rare epilepsy landscape analysis

July – December 2019

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December 1, 2019

I. EXECUTIVE SUMMARY

Rare epilepsy organizations are on the rise! Rare organizations have steadily risen since 2008**.** Widespread adoption of the Internet and social media have connected geographically disparate families with rare diagnoses. Next-generation sequencing has led to a proliferation of newly discovered genes. Both have contributed to the rise of rare epilepsy organizations (Rares) and support groups**. If the hypothesis that genetic mutations cause 70-80% of epilepsy cases is true - will Rares remain rare? And what are the implications for their steady growth?**

There is diversity in rare organization maturity, staffing, and funding. Nonetheless, **delivering information & support, building community, and funding research are deemed mission critical across the Rares.** There is a strong culture of collaboration and sharing among the Rares. **There is widespread recognition that collaboration fuels initiatives that could otherwise not be accomplished by Rares individually, especially for the Rares with the most limited resources.**

Even among the Rares – there is rare and ultrarare. Statistics for incidence and prevalence – where available – were highly varied. Incidence ranged from more common Rares like Tuberous Sclerosis Complex with 166/1M to conditions like Ring14 reporting incidence of 1 in one million. **The growth, breadth, and complexity of the rare epilepsies underscores the importance of quantifying incidence and prevalence, as well as the national public health burden of these collective diseases.**

The majority of Rares lack cures. Whether each individual rare condition was reported as "understood well" (few) or "a little or not at all"(many), for the majority, there are **no cures**! And the list of comorbidities – many more disabling than the seizures – continues to expand. **The promise of precision medicine provides a beacon of hope especially for genetic epilepsies. However, cures for seizures and comorbidities require scientific investment and research**.

Yet, there is a scarcity of rare epilepsy research and funding. Only 10 Rares reported receiving funding from NIH/NINDS, FDA, or PCORI. 14 Rares reported investing $3.6M in research in the last year**. Rares cannot redress funding disparities alone. New, innovative rare mechanisms are needed to engage more researchers and resolve gaps.**

The Rares are stretched serving urgent needs of their constituents. Resultingly, their voice has long been missing from key policy forums. As one example, only 10 Rares were aware of the upcoming 2020 Curing Epilepsy Meeting which benchmarks progress, establishes priorities, and informs investments by NINDS/NIH. **Rares want to influence national research and funding priorities but require coordinated leadership and infrastructure to convert aspirations to action.**

Specialty, quality rare care is sparse. Less than half the Rares reported disease experienced clinics or specialized hospital centers. Further, **Rares reported a dearth of rare clinical guidelines for diagnosis, evaluation, and treatment. Rares call for the development of specialty care centers and consensus based clinical guidelines that are based on best-practices and scientific criteria and monitored for performance. Just two of many initiatives Rares realize they can better accomplish collectively.**

US Rares are caring for the world. The majority of US based Rares identify as international serving the needs of patients and caregivers in the US and abroad. **The Rares are taking on the global burden of their diseases even with 20 Rares reporting no paid staff relying exclusively on volunteers executing operations.**

Rare epilepsies and the organizations that represent them are growing.
No single Rare can tackle the many challenges for the most vulnerable patients and their caregivers alone.
The landscape has dramatically changed. The paradigms have not.
Critical priorities are aligned and ripe for collaborative endeavors**.**
Collectively, rare voices are strong. It's time to Reimagine the Rares and their future.

II. OVERVIEW

RARE EPILEPSY LANDSCAPE ANALYSIS (RELA) RATIONALE

There has been an explosion of rare epilepsy organizations (Rares) founded and fueled by the passion of caregivers and patients impacted by each disease. Many of these organizations were born by necessity to address the information, support, treatment, and research needs of patients struggling with the most severe forms of epilepsy and their comorbidities. The rare epilepsy explosion has been spurred by advances in genetics and imaging which have accelerated the discovery of epilepsy genes and other causes with even more on the horizon. Moreover, the Internet and social media have similarly accelerated the capacity for disparate individuals to find one another online irrespective of geographic boundaries and create community and organize into informal support groups and more formal nonprofits.

As new rare organizations emerge, fracturing among the rare epilepsies and with other general epilepsy organizations has increased as well. The "epilepsy ecosystem" has become more complex. Still, initiatives like the Rare Epilepsy Network (REN) registry suggest the power of collaboration toward common goals. **Many individuals and organizations have expressed the desire and need for infrastructures** to share existing expertise, lessons learned, resources, templates, and best practices, as well as identifying new high value initiatives that could better be accomplished by a coalition versus individual organizations. However, the infrastructure for collaboration has not kept pace with the growth of the epilepsy ecosystem. Not only must Rares determine their internal strategic objectives, but there is a multitude of coalitions including REN, Epilepsy Leadership Council (ELC), Rare & Catastrophic Seizure Coalition (RCSC), Global Genes, NORD and more to navigate as well. For organizations - especially those relying on volunteers or small staffs - it can be time consuming to maintain a seat at every table, prioritize participation, and even discern what resources and benefits each coalition has to offer.

RELA INCEPTION & GOALS

As the co-founder of a rare epilepsy organization, I conceived of the RELA because **I know what it feels like to be stretched to maximum capacity** and often feel as if I am not being as efficient or productive as I need to be despite the urgency of need in my community. See RELA Announcement Appendix A. There are so many shared priorities with other Rare epilepsy organizations and in many instances, I believe we would **advance our efforts faster working together than in isolation**. Although I have been in the field for 10 plus years and consider myself reasonably well-informed, this undertaking has already led me to discover new insights about which coalitions to turn to for what resources. The RELA survey was conceived as an effort to take stock of the emerging epilepsy ecosystem in order to be more strategic in the utilization of scarce dollars, people, and resources. It is my sincere hope that the RELA survey findings will help the Rare community: 1) understand the breadth and depth of rare organizations that comprise the Rare epilepsy ecosystem; 2) illuminate high priority shared opportunities; 3) educate broad epilepsy stakeholders on the challenges and opportunities unique to Rares and 4) identify existing and potentially new infrastructures to better facilitate collaboration, professional development, capacity building and more.

