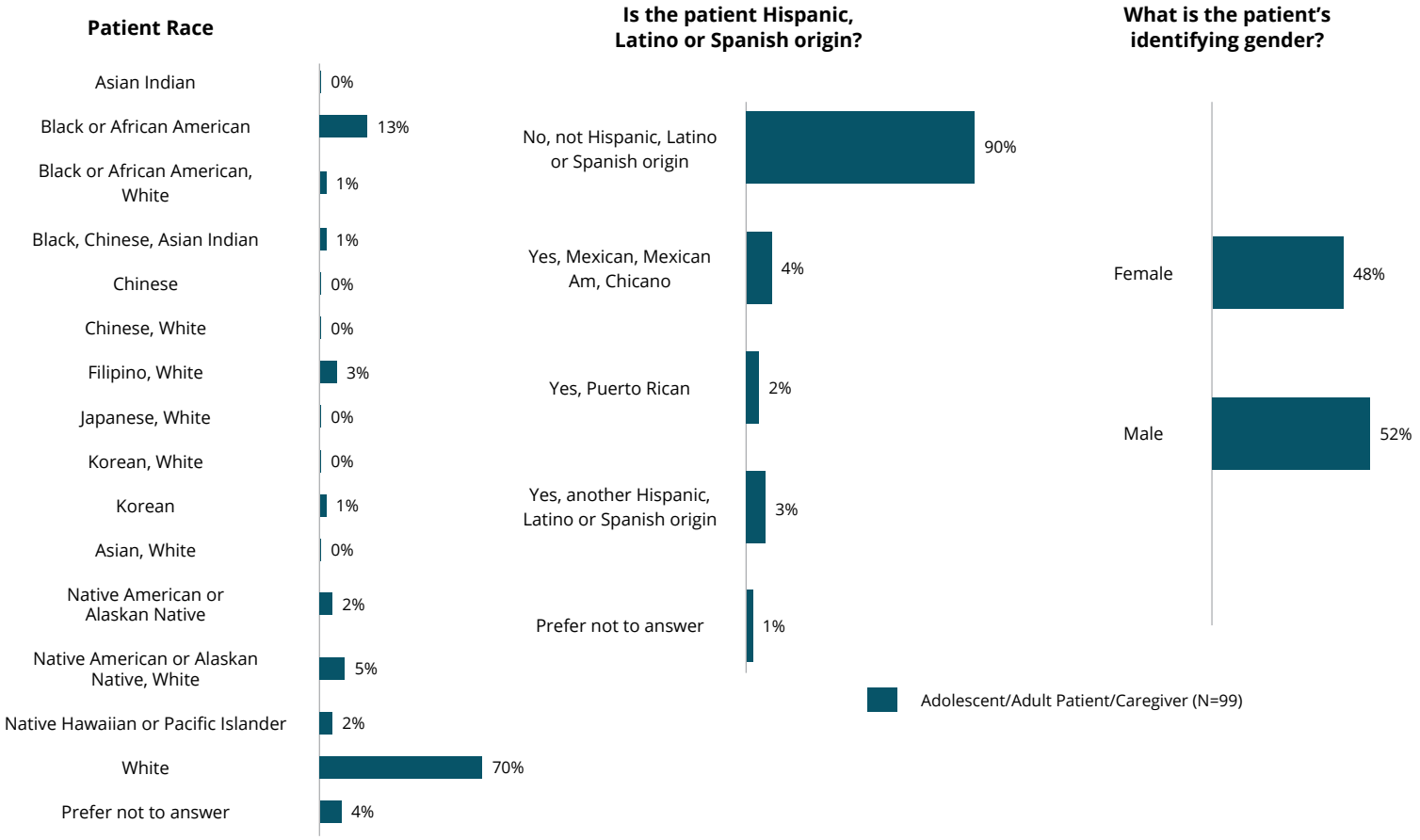
Pediatric (n=30)

## 2.2 Survey Key Findings and Insights - Adult/Adolescent Patient/Caregiver

### 2.2.1 Respondent: Adult/Adolescent Patient/Caregiver

Average age at time of diagnosis: 21 years, n=99; approx. 40 unique diagnoses represented; patient demographics = 70% white, 13% Black or African American, 3% Filipino/White, Native American or Alaskan Native/White 5%, Native Hawaiian or Pacific Islander 2%, Korean 1%; 52% male/48% female.

## Patient Demographics




**Diagnosis (n=99)**

- Physicians who gave the diagnosis were usually a Neurologist (35%) or a Geneticist (17%), Pediatric Neurologist (16%), Other Specialist (17%), General Practitioner/internal medicine (9%) and less often, another doctor (4%), or the Emergency Medicine (1%).
    - » Other specialties include: Rheumatologist, Pediatric Epileptologist, Orthopedist, NIH Undiagnosed Diseases Network (UDN), Neurosurgeon, Neurointerventional Radiologist, Developmental Pediatrician, and Hematologist.

# Patient Diagnosis History

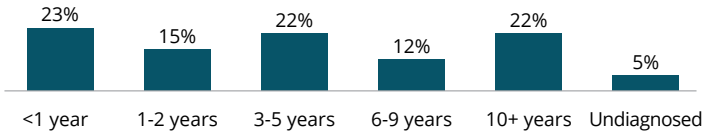
**What is the diagnosis (if known) of patient?**

- Angelman Syndrome (2)
- Addison Disease
- Anderson Twail Syndrome
- Ataxia Pancytopenia
- Arachnoiditis (3)
- Autism then MED13 mutation
- Bulbar ALS
- Cauda Equina Syndrome
- Cadasil (2)
- Central Pain Syndrome
- Demyelinating disease of the CNS
- Dravet syndrome (7)
- Dup15q Syndrome (5)
- Dystonia-27
- EEF1A2 gene mutation
- Epilepsy
- FAM177A1
- FOXP1 Syndrome
- Glut1 Deficiency
- Inclusion Body Myopathy
- Jouberts Syndrome and Congenital Central Hypoventilation Syndrome
- Kleine-Levin syndrome
- Lennox Gastaut Syndrome (2)
- Lessel-Kreienkamp syndrome
- Lgs, cp, cvi, non verbal
- Neuropatia
- NOMID
- Other (5)
- Phelan McDermid Syndrome (3)
- PMSF
- Rasmussen encephalitis
- Ring14 Syndrome - Ring Chromosome 14
- Sanfilippo Syndrome (MPSIIIB)
- SCn2A
- seizure disorder
- SMEI, exotic deletion 25-26
- Tarlov Cyst
- Unknown/undiagnosed (6)
- WHS, Lissencephaly, Agenesis of Corpus Collosum, Cerebral Palsy

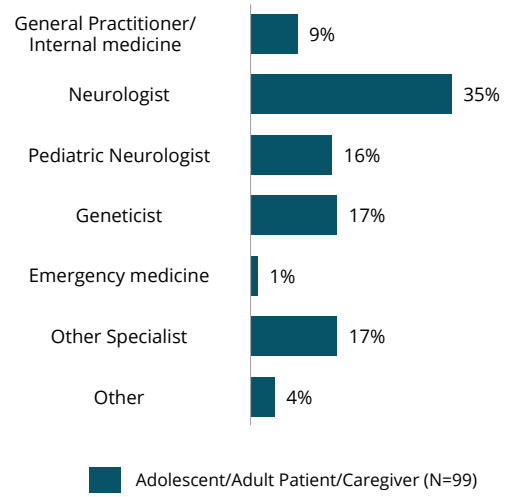
**Age at time of diagnosis (mean)**

**Adolescent/Adult 22 years**

**Please select the time period between the patient's onset of symptoms to their formal diagnosis.**




**What type of physician gave the patient their formal diagnosis?**

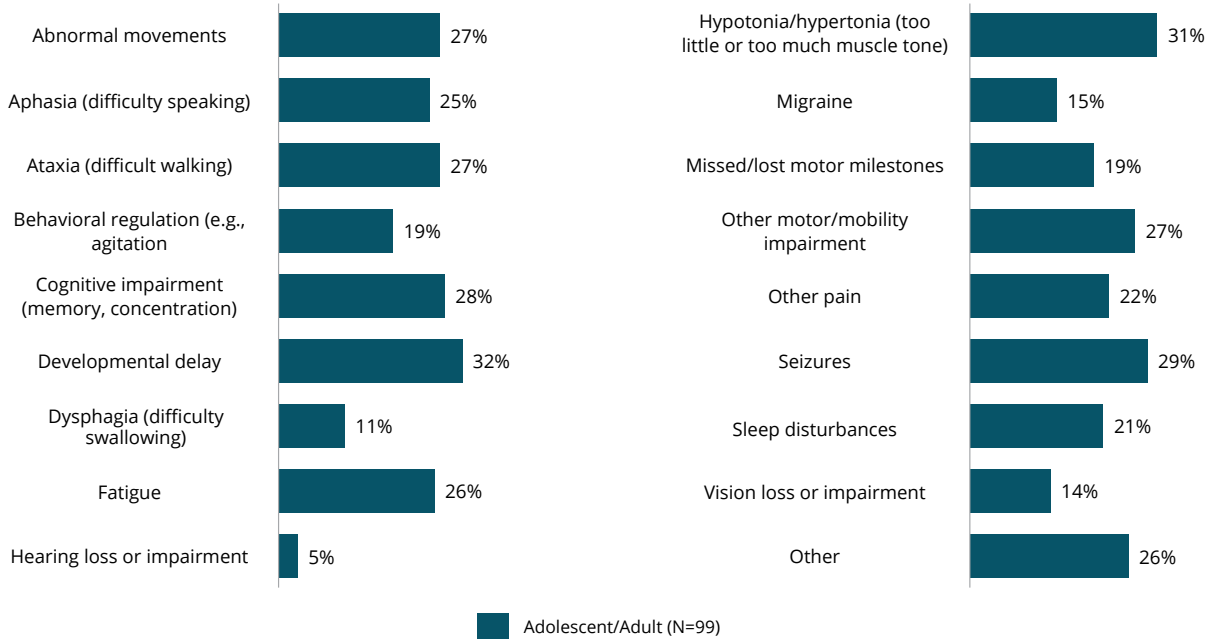



## Diagnosis (n=99)

- Average patient age at time of diagnosis is 22 years.
- Commonly reported initial signs/symptoms that led to the diagnosis: Developmental Delay (32%), Hypotonia/ hypertonia (31%), Seizures (29%), Cognitive Impairment (28%), Abnormal movements (27%) Ataxia (27%), Fatigue (26%), Aphasia (25%), Other (26%), Other motor/mobility impairment (27%), Sleep Disturbances (21%), Behavioral Regulation (19%), Other Pain (22%), Migraine (15%), and Vision Loss or Impairment (14%)
    - » Other signs/symptoms include: cutaneous lesions, nausea and vomiting, neuropsychiatric illness, hallucinations, gait pattern, numbness, spasticity, altered sensations, among others.