METHODS

A six-month grant was awarded to support a qualitative study of the Rares' landscape, to commence July through December 2019. The project began with in-depth interviews with Epilepsy Foundation (EF) leadership on Rare perceptions and programs and services within EF. Following, discussions with Rare & Catastrophic Seizure Club (RCSC), Rare Epilepsy Network (REN), Epilepsy Leadership Council (ELC), American Epilepsy Society (AES), National Institute for Neurological Disorders & Stroke (NINDS), National Organization for Rare Diseases (NORD), Citizens United for Research in Epilepsy (CURE), Child Neurology Foundation (CNF) Centers for Disease Control (CDC) and many individuals led to the identification of 75 Rare organizations. Phone interviews with select organizations and individuals were undertaken in late May. A kick-off call commenced on June 24 with Rare groups to announce the initiative and obtain areas of priority and interest. A volunteer advisory committee was established. A 10 part 111 question survey covering background, founding, disease impact, patient/caregiver information, research, professional education, advocacy and awareness, management and operations, resources and financials and fundraising was developed and tested in collaboration with the advisory committee, epilepsy stakeholders and others. The survey was built in Qualtrics and launched on Sept. 24, 2019. The deadline was extended three times to maximize participation. The survey was closed on Nov. 9, 2019. 44 complete responses were received and comprise the basis of this analysis. Of the 44 responders, all except 1 opted into the Appendix including attributed text responses to questions. 15 responses were incomplete and omitted. 15 Rares did not participate.

III. SURVEY INVITEES

The RELA survey focused primarily on United States based Rare epilepsy organizations – both 501c3s as well as those that are informally organized as support or Facebook groups. The following 75[1] organizations were identified via extensive outreach. With an increasing number of epilepsy related genes being discovered, these organizations likely represent just the tip of the iceberg of currently existing and to be formed Rare support groups and organizations.

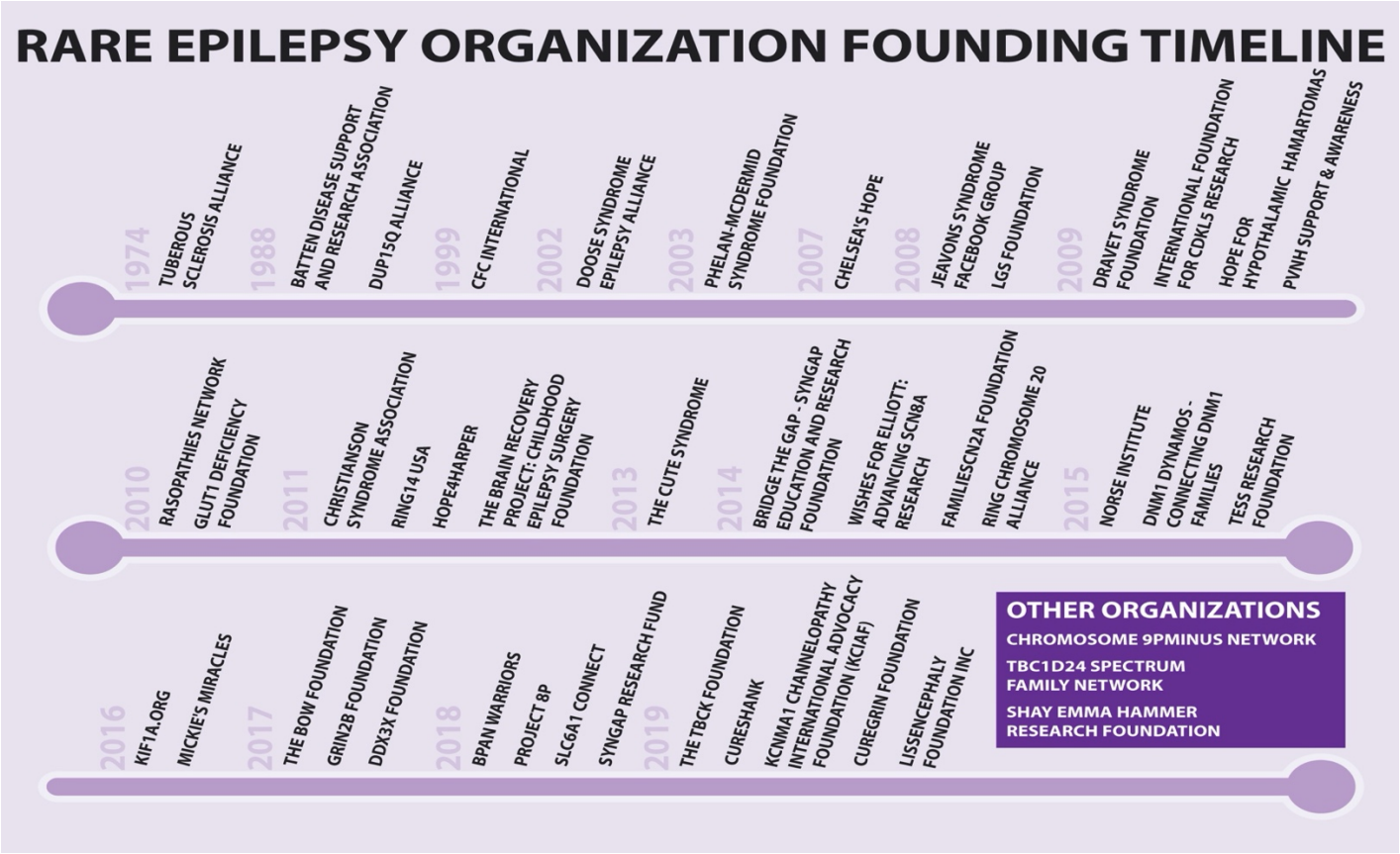
1. Aaron's Ohtahara Foundation
2. Aicardi Syndrome Foundation
3. Alternating Hemiplegia of Childhood Foundation
4. Angelman Syndrome Foundation
5. Aspire for a Cure
6. Austin's Purpose (Grin2A)
7. Batten Disease Support and Research Association (BDSRA)
8. BPAN Warriors (BPAN)
9. Bridge the Gap - SYNGAP Education and Research Foundation (Bridge the Gap)
10. CFC International Cardio-Facio-Cutaneous Syndrome (CFC International)
11. Chelsea's Hope Lafora Children Research Fund (Chelsea's Hope)
12. Christianson Syndrome (Christianson)
13. Chromosome 9p minus Network (9p minus)
14. CSWS Epilepsy & Landau-Kleffner Syndrome (ESES) Foundation
15. Cure AHC - Cure Alternating Hemiplegia of Childhood
16. Cure GRIN Foundation (Cure GRIN)
17. CureSHANK (CureSHANK)
18. DDX3X Foundation (DDX#X)
19. DNM1 Dynamos – Connecting DNM1 Families (DNM1)
20. Doose Syndrome Epilepsy Alliance (Doose)
21. Dravet Syndrome Foundation (Dravet)
22. Dup 15q Alliance (Dup 15q)
23. FamiliesSCN2A Foundation (Families SCN2A)
24. FOXG1 Research Foundation
25. GLUT1 Deficiency Foundation (GLUT1)
26. Grin2B Foundation (Grin2B)
27. Hope for HIE
28. Hope for Hypothalamic Hamartomas (Hope for HH)
29. Hope4Harper (Harper)
30. Infantile Spasms Community
31. Infantile Spasms Project
32. International Foundation for CDKL5 Research (IFCR)
33. Jeavons Syndrome
34. KCN2q Cure
35. KCNMA1 Channelopathy International Advocacy Foundation (KCIAF)
36. KiF1A Associated Neurological Disorder (KIF1A)
37. LGS Foundation (LGS)
38. Lissencephaly Foundation Inc.
39. Liv4TheCure
40. Mickie's Miracles
41. Milestones for Children
42. Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE) [2]
43. NORSE Institute (Norse)[3]
44. PCDH19 Alliance
45. Phelan-McDermid Syndrome Foundation (PMSF)
46. Pitt Hopkins Research Foundation
47. PMG Awareness Organization[4]
48. Project 8p (8p)
49. PVNH Support & Awareness (PVHN)[5]
50. RASopathies Network
51. RE Children's Project
52. Rett Syndrome
53. Ring Chromosome 20 Alliance (Ring 20)
54. Ring14 USA Outreach (Ring 14)
55. RogConBio[6]
56. Ben's Dream – the Sanfilippo Research Foundation
57. Shay Emma Hammer Research Foundation (SEHRF)
58. SLC6A1 Connect (SLC6A1)
59. STXBPI Disorders[7]
60. SynGAP Research Fund (SynGAP)
61. TBC1D24-Spectrum Family Network (TSFN)[8]
62. Tess Research Foundation (Tess)
63. The Bow Foundation (Bow)
64. The Brain Recovery Project Childhood Epilepsy Surgery Foundation (Brain Recover)
65. The Carson Harris Foundation
66. The Champ 1 Research Foundation
67. The Cute Syndrome Foundation (Cute)
68. The Hemispherectomy Foundation
69. The Jack Pribaz Foundation (KCNQ2)
70. The Neurofibromatosis Network
71. The Sturge-Weber Foundation
72. Theo's Village: The TBCK Foundation
73. Tuberous Sclerosis Alliance (TS Alliance)
74. United Mitochondrial Disease Foundation (UMDF)
75. Wishes for Elliott (Wishes)

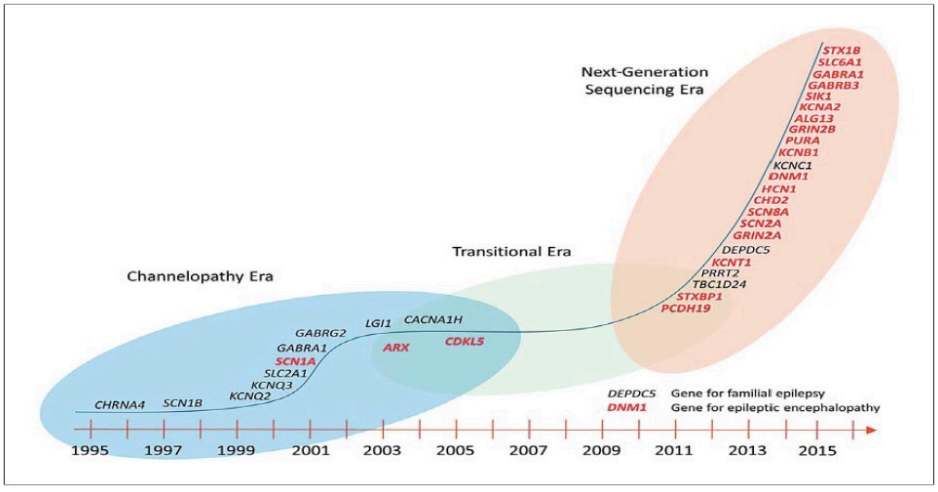
[1] Abbreviated names for organizations follow each name in parens for reference throughout the document.
[2] Single individual as contact. Not aware of a website or Facebook page.
[3] NORSE stands for New onset refractory status epilepticus.
[4] PMG stands for Polymicrogyria.
[5] PVHN stands for Periventricular nodular heterotopia.
[6] Rog Con was originally identified as a Rare but excluded as a commercial entity.
[7] Single individual as contact. Not aware of a website or Facebook page.
[8] Single individual as contact. Not aware of a website or Facebook page.

IV. BACKGROUND

75 organizations were invited to participate in the Rare Epilepsy Landscape Analysis (RELA) Survey. 44 Rare epilepsy organizations completed the RELA survey and are included in the analysis that follows. **Participation from 59% of the Rare community speaks volumes to this community's initiative and desire to learn, share, collaborate, and grow.**

The Rise of Rares. While there was sporadic growth of Rares from the 80's through the early 2000's, the number of rare epilepsy organizations has been steadily on the rise since 2008.