# Signs and symptoms leading to diagnosis

**What were the patient's initial signs/symptoms that led to a diagnosis**

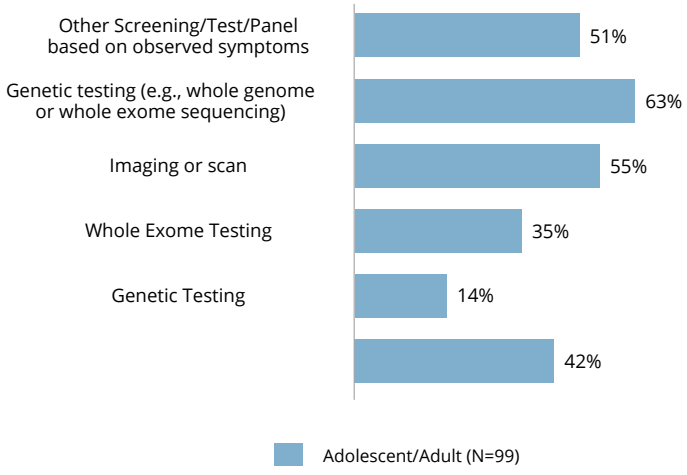



**Testing (n=99)**

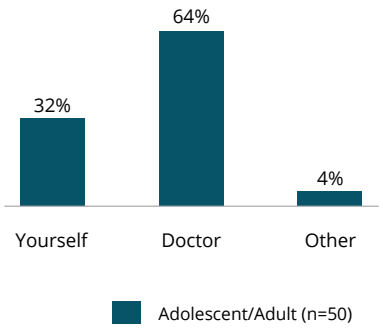
- Tests that were conducted to receive a diagnosis include: other screening/test/panel based on observed symptoms (51%), genetic testing (whole genome or whole exome testing) (63%), imaging/scan (55%), clinical diagnosis based on visible symptoms (35%), general lab (42%), and other (14%)
- Screening/test/panel based on observed symptoms (n=50); 64% reported that the doctor requested the screening/test/ or panel, and 32% requested it themselves (on behalf of the patient)
    - » Other tests include nerve testing, lumbar puncture, hearing tests, eye exams, spinal taps, karyotype testing

# Test conducted for diagnosis

**What types of testing were conducted to receive a diagnosis?**



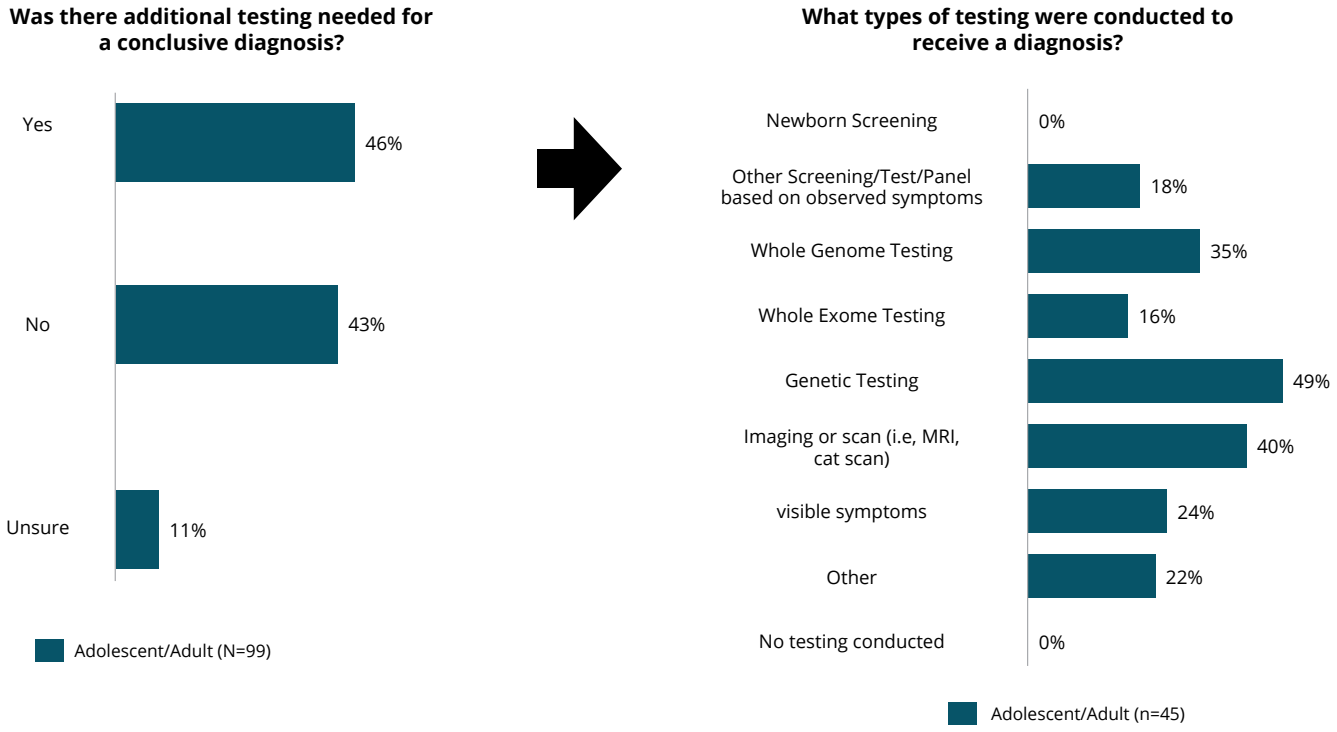

**Who requested the screening/test/panel?**



**Additional Testing (n=99)**

- 46% reported that additional testing was needed for a conclusive diagnosis (43% said no, and 11% were unsure).
  - » Of the 46% (n=45) that indicated additional testing was required, testing included: genetic testing (49%), imaging or scan (40%), whole genome testing (33%), visible symptoms (24%), other (22%), and whole exome testing (16%).
- Other additional tests include: bone marrow puncture, sleep study tests, inflammatory panel, nerve conduction velocity exam

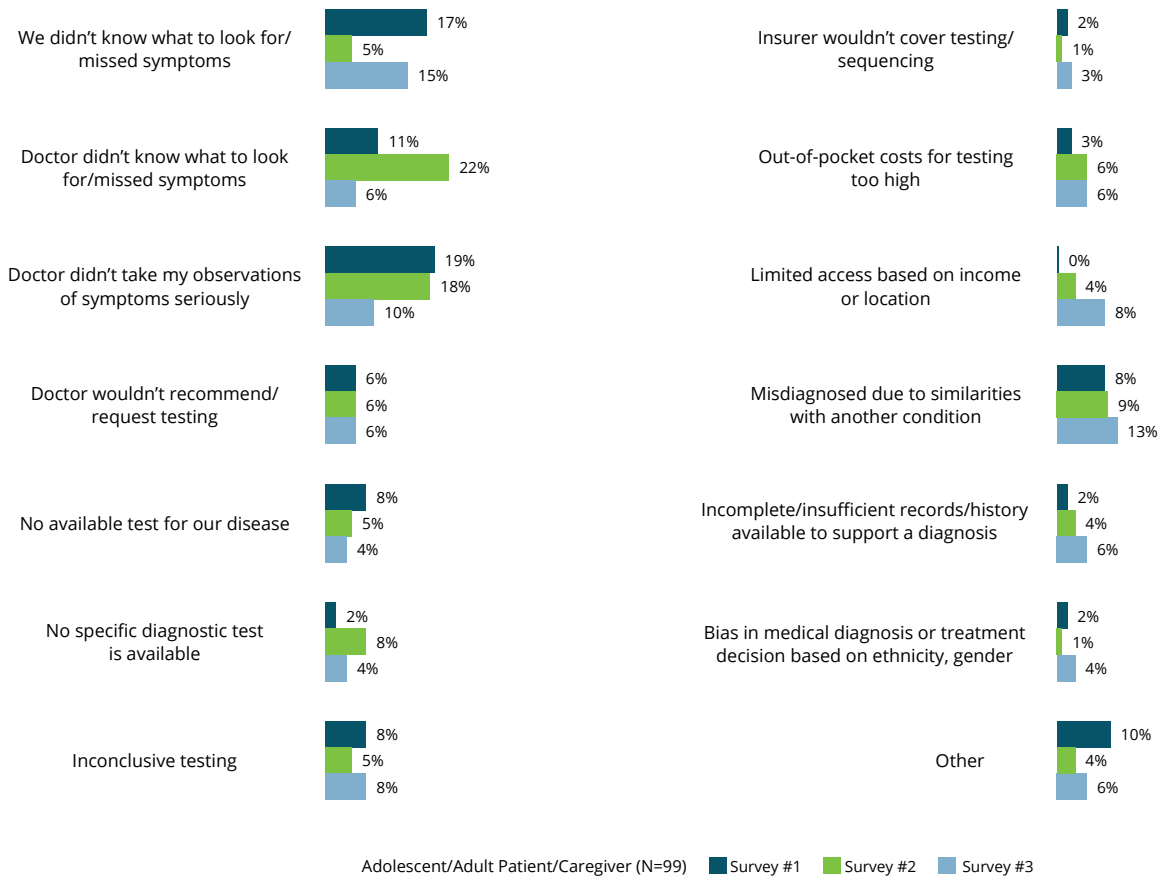
## Additional testing for a conclusive diagnosis




**Diagnostic Challenges (n=99)**

- Adolescent/Adult Patients/Caregivers noted challenges experienced in pursuing a diagnosis including: doctor not knowing what to look for/missed symptoms, doctor not taking patient's observations of symptoms seriously, misdiagnosis due to similarities with another condition, doctor not recommending testing, no available tests for the disease, out of pocket costs too high, inconclusive testing or incomplete/insufficient records/history available to support a diagnosis, limited access based on income/location, bias in medical diagnosis or treatment decision based on ethnicity/gender, inconclusive testing, and lack of coverage from insurer. Other reasons include disease being new, didn't fit clinical definition, and not standard of care.