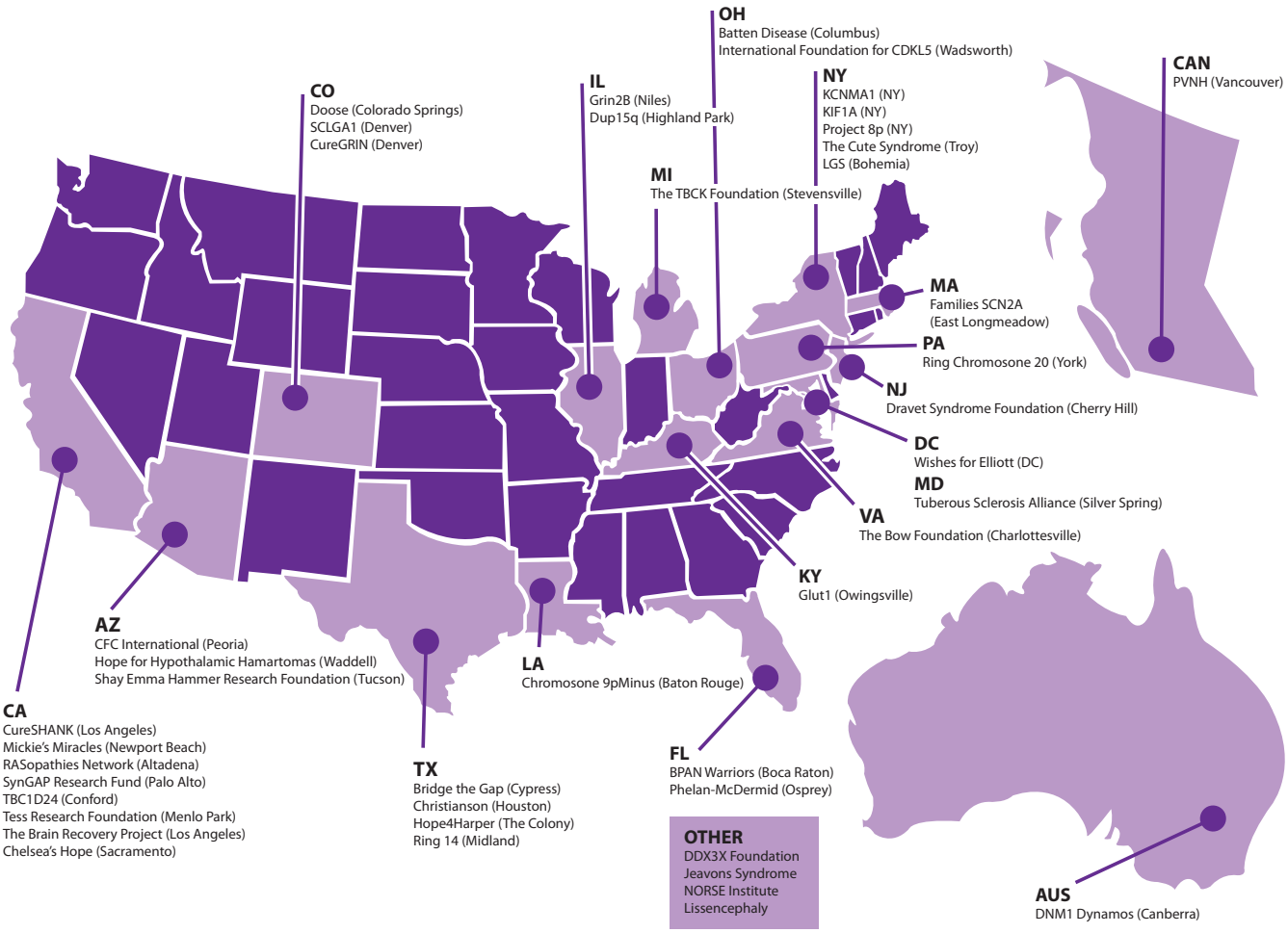


Some of the growth has been fueled by the discovery of new genes as part of the Next-Generation Sequencing Era as it has been coined. Image credited to Helbig, I and Tayoun ANA, Mol Syndromol, 2016. The late 2000's has seen one gene discovered after the next with more on the horizon. Per a 2017 article published in The European Journal of Epilepsy titled *Seizure*, 977 genes were found to be associated to epilepsy and 84 of those genes were considered epilepsy genes or genes that cause epilepsies or syndromes with epilepsy as the core symptom.[9]

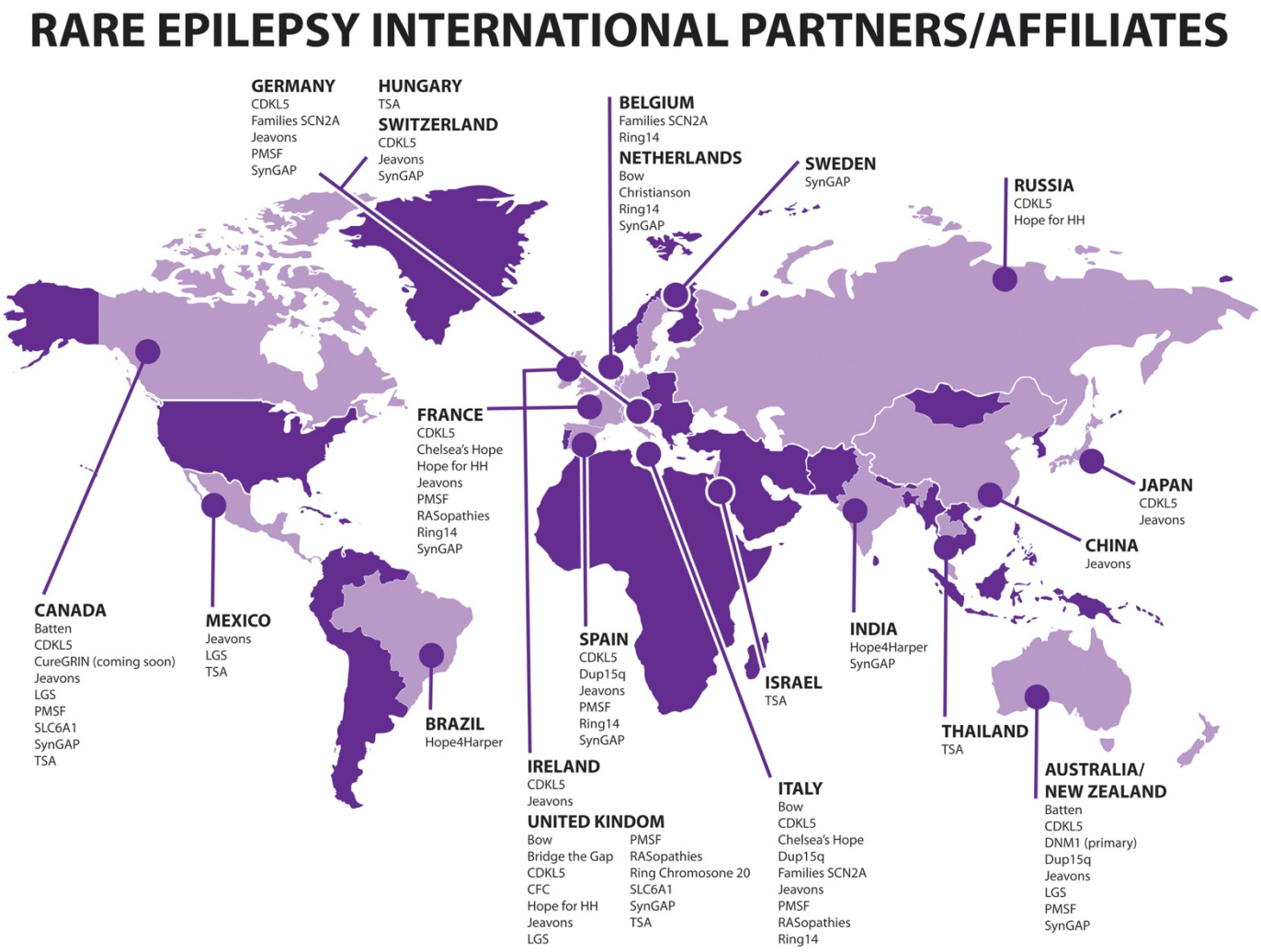
[9] https://doi.org/10.1016/j.seizure.2016.11.030

RARE Organizations in the US. Rare Epilepsy Organizations are dispersed around the United States and abroad. New York and California had the largest concentration of Rares. 35 Rares identified as international or global; 8 identified as National only. Several organizations that identified as national shared that they support international families as needed. Moreover, several US organizations shared they were part of a global partnership in their disease space. Most organizations have only a single location. Exceptions included Hope4Harper with chapters in TX & CA; DNMI which is based in Australia but has a Chapter in CA and TS Alliance noted 46 community alliances across the United States.

RARE EPILEPSY ORGANIZATIONS BY STATE



RARE Organizations' International Affiliates & Partners. 17 organizations reported they did not have international affiliates. 5 had a single international affiliate; while 4 organizations reported either 2, 3-5 or 6-10 international affiliates. 8 organizations responded "other" qualifying expansion into new areas, noting that they had active members in countries and were working to establish legal affiliates. PMSF cited both global partners as well as links to Facebook groups in 13 countries. Ring14 shared they were part of Ring14 International which coordinates the national organizations.



RARES in the Same Disease Space. 22 respondents said there are other groups in their same disease space and 18/22 partner with other organizations in the same space. See Appendix B for Rares Grouped by Same Disorder. 20 groups were unaware of other groups in the same space. 7 groups expressed they do not partner with others.

V. RESULTS

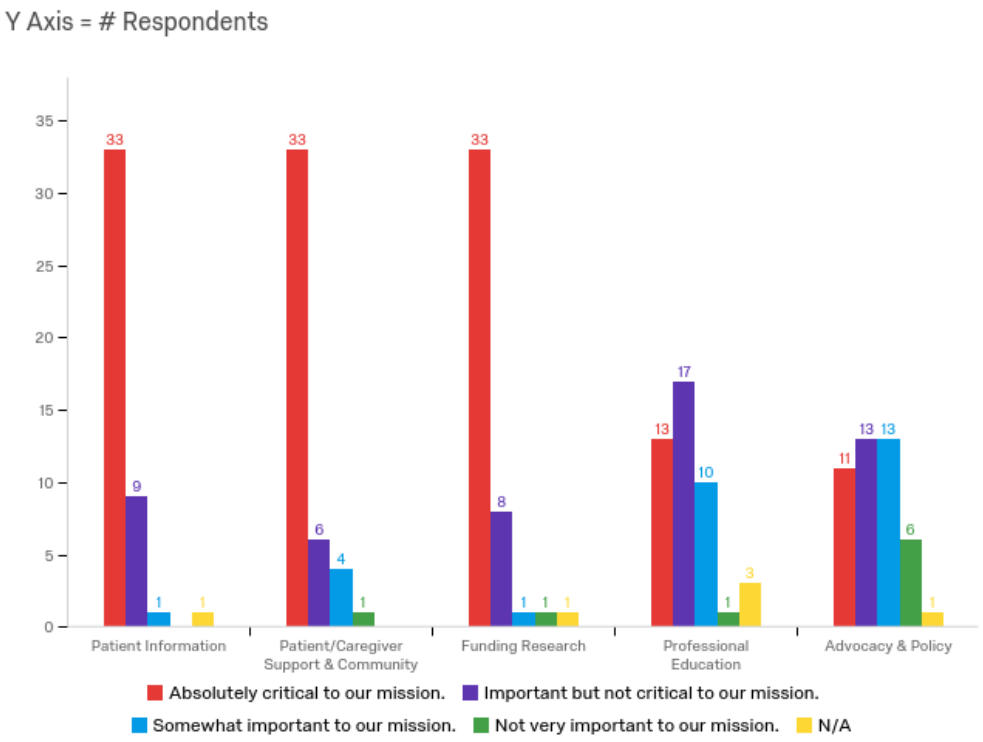
A. FOUNDING, PRIORITIES & CHALLENGES

> ***RARE INSIGHT:*** *When our daughter, Lucy, was diagnosed with GRIN2B-Related Neurodevelopmental Disorder in November of 2014, there was no organization, support system or network of families anywhere in the world. Our family was devastated and felt alone without any sort of family support system or structure. Slowly, through social media, we discovered other families around the United States and around the world.*

Founding stories as shared by the survey respondents can be found in Appendix C. Common themes include:

- Founding by parents of children with very rare condition
- Motivated by lack of information, research, treatments
- No entity providing information, support or community
- Internet/list-serve/chat groups instrumental in connecting disparate families and decreasing isolation
- Originate often for information and support but frequently transition to research giving lack of research dollars generally and underfunding globally

Mission Critical. Patient Information (33), Patient Support & Community (33) and Funding Research (33) were tied as critical to the overarching mission of the organizations surveyed. Although Professional Education was deemed important but not critical it repeatedly came up in the following question where organizations were asked to describe their top 3 priorities. Advocacy and policy were ranked by 26 Rares as important or somewhat important to mission.



Strategic Priorities. For a complete list of Strategic Priorities see Appendix D. Several that cut across many organizations included:

- Creating opportunities to support families and build community online and in person
- Raising awareness of diseases among professionals
- Accelerating research and grants
- Developing consensus based guidelines for treatment

Strategic Challenges: Top Strategic Challenges are shared in Appendix E. Common themes across Rares included:

- Lack of family engagement in time, funding, and research
- Difficulty prioritizing activities in light of short staff and limited funding
- Under diagnosis of the disease coupled with small patient populations which undermine access/interest of pharmaceuticals and clinical trials
- Lack of coordination and communication among researchers and clinicians

B. DISEASE IMPACT

Diagnosing Rares. Many Rares rely on a combination of tools for diagnosis including clinical evaluation, EEG, Genetic/Molecular testing, MRI and axillary skin biopsy. The following diseases reported diagnosis was based exclusively on Genetic/Molecular testing: GRIN2B, GNAO1, GAT1, KIF1A, Ring Chromosome 20, SCN2A, STK9, CDKL5, Chromosome 8p, SCN8A, WDR45/WIPI4, 22q Deletion, Shank3 mutation, CLN1, CLN2, CLN3, CLN4, CLN5, CLN6, CLN7, CLN8, CLN10, CLN11, CLN12, CLN13, CLN14, SYNGAP1, Ring 22, SLC13A5, DNM1, SLC9A6, TBC1D24, SYNGAP1, and TBCK. In regard to diagnosis, PVNH described the significance of referrals from other specialties like GI, cardiology, and pulmonology. NORSE explained, " NORSE is a clinical presentation not a diagnosis. It is also arrived at by a process of exclusion so that many tests are done to rule out specific causes. NORSE occurs in "a patient without active epilepsy or other preexisting relevant neurological disorder, with new onset of refractory status epilepticus without a clear acute or active structural, toxic, or metabolic cause."[10]

Population Burden. Variable reports were received for incidence and prevalence making comparisons challenging. Several Rares had no stats for incidence or prevalence and it was unclear if they do not exist or they were not aware of them. Others indicated that disease was likely underreported. By definition as Rare, these are conditions that affect fewer than 200,000 people. International burden estimates (i.e., prevalence, incidence) submitted by individual Rares are below and include reference in footnote where provided.

[10] https://onlinelibrary.wiley.com/doi/full/10.1111/epi.14016

Population Burden – International Incidence Estimates Submitted by Survey Respondents.