**What were the most significant challenges you experienced in pursuing a diagnosis?**

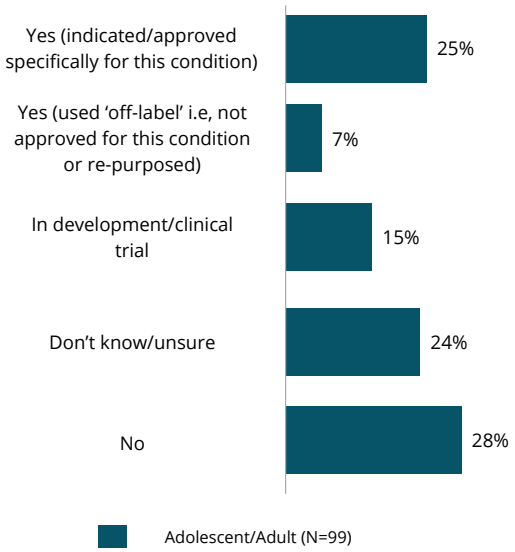



**Testing (n=99)**

- While 25% indicated that there is approved/available treatment specifically for the disease/condition, 28% indicated there are no available treatments, 24% don't know/unsure, 15% in the development/clinical trial stage, 7% used off-label or repurposed drugs.
  - » Of the 25% who indicated that there are one or more available treatments for the disease/condition (n=25), 75% of these available treatments are to manage symptoms (supportive care) and 25% to treat the condition

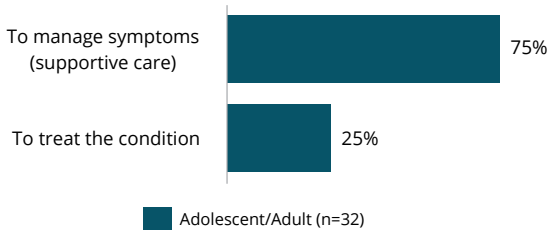
# Treatment Availability

**Was there additional testing needed for a conclusive diagnosis?**




- Off label treatments, and surgeries typically cause more harm than good.
- Eat Chinese traditional medicine
- Lithium but very dangerous side affects and doesn't work with over 60% of Kleine-Levin syndrome patients
- Deep brain stimulation
- Jak-inhibitors

**What types of testing were conducted to receive a diagnosis?**




**What is/are the available treatment(s) for?**

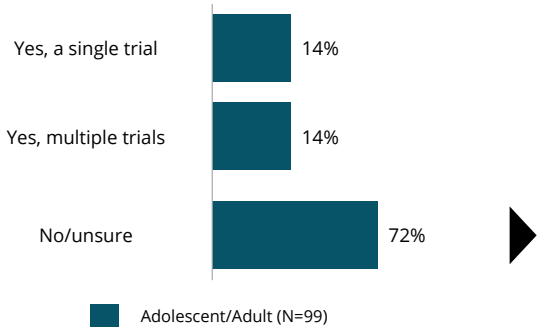
- Surgical revascularization
- Solaris, Uplinza
- Pediatric Neurologist
- Neurology
- Medication, implantable devices, neurosurgery
- Ketogenic diet
- Hormone therapy
- Glucocorticoid
- Fintepla, Epidiolex stiripentol
- Epidiolex
- Decompression and laminectomy surgery
- Brain bypass surgery
- Beta blockers, calcium channel blockers, diuretics, ICD/pacemaker
- Anticonvulsive
- Anakinra (kineret)

**Clinical Trials (n=92)**

- 14% have a single trial available in their disease area, 14% have multiple active clinical trials available, and 72% have no trial or are unsure.
  - » Of those with a known trial or trials (n=14), 43% are gene therapy trials.
  - » Of those who were not aware of an active trial or unsure, most searched for clinical trial information on/at Google/Facebook/social media, clinicaltrials.gov, the NIH, asking the hospital or doctor, or looking to a rare foundation.
- Select clinical trial experience feedback from adult/adolescent patients/caregivers includes:
- Barriers/challenges:
  - patient does not qualify due to age and not having frequent enough seizures
  - treatment is not very effective
  - side effects of the medication were unacceptable
  - difficult to arrange doctor's appointments
  - not able to contact the study clinicians
  - patient does not meet criteria due to severity of condition type
  - adults not included in trial

# Clinical Trials for Disease

**Is there an active clinical trial or multiple trials in your disease area?**




**Where do you go first to search for/get information on a trial?**

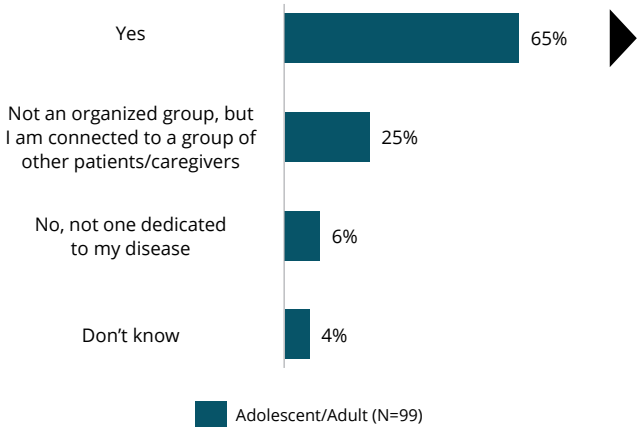
- Google/Facebook/Other website, social media (25)
- Hospital/Doctor (16)
- Clinicaltrials.gov (9)
- Dup15 Alliance
- Foundation (4)
- NIH (2)
- ACMCRN education
- On a list of research studies
- National and International clinical trials website
- No trial due to no diagnosis
- There are so few with DX due to absence of testing so no chance of clinical trial
- UCLA through the UDN

**Patient Advocacy Groups (n=92)**

- 52% noted that there is a patient advocacy/support group in their disease community, 26% did not have an organized group but were connected to groups of other patients/caregivers, 14% noted there is not one dedicated to their disease, and 8% did not know if there is one
  - » Of the 52% (n=51) who have a patient advocacy group, 84% shared that they were actively involved with the group
- Support groups helped adolescent/adult patient/caregivers with the doctor/specialist (55%), available treatment (37%), clinical trials (29%)
  - » Of the 26% who do not have an organized group but are in contact with other patients/caregivers, Facebook and social media, and friends were listed as ways they are connected.

# Patient Advocacy Groups

**Is there a patient advocacy/support group/ groups in your disease community?**




**Please list the patient/support group/groups that you are aware of in your disease community.**
**(n=51)**

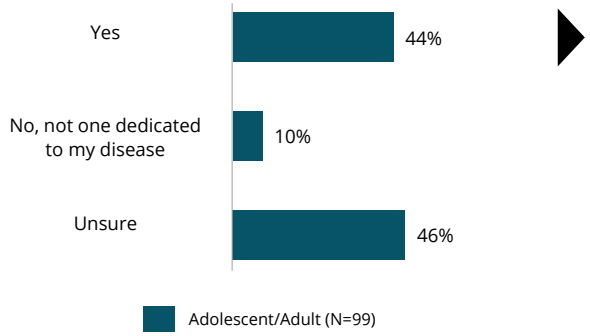
- ACMCRN
- Angelman Syndrome Foundation
- Arachnoiditis FB
- A-T Children's Project
- Australia, UK , US , Italy, Spain, France, Germany
- CAPS RareConnect
- Cauda Equina Foundation
- Community hospitals and so on
- Cure cadasil, U of Michigan
- cureCADASIL Association
- CURE SANFILIPPO
- CureVCP Disease
- Dravet Syndrome Foundation (6)
- DSF FB Caregivers of Adults (16+) with Dravet, FB SCN1A Related Seizure Disorder, FB Dravet parent and caregiver support
- Dup15q Alliance (6)
- Facebook groups, Rare Connect, FOXP1 Foundation
- Familiescn2a
- Glut1 Deficiency Foundation
- KLS Support UK
- Lennox Gastaut Syndrome Foundation (2)
- LGSF, LGSF FB PAGE, DSCC/MFTD WAIVER FB
- Moyamoya Foundation Co.
- MPS SOCIETY
- Neurosphinx , centre de reference C-MAVEM Hopital Kremlin Bicetre Paris
- NORD's Rare Diseases Action Network
- Nursing
- PMS Foundation (4)
- Ring14 International, Ring14 USA
- Tarlov Cyst Society International- I am it's founder
- The Sumaira Foundation for NMO
- WHS 4P- Lissencephaly

**Patient Registry (n=99)**

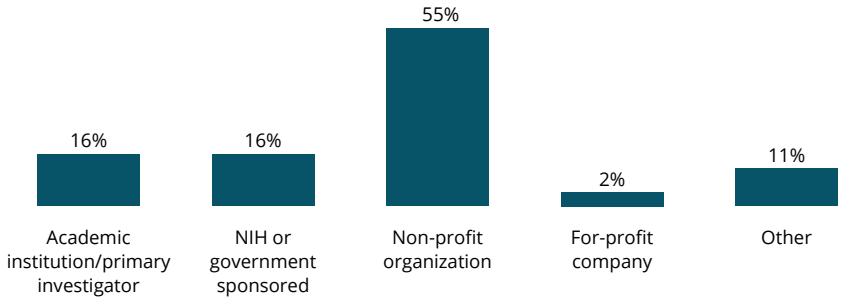
- 44% stated that there is a patient registry available for their disease/condition, 46% are unsure, and 10% said there is not one dedicated to their disease.
  - » Of the 44% (n = 43) that stated that there is a patient registry available for their disease/condition, the group managing/recruiting for the registry includes: nonprofit organization (55%), NIH or government sponsored (16%), academic institution/primary investigator (16%), Other (11%), and for-profit company (2%)
    - Adolescent/Adult patient/caregivers were asked if their involvement in the registry was helpful in getting them involved in the clinical trial: Yes (28%), No (33%), and Unsure (40%)
  - » Of the 10% (n=10) who indicated there is not a patient registry dedicated to their disease, 40% indicated there is a broader registry they are participating in and 60% said there is not.