Organization	Gene	International Incidence (Percent)	Converted to 1 million denominator for comparison
Tuberous Sclerosis Alliance[11]	TSC1, TSC2	1/6,000	166/1 Million
FamilieSCN2A Foundation	SCN2A	1/10,000	100 /1 Million
Dup15q Alliance	15q11.2-13.1	1/10,000	100/1 Million
CureSHANK	22q13 Deletion or SHANK3 mutation	1/15,000	66/1 Million
Dravet Syndrome Foundation[12]	SCN1A	1/16,000	62/1 Million
Glut1 Deficiency Foundation[13]	SLC2A1 gene	1/24,000	41/1 Million
SLC6A1 Connect	GAT1	1/38,000	26/1 Million
International Foundation for CDKL5 Research[14]	CDKL5	1/40,000-1/60,000	16-25/1 Million
Chromosome 9pMinus Network	Chromosome 9	1/50,000	20/1 Million
Hope for Hypothalamic Hamartomas	Hypothalamic Hamartoma	1/200,000	5/1 Million
CFC International	BRAF, KRAS, Map2K1, Map2K2, YWHAZ	1/880,000	1/1 Million
Ring14 USA[15]	ring chromosome 14	unknown, but <1/1,000,000	1/1 Million
Chelsea's Hope[16]	EMP2A, EMP2B	1-4/1,000,000	1-4/1 Million
Organization	**Gene**	**International Incidence (Number)**	
Phelan-McDermid Syndrome Foundation[17]	Ring 22, 22q13 deletion, SHANK3 mutations	150	
Bridge the Gap - SYNGAP Education and Research Foundation[18]**; SynGAP Research Fund**[19]	SYNGAP1	350-400	
Mickie's Miracles	ISAN	2,000-4,000 new cases per year	

[11] Tuberous Sclerosis Complex: Genes, Clinical Features, and Therapeutics Edited by DK Kwiatkowski, VH Whittemore, and EA Thiele. Wiley-Blackwell 2010 https://www.tsalliance.org/healthcare-professionals/key-medical-publications/

[12] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4621800/, https://onlinelibrary.wiley.com/doi/full/10.1111/dmcn.12709 https://onlinelibrary.wiley.com/doi/full/10.1111/epi.12927

[13] https://academic.oup.com/brain/article/142/8/2303/5532195

[14] There are multiple sources (Olson and Demarest both have 2019 clinical papers linked) - this is a link to search CDKL5 papers: https://rareomics.healx.io/disease/cdkl5-disorder

[15] http://ring14usa.com/index.php/research/bibliography/; https://ojrd.biomedcentral.com/articles/10.1186/s13023-017-0606-4

[16] https://www.valerion.com/advances-in-neurodegenerative-disease-research-and-therapy/; https://www.valerion.com/technology/lafora-disease/; https://www.cell.com/cell-metabolism/fulltext/S1550-4131(19)30375-4?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1550413119303754%3Fshowall%3Dtrue; https://www.aesnet.org/meetings_events/annual_meeting_abstracts/view/546387; http://www.jbc.org/content/293/19/7117; https://indiana.pure.elsevier.com/en/projects/lafora-epilepsy-basic-mechanisms-to-therapy; https://www.nature.com/articles/s41582-018-0057-0; https://www.jle.com/fr/revues/epd/e-docs/lafora_disease_308085/article.phtml?tab=texte; https://www.ionispharma.com/indications/lafora-disease/

[17] https://www.genecards.org/cgi-bin/carddisp.pl?gene=SHANK3; https://www.ncbi.nlm.nih.gov/books/NBK1198/

[18] https://www.ncbi.nlm.nih.gov/pubmed/31454529; https://www.ncbi.nlm.nih.gov/pubmed/31395010; https://www.ncbi.nlm.nih.gov/pubmed/30789692

[19] http://epilepsygenetics.net/syngap1-this-is-what-you-need-to-know/

Population Burden – International Prevalence Estimates Submitted by Survey Respondents.

Organization	Gene	International Prevalence (Number)
DNM1 dynamos - Connecting DNM1 Families[20]	DNM1	50-60
Christianson Syndrome Association[21]	Slc9a6	51
The TBCK Foundation[22]	TBCK	60
Ring Chromosome 20 Alliance	Ring chromosome 20	150
The Cute Syndrome[23]; Shay Emma Hammer Research Foundation[24]	SCN8A	250-300
Chelsea's Hope		250
CureGRIN Foundation	GRIN1, GRIN2A, GRIN2B, GRIN2D	500
CFC International	BRAF, KRAS, Map2K1, Map2K2, YWHAZ	600
Dup15q Alliance	15q11.2-13.1	1,000
Glut1 Deficiency Foundation	SLC2A1	1,000
Phelan-McDermid Syndrome Foundation	Ring 22, 22q13 deletion, SHANK3 mutations	1,000
Hope4Harper[25]	STK9, CDKL5	6,000
Batten Disease Support and Research Association[26]	CLN1, CLN2, CLN3, CLN4, CLN5, CLN6, CLN7, CLN8, CLN10, CLN11, CLN12, CLN13, CLN14	14,000
Hope for Hypothalamic Hamartomas	Hypothalamic Hamartoma	30,000
DDX3X Foundation[27]	DDX3X	468,000-930,000
Tuberous Sclerosis Alliance	TSC1, TSC2	1 million
LGS Foundation		1 million
Organization	**Gene**	**International Prevalence (Percent)**
Bridge the Gap - SYNGAP Education and Research Fnd	Syngap1	2-8%/10,000 with ID
Mickie's Miracles	ISAN	1.5 to 2 /10,000 children
SLC6A1 Connect	SLC6A1	1/38000
Project 8p	Chromosome 8p	1/30,000
RASopathies Network[28]		roughly 1/1000

[20] The information above is based on the information shared among various families within the organization (Facebook Private Group).

[21] CSA data base for prevalence Dr Morrow info on What is CS on CSA website as events page www.csa-cares.org

[22] CHOP TBCK Research page

[23] Influence of age at seizure onset on the acquisition of neurodevelopmental skills in an SCN8A cohort Alejandra C. Encinas1 | Ida (Ki) M. Moore2 | Joseph C. Watkins1,3 | Michael F. Hammer1,4 The spectrum of intermediate SCN8A-related epilepsy Katrine M. Jo

[24] scn8a.net see references in section on published scientific articles

[25] https://www.jneurosci.org/content/early/2019/04/05/JNEUROSCI.2041-18.2019/tab-article-info?versioned=true https://www.louloufoundation.org/announcements.html

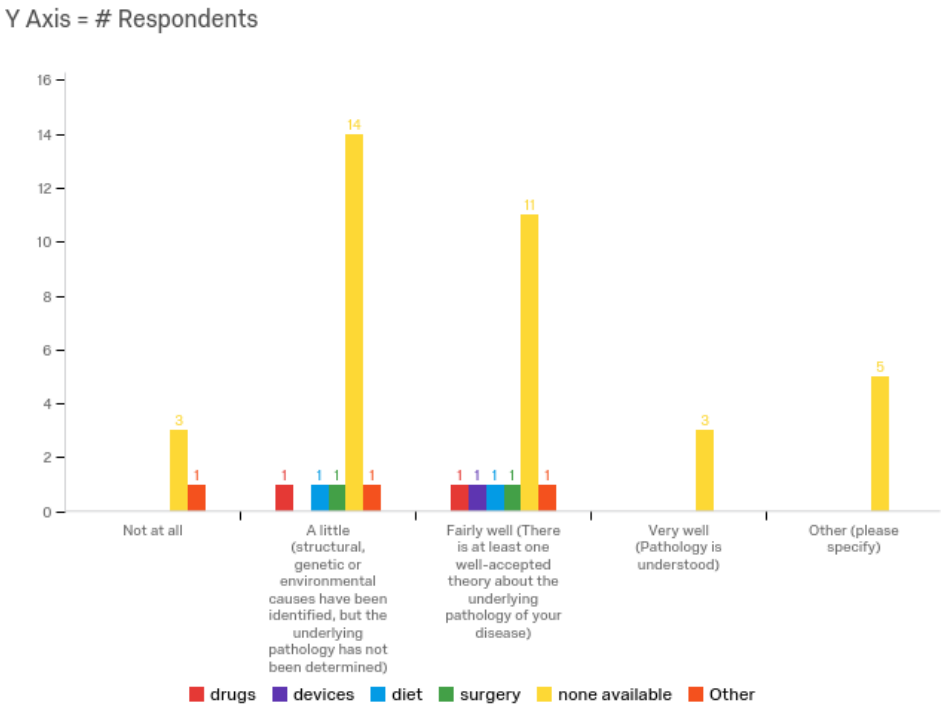
[26] The Neuronal Ceroid Lipofuscinoses (Batten Disease) (Contemporary Neurology Series) 2nd Edition by Sara Mole (Author), Ruth Williams (Author), Hans Goebel (Author)

[27] Snijders Blok, et al. Mutations in DDX3X Are a Common Cause of Unexplained Intellectual Disability with Gender-Specific Effects on Wnt Signaling, American Journal of Human Genetics. July 30, 2015

[28] As reported by RASopathies Network: * CS prevalence: 1:380,000 - Giannoulatou et al. https://www.pnas.org/content/110/50/20152 2013

C. Rare Diseases

Disease Understanding. When Rares were asked "how well understood is the underlying pathology of each disease," most of the diseases were reported by Rares as understood "just a little." At the extremes, only 3 Rares were reported as "understood very well" including: Tuberous Sclerosis complex, SCN2A and Dravet. Four Rares were reported as "are not understood at all" including: Jeavons, Norse, CDKL5, and TBC1D24. 16 believed they were "understood a little" and 13 thought they were "understood fairly well." The other point that was emphasized is that even within several rare diagnoses there are often many types. For example, there are 13 forms of Batten disease each with a different genetic cause. Also, there are many causes of PVNH and while more is known about the prevalent form FLNA accounting for 50% of the cases, there is still much unknown about others.



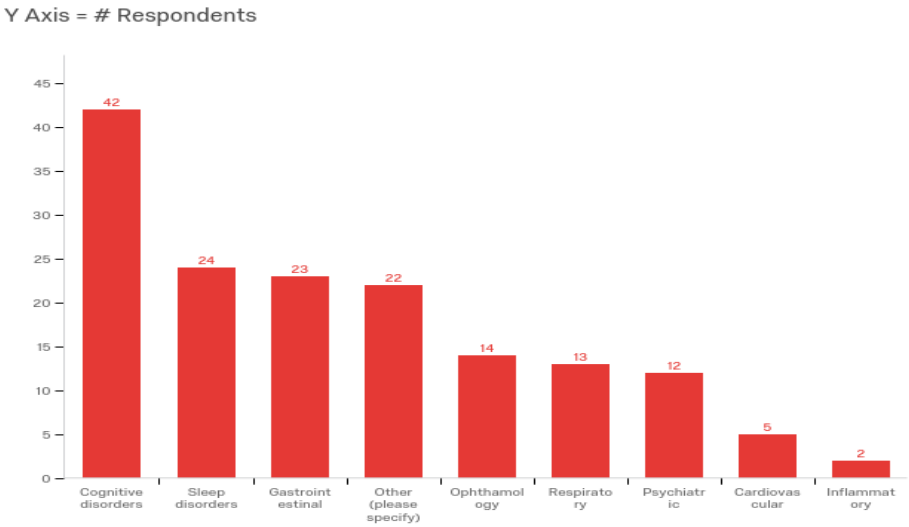
Rare Cures. For 3 of the conditions believed to be understood very well, no cures were reported as available. The majority of Rares reported no cures are available highlighted in the Yellow bars at right and highlighted later in this analysis.

Shared Genes, Channels & Pathways. Some conditions reported sharing genes, channels and other pathways with other rare epilepsies as follows:

Pathway, Gene, Channel	Shared Syndromes
15q	Dup15q; Angelman, Prader-Willi
Rett	Rett (MECP2); CDKL5; FoxG1; STK9
Ion Channelopathy Sodium Channelopathy	Dravet (SCN1A); SCN2A; SCN8A; SLC13A5 (ion channels transporter?)
GRIN NMDA Receptors	GRIN1, GRIN2A, GRIN2B, GRIN2D
RASopathies	Noonan Syndrome; Cardio-Facio Cutaneous Syndrome; Costello Syndrome; Neurofibromatosis; Leguis Syndrome; Capillary malformation arteriovenous malformation syndrome; Central conducting lymphatic anomaly; Lymphastic disorders with RAS/MAPK; (RAS; RAP Glutamate?)
Medulloblastoma, Leukemia, Lymphoma	DDX3X
Ring	Ring14 Syndrome Ringq deletion FOXG1
Neurotransmission via impaired synaptic vesicle endocytosis	DNM1
PMS	Ring 22; 22q13 deletion; SHANK3 mutation; HCN Channelopathy; mGluR; AMPAR; NMDAR; TS (may share a molecular pathway with PM)
Glycogen Storage Dx	LaFora; Pompe
MTOR Pathway	TBCK gene; TSC 1 & 2
Hedgehog Pathway	Hypothalamic Hamartoma