## Patient Registry

**Is there a patient registry in your disease/condition?**

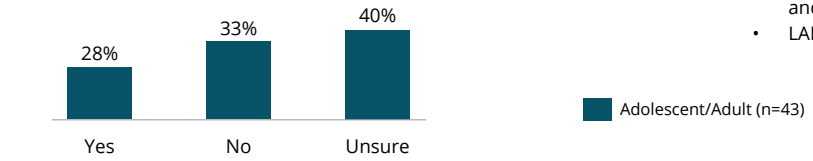



**Who is managing/recruiting for the registry?**




- WWW.PMSF.ORG
- www.G1DRegistry.org
- Simons Searchlight
- Pmsf.org (3)
- RARE-X Clinical Research Data Collection Program
- Natural History Study by ACMCRN and StuffthatWd
- LADDER Database (3)
- Global Genes
- CONNECTMPS
- Cure VCP Disease Registry at Sanford Research (CoRDS)
- Coordination of Rare Diseases at Sanford (CoRDS) Registry (2)
- CMDIR
- CADASIL Family Registry

**Was your involvement in the registry helpful in getting you involved in a clinical trial?**




## 2.3 Survey Key Findings and Insights - Clinician/Researcher

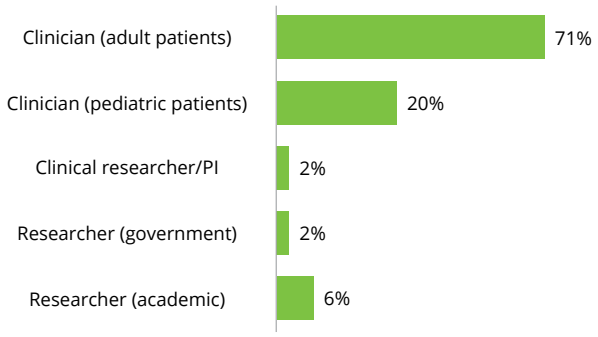
### 2.3.1 Respondent: Clinician/Researcher

n=55, average 22 years in practice; 30% of patients seen are from communities of color; specialties: Neurology 36%, Family Medicine 31%, Pediatric Neurology 18%, Internal Medicine 4%, Other 11%; number of patients with rare neurological conditions managed: 20+ 47%, 6-10 24%, 11-20 15%, 3-5 11%, 1-2 4%; roles: 71% clinicians-adult patients, 20% clinicians-pediatric patients, 2% clinical researchers/PIs, 6% researchers (academic), and 2% researchers (government); 53% white, 87% not of Hispanic, Latino or Spanish Origin, 73% male/27% female.

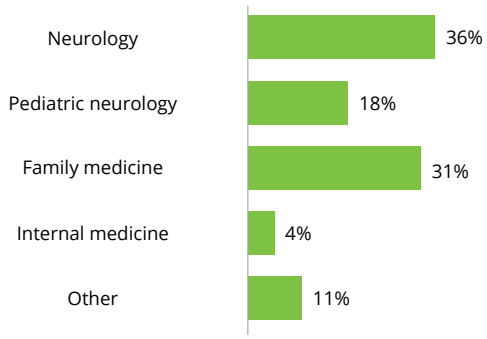
# Clinician/Researcher Demographics

**Years in practice**
**22 years (mean)**

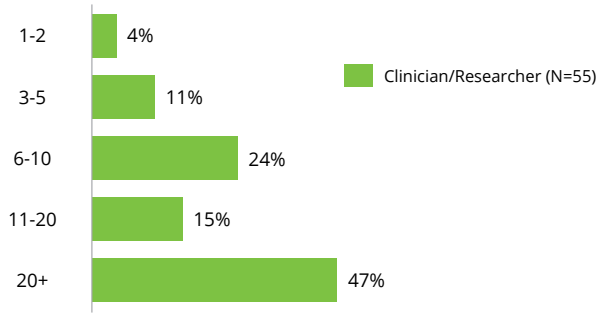
**Role**



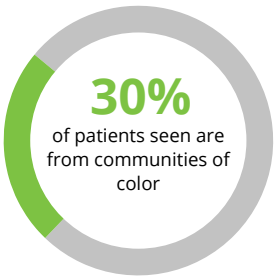

**Specialty**




**# of patients with rare neurologic conditions managed**




**% of patients with rare disease that you manage are from communities of color**



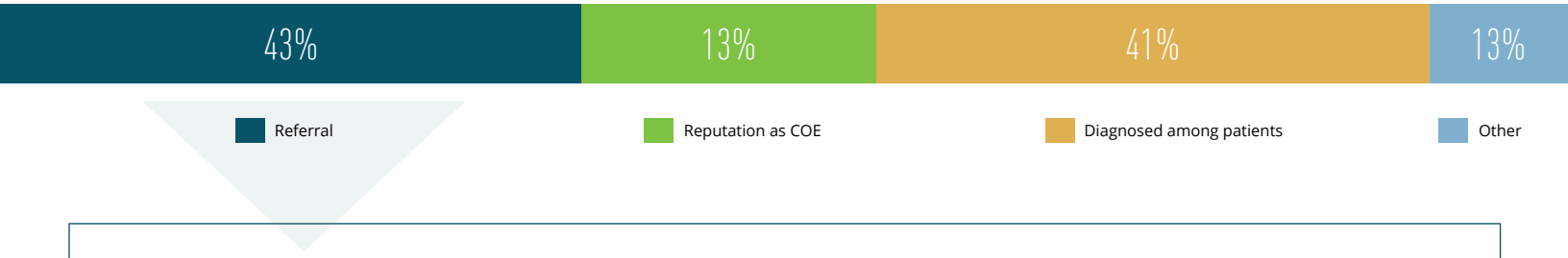

**Diagnosis (n=53)**

- When ranking the significance of factors with regard to diagnosis and access to care for a patient with a rare CNS condition, clinicians/researchers ranked education, economics, location (distance to specialist), location (distance to center of excellence), and clinical trial availability as more than moderately significant to very significant; gender, ethnicity (genetic basis), ethnicity (cultural considerations) were ranked between slightly significant and moderately significant.
- Summary of signs/symptoms that clinicians/researchers cite are most likely to lead to a diagnosis or additional testing in patients with rare disease include (in order of greatest frequency): abnormal movements, aphasia, ataxia, behavioral regulation, cognitive impairment, developmental delay, seizures, missed/lost motor milestones, hypotonia/hypertonia, migraines, fatigue, hearing loss or impairment, vision loss or impairment, and other motor/mobility impairments
- Most commons methods for a conclusive diagnosis include (in order of greatest frequency): genetic testing, imaging/scan, visible symptoms/examinations, clinical diagnosis, whole exome testing, whole genome sequencing, newborn screening, and other screening/testing/panels based on observed symptoms
    - » Other screening/test/panel based on observed symptoms includes blood and CSF testing, chemistry panels, neurophysiological testing, chromosomal array and specific sequencing

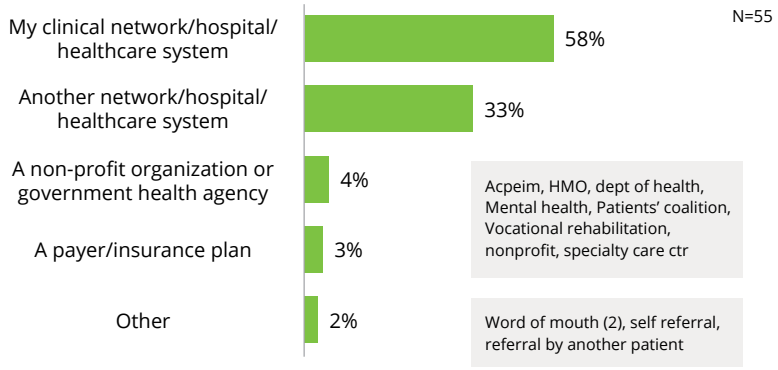
**Patient Identification (n=55)**

- 43% indicated that their rare disease patients come from a referral, 41% are diagnosed among patients, and 13% are via the center of excellence.
    - » Of the 43% that indicated that their rare disease patients come from a referral, the patients were referred from the practitioners' clinical network/hospital/healthcare system (58%), another network/hospital/health care system or clinic (33%), a nonprofit organization or government health agency (%), and a payer/insurance plan (3%)

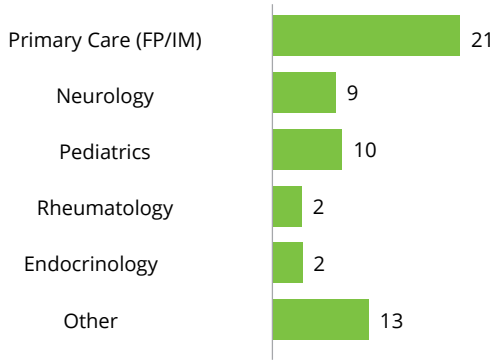
## Source of patients with rare disease




**What percent of your patients were referred from the following:**




**What clinician specialist referred the patient to you?**



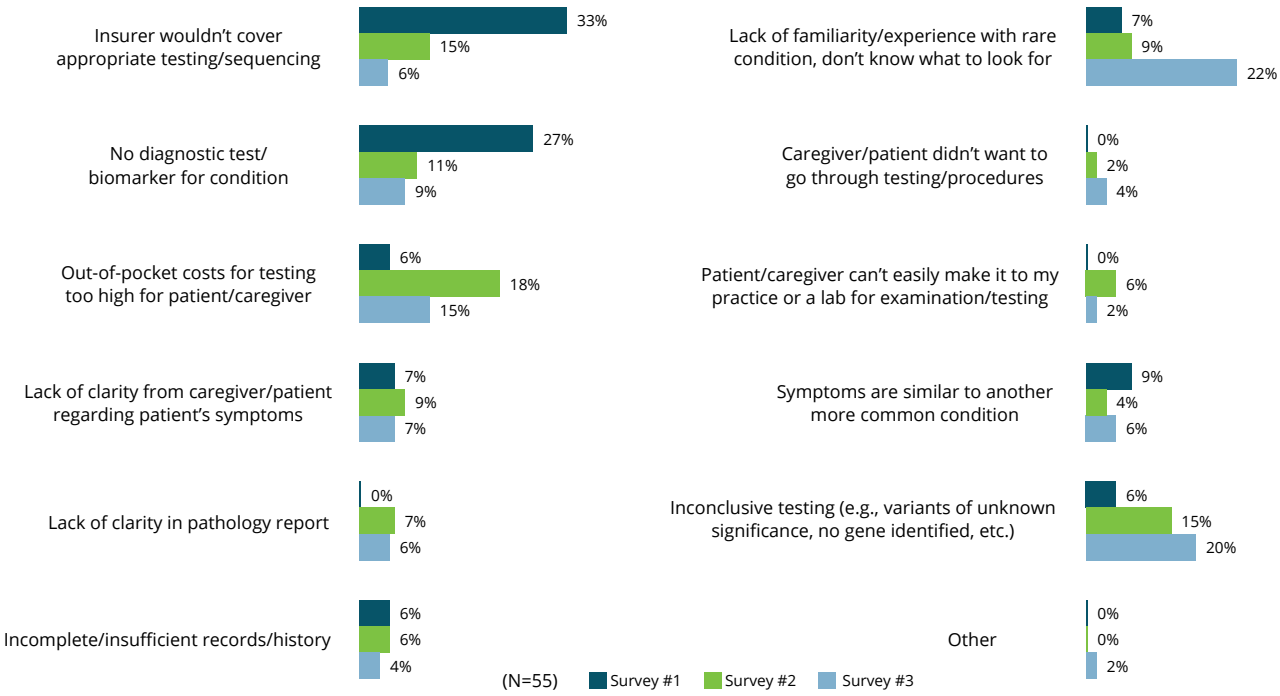

- The referrals were from the following clinical specialists (in order of most frequency): Primary Care, Other, Pediatrics, Neurology, Rheumatology, and Endocrinology

**Diagnostic Challenges (n=55)**

- Most significant challenges in getting to a definitive diagnosis in a rare CNS condition for patients include (in order of greatest frequency): insurer wouldn't cover appropriate testing/sequencing, no diagnostic test/biomarker for the condition, lack of familiarity or experience with rare condition/ don't know what to look for, out of pocket costs too high for patient/caregiver, inconclusive testing (variants of unknown significance, no gene identified), symptoms similar to another more common condition, insufficient records history, lack of clarity in pathology report, patient/ caregiver did not want to go through testing/procedures.

# Most significant challenges in getting to a definitive diagnosis

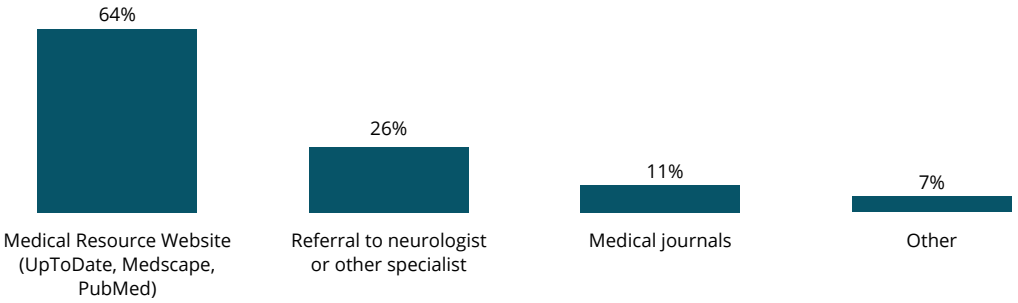
**Most significant challenges in getting to a definitive diagnosis in a rare CNS condition for your patients?**



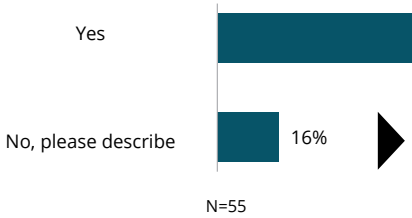

**Information Resources (n=55)**

- Once the patient is diagnosed, clinicians/researchers refer to the following sources of information if they are not familiar with the patient's condition: medical resource website, i.e., UpToDate, Medscape, PubMed (64%), referral to neurologist or other specialist (26%), medical journals (11%), other (7%)
- 84% of clinicians/researchers indicated that the resources are usually sufficient to help determine the best treatment pathway
    - » Of the 16% who said no, reasons include: usually superficial overview, treatment not available, information is too broad
- 80% refer parents/caregivers to patient advocacy organizations, 20% do not

**Once diagnosed, where do you typically go to get more information on the patient's condition if you're not familiar with it?**




**Is there a patient registry in your disease/condition?**



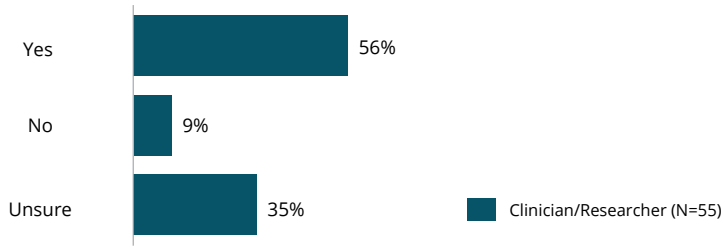

- Usually superficial review then I have to pull a larger text
- Treatment often not available (or identified)
- The information from websites is sometimes very broad and if I need more help I will google the dx and look for Neurological Centers that have a large population of these patient types
- Need more info for testing
- Most rare diseases don't have specific treatment pathways agreed
- Most often there is no treatment
- More what to expect
- More resources (2)

## Clinical Trials (n=55)

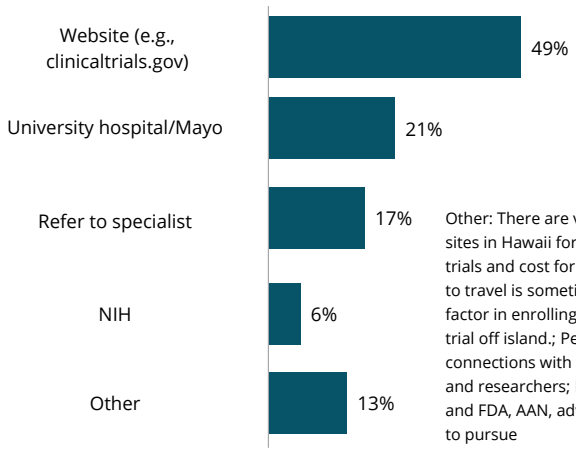
- Once the patient is diagnosed, clinicians/researchers look to the following resources for active clinical trials in the disease or condition area: website, i.e. clinicaltrials.gov (49%), university hospital (21%), refer to specialist (17%), other (13%), NIH (6%)
  - » Other (13%) responses included: limited in region (Hawaii), personal connections with pharma and researchers, CDC, FDA, advise the patients to pursue
- 85% indicated that the resources are sufficient to determine if the trial is appropriate for the patient
  - » Of the 15% that said no, reasons include: need more information, unsure if another trial is a better option, unclear inclusion and exclusion criteria, trial often not known by referring sources, not always in Latin American countries
  - » 56% indicated the resource is sufficiently comprehensive to find a trial if there is one, 35% unsure, and 9% said it is not sufficient

# Identifying clinical trials

**Is this resource sufficiently comprehensive/ updated to find a trial if there is one?**

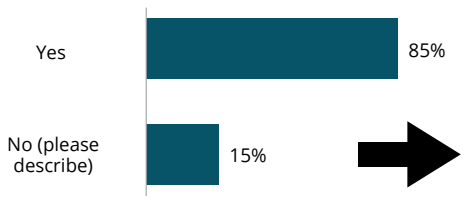



**Once a patient is diagnosed, where do you look for an active clinical trial in a disease/condition area?**




Other: There are very limited sites in Hawaii for clinical trials and cost for patients to travel is sometimes a factor in enrolling in a clinical trial off island.; Personal connections with pharma and researchers; I don't; CDC and FDA, AAN, advise patient to pursue

**Is this resource sufficiently comprehensive/ updated to find a trial if there is one?**



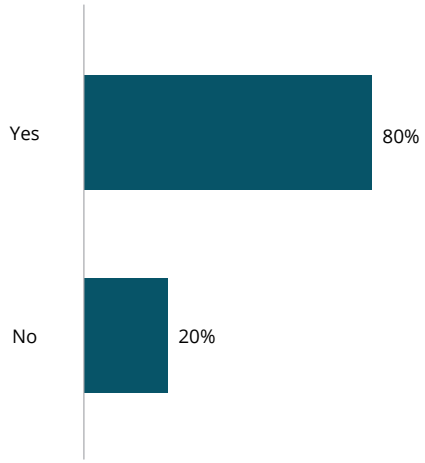

- Need more info (3)
- Unsure if there is a local trial which may be better
- Unclear, uncertain
- Unclear inclusion and exclusion criteria
- Not always is clear and not always is in Latin American countries
- More detail often required to follow up with trial leads
- Clinical trial criteria often not known by referring sources

**Patient Resources on Clinical Trials (n=53)**

- Clinicians/researchers provide patients with information about clinical trials they can participate in by referring to clinicaltrials.gov (38%), referring to another organization they know participates in clinical trials (18%), internal supports such as other staff that provides the information (13%), send them to a patient advocacy organization or registry for clinical trial recruitment (15%), other (4%).
    - » 13% noted that they do not participate in clinical trials

## Referral of patients to advocacy organizations

**Do you refer parents/caregivers to patient advocacy organizations?**




**What are the top advocacy organizations you refer to?**

| | | |
|---|---|---|
| Acpeim | FORWARD | National Institutes of Health (NIH) (3) |
| Adp | Fragile X Association Australia | National Organization of Rare Disorders (NORD) (7) |
| AGENDA | Fragile x Israeli and Fraxa | Neurofibromatosis |
| ALS society (4) | GETA (Genetic Epilepsy Team Australia) | NF Network/NF Northeast (2) |
| ALUT- autism in Israel | Global Genes | NMD |
| Alzheimer's Association (3) | Hawaii Parkinson's Association | NMO division of the National Multiple Sclerosis Society |
| AMA | Hunter's Hope for Leukodystrophy | Nsu |
| AMS | Hopkins Rare Disease (2) | NYMAC |
| AAN/American Neurological Association (3) | Huntington's Disease Society of America (3) | Rareability |
| AAFP | Hopkins Rare Disease (2) Huntington's Disease Society of America (3) | Rare chromo |
| ABFP | Hydrocephalus association | Rare disease foundation (2) |
| Ascension | Ilae | RDCRN |
| Ataxia groups | Indiana University school of medicine | relevant patient support groups for the gene/support groups (5) |
| autism society of Indiana | LGS foundation | Rett syndrome Research Foundation |
| Brain injury association of america | Live Strong | RSA |
| Children's Tumor Foundation | Local support group | Shriners |
| Clusterheads | Mhc | sma group(2) |
| Cornelia de Lange Foundation | MDA | Tuberous Sclerosis Alliance |
| Epilepsy Foundation (8) | Migraine | ULDF |
| Erytromeallgia | Mitoaction | UMDF (2) |
| Eurodis | Movement disorder society (3) | UNIQUE (rare chromosome) (2) |
| EFNA | MS Society (3) | United ability |
| Fecoer | msa group | |

# Addendum B: PIE4CNS Workshops

### 3. Workshops

Global Genes developed and conducted three facilitated workshops as part of the PIE4CNS initiative:

- Workshop 1 - October 21st, 2021; Pediatric Rare CNS
- Workshop 2 - November 4th, 2021; Adult Rare CNS
- Workshop 3 - November 17th, 2021; Health Equity in Rare CNS

| Workshop | Attendees | Participants |
|---|---|---|
| 1 | 30 | Advocates, Clinicians, Researchers, Patients, Caregivers |
| 2 | 23 | Advocates, Clinicians, Researchers, Patients, Caregivers |
| 3 | 30 | Advocates, Clinicians, Researchers, Patients, Caregivers |

The workshops were facilitated by Paul Cooper, CPF, of Face to Face Strategies, an experienced facilitator with a history working with groups focused on CNS disorders and with Global Genes. Workshop participants shared perspectives on patient identification, engagement, and inclusiveness across rare CNS conditions. The activities were designed to capture which challenges and opportunities were most meaningful to participants.

The workshops included opening discussions among workshop participants of key challenges and barriers to effective patient identification, inclusion, and engagement specific to rare pediatric and adult CNS conditions, and to health equity, informed by survey results but also drawing on participants' distinct experiences and perspectives.

Following the initial discussions of challenges and issues, the participants self-selected to participate in two consecutive break-out groups called "Intervention Cafés" around four potential areas of intervention: Education & Dialogue, Care Coordination, Advocacy, and Research, with the opportunity for groups to identify an additional category if one arose during the discussion of challenges (though in all three workshops, the participants stuck to the four suggested categories).

## Working Definitions for Today

**PATIENT IDENTIFICATION**
is the appropriate, adequate, and timely matching of a patient to available interventions and support throughout the continuum of care

**PATIENT ENGAGEMENT**
is assuring, through personalization and empowerment, that individuals have ownership of their own health journeys

**PATIENT INCLUSION**
is the removal of barriers that might hamper an individual's ability to fully participate in their health journey

# Intervention Cafe

**What interventions can bridge the gap?**

- Choose a subgroup area that energizes you (2-8 people)
- Brainstorm with your colleagues
- Switch subgroups at any time
- After the break, you can go back to the same subgroup – or choose another


During the Intervention Café breakouts participants focused on interventions that could help bridge the gap between where they are and where they aspire to be with respect to patient identification, inclusion, and engagement, and what potential solutions could be applied in the four intervention areas.

After the breakout sessions the participants reviewed the results from the sessions to find areas of alignment and to pinpoint which interventions resonated with them.

Summaries and outputs from the discussions of barriers and challenges and corresponding recommended interventions are included below for each of the sessions.

**3.1. Workshop 1 (Pediatric; 30 participants)** Takeaways from participant opinion on what supports or inhibits patient Identification, Engagement, and Inclusion goals.

- **Genetic testing and counseling**: There is a need to get access to genetic testing and inclusive and accessible genetic counseling resources, and a need for genetic counselors.
- **Barriers**: A multitude of barriers exist, including health disparities, cultural barriers, reaching underserved patients, access to therapy, and state insurance or Medicaid.
- **Clinicians**: Doctors not trained in pediatrics, missing root cause, settling on easy diagnosis, not trained in rare diseases, limited time with patients, not appreciating patients' emotional state, and not working with the patient and caregiver as partners.
- **Other factors include**:
  - Access to support.
  - Lack of social workers.
  - The parent's concern is not being taken seriously.
  - The patient perspective is being overlooked.
  - Devaluation of the multidisciplinary team approach.
  - Avenues for patients connecting with scientists.

## What supports or inhibits these goals:


### 3.1.1 Take away from the Intervention cafes: Workshop 1

*What interventions will help bridge the gap between where we are and where we aspire to be?*

#### Education & Dialogue

Key Interventions:

- Education for healthcare team - Build understanding of what the families go through and educate medical students on how to partner with RARE patients
- Global, intra-institutional, inter-institutional collaboration on educational initiatives so resources are not wasted
- Provide opportunities for dialogue between researchers/PIs/clinicians/advocacy groups and stakeholders. Possible venues include symposia and inviting HCPs into social channels
- Resources for parents with a new diagnosis and patients transitioning from pediatric to adults. The resources could be videos of patients, patient advocates, and experts and made easily available through websites
- Incorporate PCPs, NPs, and PAs into the educational mix as they're often the key point of contact and make as much of the content as possible CPD/CME-certified (emphasis on sub-specialty of genetics and then perhaps tie to rare disease).

#### Care Coordination

Key Interventions:

- The pediatric to adult transition is a black hole. Need an educated care coordination team to facilitate a smooth transition*
- Integrate care coordination and nursing healthcare plans into medical profession
- Sharing medical records like imaging that is easily accessible through digital source
- Identify what the health system can provide though discussions with stakeholder, lobbyists, and policymakers in a roundtable setting

** Several studies recognize a fundamental difference between pediatric and adult healthcare providers' health care delivery. The transition of pediatric to adolescent/adult health care is also marked by the transition from care supervised by parents and caregivers to self-care, and possibly when the adolescent is going through other developmental changes. For a smooth transition, most studies agree on improving education in transition practices for pediatric care providers, establishing formal transition policies and structures at the institutional level, and training health care professionals in care delivery for adolescent/adult patients.*

### Advocacy

Key Interventions:

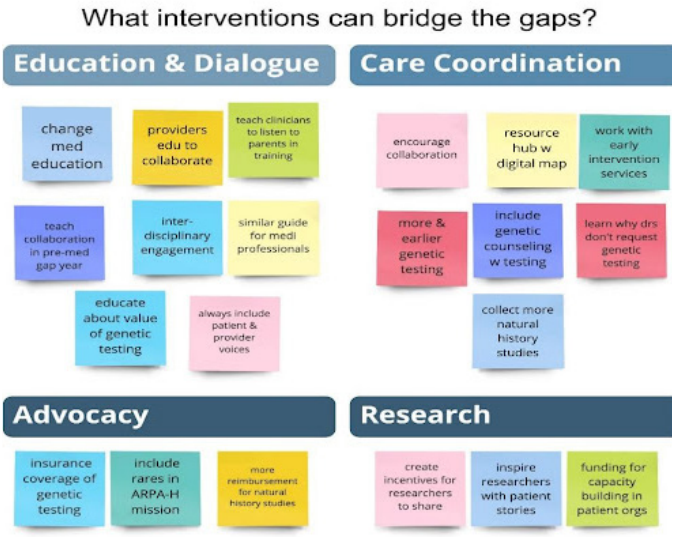
- Approaching policymakers with personal narratives/stories from the families to create political champions
- Get celebrities interested and help drive awareness
- Biotech companies beginning to understand there is significant revenue stream with these diseases
- Creating a comfort zone for parents and patients to ask questions to the health care team. The partnership between doctors and families could foster trust
- Advocating with policymakers for more federal funds
    - » Especially for new treatments, newborn screening, and genome sequencing
- Promote physicians to form networks around Identifying rare diseases

### Research

Key Interventions:

- Genetic testing is inexpensive and if it is done sooner could reduce the diagnostic time frames
- Rare disease research needs more funding. Get the rare disease research agency in D.C. (ARPA) to get Rare Disease on the NIH agenda
- Patient organizations and advocacy groups leverage spotlighting patient voices and experiences of families to help drive research
- Use Critical Path Institute portal for collaborative data sharing
    - » Lower barrier to entry for researchers, like access for researchers to use data already collected. This will help inform future direction vs. starting from scratch
    - » Use Rare-X platform as a potential incentive to use data across platforms
- Bring specialties together and have a national rare research conference

### Workshop 1: Prioritized Interventions




**3.1.2 Workshop 2 (Adult, 23 participants)** Takeaways from participant opinion on what supports or inhibits patient Identification, Engagement, and Inclusion goals.

- **Genetic testing and counseling**: Lack of genetic counselors and need for genetic testing for the older population
- **Barriers**: A multitude of barriers exist, and it includes geographic accessibility, cultural barriers, personal finances, philosophical, access to treatments, insurance restrictions, and insurance codes
- **Clinicians**: Clinician's experience and knowledge, listening, lack of adult neuro training, challenge of managing care, and clinicians not appreciating patients' challenges. Lack of education of mental health professionals on rare diseases, lack of proper diagnosis, and patients feeling ping-ponged
- **Pediatric to adult transition**: Variable symptoms with pediatric, providers not coordinating care, striation of departments, and lack of coordination
- **Other**: Factors stated include being part of an advocacy organization, many rare factors, and not getting identified


### 3.1.3 Takeaways from the Intervention cafes: Workshop 2

*What interventions will help bridge the gap between where we are and where we aspire to be?*

#### Education & Dialogue

Key Interventions:

- Annual healthcare professional summit to encourage patient participation in addition to the Interdisciplinary treatment team. Facilitating cross talk between the two
- Foundations and organizations could facilitate education about case management, mental health, patient navigator for families, patients, foundations, physicians, researchers, and advocates.
- Partnership and collaboration between doctors and researchers to share ideas, research, and how to take steps forward
- Healthcare provider education is important, including NPs, PAs. Doctors aren't communicating and looking at patients as pieces of a whole rather than the whole patient
- Bring awareness of genetic testing to physicians in some of the less populous areas
- Get to neurologists–they are the key piece of the puzzle for CNS. Get buy-in from big neurology groups to educate neurologists on coordinated care, and embracing the option to coordinate and embrace rare.
- Educating medical students while they are still in school to have awareness about what is going on in the rare disease space

#### Care Coordination

Key Interventions:

- Team of volunteers that educate providers on referrals to those dedicated to adult patients, their needs, and identification, including genetic providers (e.g., Project Echo which stands for the Extension of Community Healthcare Outcomes)
- Registries that make records available to families are important because records are often destroyed after 10 years/ transition from pediatric. Include x-rays, CT scans, etc.
- Educate families on how best to coordinate care–build resources such as binders, guidelines they can share with physicians; charts and diagrams that show what your team looks like (include social worker, support group, etc).
- Care navigators provided by insurance companies and certain societies
- Create a referral system to work with providers
- Patient representatives who coordinate care and know how to obtain reimbursement, where to go for care, etc. (e.g. health system in EU)

#### Advocacy

Key Interventions:

- Educating healthcare providers about clinical presentation may be different in adults
- All members need to have a voice (i.e., patients, doctors, researchers, educators)
- Rare disease education program
    - » Educate advocates on how to teach others about rare disease, including using the proper terminology/lingo/ approach when to speaking to others (centered approach)

## Research

Key Interventions:

- A pipeline to facilitate development and standards across related diseases/research areas driving more efficiencies Research networks
- Accelerating diagnosis to identify more patients, more education for physicians
- Increasing engagement from adult patients in research and registry
- Creating more tools (PROs, wearables, etc.) to ensure that patients can participate in research more easily–accessibility
    - » Trial design, etc.
- More collaborative research networks and data sharing to reduce data silos and accelerate research
    - » More effective collaboration - sharing knowledge in journals and with patients
- Well-designed patient registries, and supporting shared access to registries, and combining resources to attract researchers/industry (critical mass of patient population)

### Workshop 2: Prioritized Interventions


**3.1.4 Workshop 3 (Health Equity, 30 participants)**
Takeaways from participant opinion on what supports or inhibits patient Identification, Engagement, and Inclusion goals.

- **Genetic testing and counseling**: Genetic counseling is not always billable, a need for well-trained genetic counselors. Genetic counselors have a coordinating role.
- **Barriers**: A multitude of barriers exist, and they include geography, race, language, uneven quality of care, some treatment not available in places, cultural insensitivities, access to services, disability status, immigration status, financial coverage, and some docs not referring quickly.
- **Clinicians**: Clinicians have cultural biases, are not prepared or informed, diagnosis is based on a stereotype, and people with the rare condition are a lower priority. Need for providers who spend enough time with patients.
- **Other**: Lack of diagnosable and understandable information and need for providers who spend enough time with patients.

**What supports or inhibits these goals:**

### 3.1.5 Takeaways from the Intervention cafes: Workshop 3

*What interventions will help bridge the gap between where we are and where we aspire to be?*

#### Education & Dialogue

Key Interventions:

- Make sure there are professionals from various cultures to deliver the message. Need voices at the table of all populations participating in different aspects of leadership with decision-making power
- Teach doctors to be collaborative team members, not going in with their own agenda and lead by listening, having inquisitiveness about the family in front of you, think of them as people not patients
- For educational resources, meet people where they are, clearly identify audiences, channels (diagnosed, misdiagnosed patients, caregivers)
    - » Leverage LinkedIn to reach professionals
    - » Facebook to reach patient/caregivers
    - » Videos: How to get a genetic test? How to work with genetic counselor?
    - » Target signs/symptoms, behaviors that might alert undiagnosed to need for testing
    - » Based on life transitions (birth-3, out of NICU, into school, into young adulthood)
- Set up multidisciplinary clinics, these are scarce for adults, it is partly about care coordination, but better to improve transition from peds to adult care.

#### Care Coordination

Key Interventions:

- Waiver services paperwork is a barrier. Need easier access
- Outreach to medical students on campus on Rare Disease Day, let them hear our voice
- Community Clinic Connection hires social workers and shares PHI (HIPPA compliant) might not be scalable
- Community health workers/health promoters are a trained peer who the patient can trust and has expertise. This is becoming a billable role
- Model of best practices from a rare disease org to guide new patients to preferred clinicians. Helps with caregiver time scarcity

#### Advocacy

Key Interventions:

- Empower the patient with access to resources, language translation, health literacy, advocacy, and Leadership Training
- Provide accessibility with resources from the onset of diagnosis, also provide physical resources and give people access to an appropriate resource/ advocate
- Build trust by listening to patients, being mindful of distinct needs, and building connections with credible leaders and institutions for patient populations
- Take a global approach by collaborating, making sure other countries have a voice
- Empower regions to advocate for themselves

#### Research

Key Interventions:

- Make research inclusive of the entire population and patient friendly
- More patient and healthcare provider involvement in design of research studies/clinical trials from bench to bedside
- Need to think about outcome measures because quality of life definition may differ from person to person (Patient-Centered Outcomes Research Institute. (PCORI) is a good benchmark with patients involved in decision making)
- Think outside the box when enrolling, for example, go to the patients for a blood draw if needed
- For sake of inclusion, research materials need to be in multiple languages

### Workshop 3: Prioritized Interventions


# Addendum C: PIE4CNS Advisory Panel

### Expert Advisory Panel

| Members | Affiliations |
|---|---|
| Anna Bican, CCRP | Undiagnosed Diseases Network |
| Terry Jo Bichell, PhD, MPH | COMBINEDBrain |
| Wendy Erler | Alexion |
| Mark Forman, MD, PhD | Passage Bio |
| Vanessa Vogel-Farley | Dup15Q Alliance, RARE-X |
| Cindy Jackson, D.O., F.A.A.P | I-ACT for Children |
| Mary Anne Meskis | Dravet Syndrome Foundation |
| Matt Might, PhD | NGLY1 Foundation |
| Kris Pierce, RN, MHSc | SCN2A Australia |
| Tracy Dixon-Salazar, PhD | LGS Foundation |

#### 4. Highlights from the advisory panel meeting 1

The advisory panel met on September 13th, 2021. This was the kick-off meeting for the PIE4CNS initiative Advisory Panel.

Each panelist shared one objective they envisioned the initiative could achieve. Objectives shared by the panel included:

- Provide input/guidance for the undiagnosed population,
- Improve diagnosis and treatment for rare CNS disorders,
- Understand the commonalities between rare disease communities and use that to accelerate diagnosis and treatment,
- Find better ways to share and overlap knowledge between unique identifications through a collaborative database,
- Shorten the diagnostic odyssey by more easily connecting pediatric patients with symptoms with the child neurologist,
- Identify the big pitfalls (diversity, inclusivity, language, ethnicity, access),
- Find better ways to collect and evaluate data,
- Devise a plan to effectively and inclusively get patients into clinical trials,
- Highlight the importance of early diagnosis and early access to clinical trials, and
- Find creative ways of working collaboratively under the PIE4CNS initiative.

The panel meeting also covered the following topics, Global Genes Impact Model and program context, PIE4CNS Initiative Overview & Focus, proposed Workshop Structure, discussion on Prospective Participants, and wrapped up with the upcoming schedule for events and meetings. The panel also discussed near-term priority issues and action items in detail, followed by a call for suggestions for stakeholders for the workshops from the advisory panel. The panel had valuable suggestions about potential stakeholders.

### 4.1 Highlights from the advisory panel meeting 2

The discussion on the Preliminary Pulse Survey Findings included questions and clarifications about the data presented. The discussion covered several topics implemented in the three workshops planned for October 24th, November 4th, and November 17th.

The highlights of the discussion are added below:

- If the patient was an adolescent at onset or at the time of diagnosis
- Unique challenges associated with related but distinct conditions among patients who might have multiple conditions
- How does a delayed diagnosis affect qualifying for an available clinical trial?
- How do patients/caregivers report multiple conditions in a registry?
- What factors could speed diagnosis or improve access to testing?
- Discussions around newborn screening and dissecting what the captured data revealed about state bias
- Cost of imaging vs. genetic testing
- Discussion about genetic testing
- Importance of using similar questions in the survey for adult and pediatric patients
- Significance of both caregivers and clinicians having resources for comprehensive care available at the pediatric level but not at the adult stage leaves the burden on caregivers to connect the dots
- Assess the survey data as to whether the patients/caregivers are unaware of the clinical trials or unsure of how to access them
- No one asks the family if they are willing to enroll in a clinical trial–need a paradigm change

### 4.2 Highlights from the advisory panel meeting 3

On December 8th, 2021, the advisory panel met for the third PIE4CNS initiative Advisory Panel meeting. The panel meeting began with a brief recap of the initiative's progress, followed by a debrief and discussion of the workshop and survey findings. The meeting also discussed planning aspects of the recommendations report dissemination.

The highlights of the discussion are stated below:

- Clinicians are trained in etiology but not symptoms
- Better education and understanding among healthcare professionals points out the need for needs assessment for PCP's and neurologists
- The panel members addressed their concern for the lack of genetic counselors and the need for organizations and institutions to rally for genetic counselors
- The panel discussed the need for awareness about clinical trials and how clinical trials did not come up in the patient survey
- Need for professionals to address the mental health of the patients and caregivers
- Collaborations across the advisory panel members
- Needs of Hispanic & African-American communities

### Highlights from the advisory panel meeting 4

On January 13th, 2022, the advisory panel met for the fourth PIE4CNS initiative Advisory Panel meeting. The panel meeting provided a recap of the initiative's progress, followed by discussion of the emerging recommendations (pending review of the final report and recommendations, which were not yet available to the panel), and the pending poster presentation of the PIE4CNS report and a possible reception at WORLD Symposia in February, if the meeting remained in-person.

## 5. Summary of Insights & Recommendations

### 5.1 Survey

- Need for more testing, screening, or panel requests from the clinicians for the adult patients
- In pediatric patients and adult/adolescent patients, clinicians do not take patients' observations of symptoms seriously and do not recommend testing.
- Misdiagnosis is common due to similarities with other conditions
- Only a small proportion of the caregivers (11%) and adult/adolescent (14%) patients reported that they are aware of multiple active clinical trials available.
- Clinicians and researchers reported the following challenges in getting a definitive diagnosis:
  - » Lack of familiarity or experience with rare conditions
  - » They were unsure of what to look for
  - » The insurer wouldn't cover appropriate testing/sequencing.

### 5.2 Workshop

#### 5.2.1 Participant opinion

- Need to get access to genetic testing and inclusive and accessible genetic counseling resources and need for genetic counselors
- Barriers in geography, language, insurance, and access to treatment
- Lack of experience and knowledge in clinicians and other healthcare professionals, lack of adult neuro training, lack of proper diagnosis, and patients feeling ping-ponged
- Lack of care coordination during the pediatric to the adult transition of the patient

#### 5.2.2 Intervention cafes

- Need voices at the table of all populations participating in different aspects of leadership with decision-making power
- Educate medical students while they are still in school to have awareness about what is going on in the rare disease space
- Research networks, collaboration, data accessibility from previous work to not start from scratch. Common place to share data such as symposia.
- Get to neurologists–they are the key piece of the puzzle for CNS
- Identify what the health system can provide though discussions with stakeholders, lobbyists, and policymakers in a roundtable setting
- Patient organizations and advocacy groups leverage spotlighting patient voices and experiences of families to help drive research

### 5.3 Advisory Panel

- Unique challenges associated with related but distinct conditions among patients who might have multiple conditions
- Assess what factors could speed diagnosis or improve access to testing
- Educating clinicians and healthcare professionals around the benefits of early newborn screening and genetic testing
- Not all clinicians are bringing up the option to enroll in clinical trials. Call for a paradigm shift.
- Clinicians are trained in etiology but not symptoms. Therefore, there is an immediate need for better education and understanding among healthcare professionals for a needs assessment.
- There is an urgent need for more genetic counselors. Organizations and institutions should rally for genetic counselors

### 5.4 Final recommendations

The following recommendations are organized according to the categories used to identify and explore potential interventions as part of the Workshops–recognizing that there is some overlap of interventions across categories. Wherever possible, we've also identified existing Global Genes or partner initiatives that could serve as a foundation for immediate progress and collaboration, as the PIE4CNS was specifically designed to stress actionable recommendations that can achieve rapid and meaningful impact.

### 5.4.1 Education & Dialogue

Key Interventions & Recommended Actions:

- **Conduct Annual PIE4CNS Summit or Symposium**, bringing together professionals and researchers with patient/caregivers and advocates to discuss key topics, including:
  - » How unique aspects of the rare disease experience can influence diagnosis, identification, and inclusion in research and care
  - » Working together to develop a lexicon of symptom descriptions and other tools to help ensure consistency and relevance to diagnosis
  - » Learning to work with other professionals is critical to improving rare disease diagnosis, care, and outcomes
  - » Exploring latest diagnostic tools and capabilities to support rare CNS condition diagnoses

- **Adapt/Develop/Launch Experiential Medical Education Programs**, bringing medical students together with rare disease patients/families to improve awareness of the rare disease experience and related diagnostic and access challenges, potentially including:
  - » **Adapt/expand Global Genes' Rare Compassion program** and incorporate into curricula, CME/CPD
  - » **Develop Virtual Grand Rounds initiative**, in partnership with professional societies and/or leading centers of excellence
  - » **Work with the Rare Disease Diversity Coalition and other organizations** to engage HBCUs and medical centers and clinics representing diverse communities

- **Create, Launch and Amplify a Multi-Channel Storytelling Initiative**, with elements including:
  - » **Leverage Global Genes' RAREly Told Stories and other partner initiatives** to create, translate, and expand a base of content to be disseminated via social channels and/or partner websites to support awareness and education
  - » **Adapt and disseminate content to be generated as part of a pilot Family Health History initiative** in conjunction with the Rare Disease Diversity Coalition
  - » **Launch a distinctive TikTok or other social platform/influencer-driven initiative** specifically designed to reach adolescent and young adult patients and to address distinct disparities or challenges they face

### 5.4.2 Care Coordination

Key Interventions:

- **Provide easily accessible navigation services** for patients and caregivers to guide users to resources (supported or made available via PIE4CNS partners)
  - » **Enhance/expand/scale Global Genes' existing RARE Concierge service** and partner with other service and support providers
  - » **Build partnerships** with major health plans, health systems, testing labs, and other non-profits that provide financial assistance or other forms of support to further expand offerings

- **Increase access to digital tools** for rare disease caregivers and patients
  - » **Adapt/Launch PHI tool** (in development) with capabilities to capture relevant information on CNS disorder signs and symptoms using consistent terminology and allowing for video capture and translation, experiences, medical history, etc. (GDPR/HIPPA compliant)
  - » **Provide educational content and sessions at Global Genes and partner events** and through our RARE Portal for caregivers/patients, clinicians, and researchers

- **Provide broader, more inclusive access to testing, genetic counseling, and related services,** globally, tied to educational efforts described above and with the ability to transfer/include analysis and testing results to a personal health information management tool
    - » **Launch pilot program** (in development) to provide testing/ sequencing and related education and genetic counseling to patients, at no or very low cost
    - » **Create a consortium to expand access to affordable or free testing and sequencing** tying into partners' initiatives where possible (e.g., CNF's efforts with illumina)
    - » **Provide educational content and sessions at Global Genes and partner events** and through our RARE Portal for caregivers/ patients, clinicians, and researchers

#### 5.4.3 Advocacy

Key Interventions:

- **Continue to support and equip rare disease patients, families, and advocates to participate in efforts to inform policymakers** about the unique needs of the rare disease community
    - » **Adapt and provide stories, data, and content** from PIE4CNS efforts described above to support partners' advocacy efforts in support of rare disease-relevant policies
    - » **Invite policymakers and influencers to participate in annual PIE4CNS Summit** (described above) and/or other partner or Global Genes and partner events
- **Elevate needs of minoritized populations in rare disease,** drawing on Global Genes' partnership with the Rare Disease Diversity Coalition in the U.S., and communities globally
    - » **Develop content, data, and evidence to share with policymakers** that more specifically illuminates the unique challenges for patients and caregivers from diverse and underserved communities (drawing on initiatives described above and other partners' EDI programs)

#### 5.4.4 Research

Key Interventions:

- **Expand development of/access to resources for collaborative research and data sharing**
    - » **Form a Rare CNS Open Research Working Group or Network** that would build consensus around data standards, registry and trial design, and inform development of cross-disease data collection, sharing, and analysis for rare CNS disorders
    - » **Drive increased and inclusive participation in patient-directed, non-profit, open data collection, analysis, and sharing platforms** (e.g., RARE-X)

### 5.5 Next Steps Toward Phase II (Taking Action) of PIE4CNS

1. Reconvene Advisory Panel to review findings and recommendations and agree on proposed areas of focus and action (February)
2. Approach potential partners and funders for Phase II (February)
3. Convene PIE4CNS stakeholders at WORLD (assuming in-person) to network, discuss and build support for Phase II initiatives (February 9)
4. Secure partners and funding for Phase II (February-March)
5. Confirm Advisory Panel members for Phase II (March)
6. Conduct Phase II multi-stakeholder kick-off meeting (April)
7. Initiate Phase II programs (April)


# Patient Identification, Inclusion & Engagement for Rare CNS Disorders (PIE4CNS)

REPORT AND RECOMMENDATIONS FOR ACTION