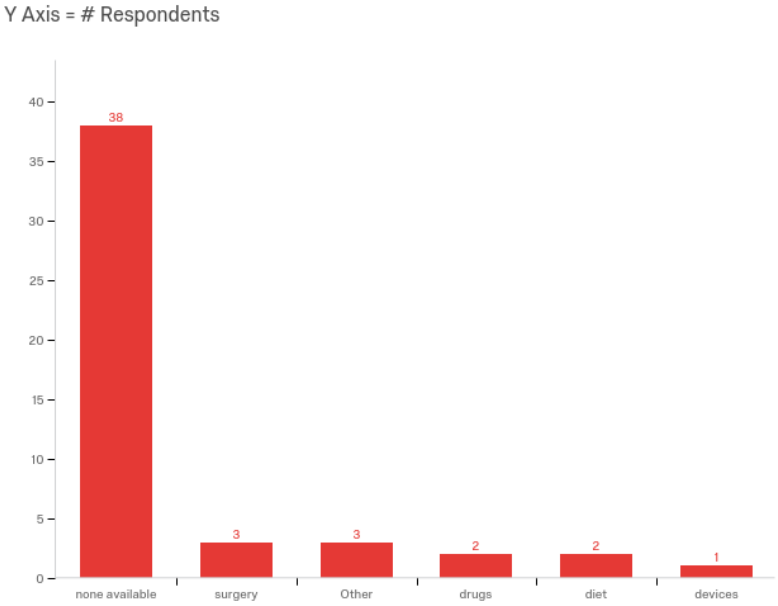
* CFC prevalence: 1:190,000 - note: A key veteran researcher, Bronwyn Kerr, who contributed to the 2013 CS prevalence report, stated that they found CFC's prevalence was double CS's - but has not published this finding * NF1 prevalence: 1:2,500 * NS prevalence: 1:2,500 to 1:1,000 *

Comorbidities in Rares. The Rare Epilepsy Network (REN) registry has collected information on comorbidities associated with their respective conditions. In this survey, only one question was asked on comorbidity. Cognitive disorders were most frequently identified among the Rares. Following cognition, sleep and gastroenterology came in at 24 and 23 respectively followed by ophthalmology (14), respiratory (13) , and psychiatry (12). Additional comorbidities raised in other the follow below.



Other Comorbidities Common to Rares:

• Apraxia • Autism • autonomic dysfunction • bruxism • cerebellar atrophy • cognitive decline • dementia • dermatological • dysphagia • dystonia • facial angiofibromas	• global delay • developmental delay • hyperkinesis • hypotonia • low muscle tone • Microcephaly • motor sensory and cognitive pathways disruptions • movement disorders • Non-Ambulatory • Nonverbal	• oropharyngeal dysfunction • orthopedic • postural instability • progressive parkinsonism • pronated feet • Relative Brain Atrophy • renal angiomyolipomas • Scoliosis • Sensory processing disorder • skin lesions • Speech Delays



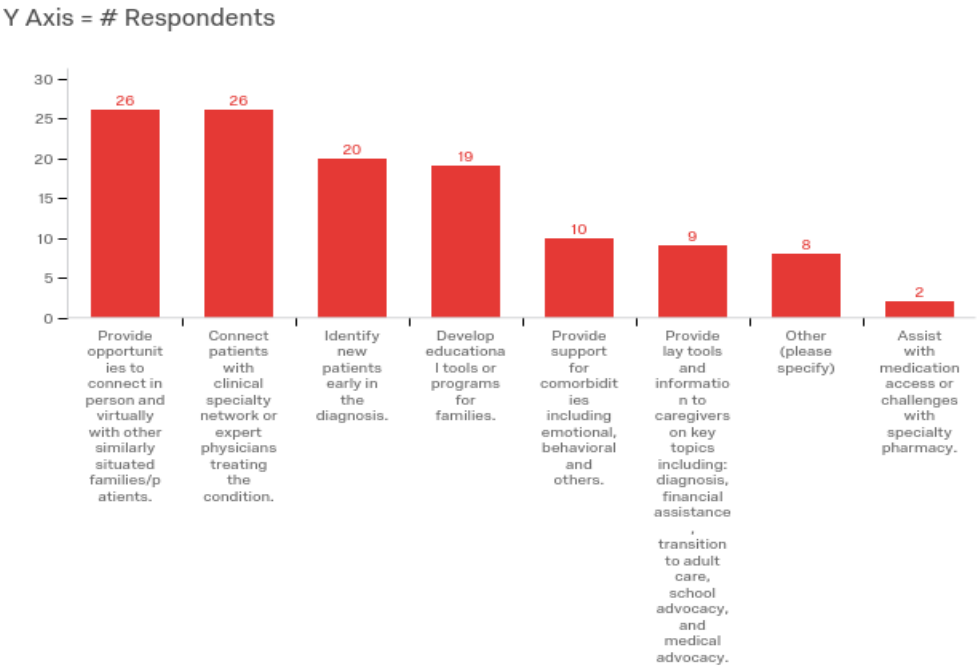
Lack of Cures. For the majority of Rares (38), no cure is available. For a very small number diet, devices, surgery and other can be effective in eliminating seizures. For other, Rares reported in Doose, some patients have gone into spontaneous remission. Some find seizure control through some medications, CBD, or the ketogenic diet. But they are not cured. TBCD124 relies on AED and antipsychotics. Uniquely, Mickie's Miracles relies on drugs, devices, diet and surgery toward cure. Brain Recovery and Hope for HH have surgery that is curative for some.

Cure Rates. For the conditions where there is a prospective cure, the cure rate is reported as 51-75% for Hypothalamic Hamartoma. For SLC13A5 and Ring Chromosome 20 the cure rate was reported as 1-5%. In other, Brain recovery project shared that cure depends on a constellation of factors: etiology, length of time seizing prior to surgery, type of seizures, whether there is a genetic component, etc. RASopathies shared, "I can speak for Costello syndrome: in 2011 at the Costello Syndrome Family Conference, we were able to say that there may be a therapy for our children; parents of even the most medically-fragile, unable-to-live-without-a-lot-of-assistance child said they would have to think very hard about a cure if it took away our children's "Costello" personality."

D. INFORMATION, SUPPORT & COMMUNITY PRIORITIES & CHALLENGES

Signature Programs & Services. Rares were asked to share signature Patient/Caregiver programs and services they have developed that could be shared. A complete list can be found in Appendix F. Signature programs included videos, brochures, meet ups, family conferences, research symposiums, patient registry, research grant programs, PSA animations, multi-disciplinary clinics, Ask Expert chats, emergency medical funding and more. The replies demonstrate the breadth of programs, resources and know how in the community and are a starting point for any organization preparing to undertake a new endeavor.

Patient Information, Support & Community Strategic Priorities. When asked for top 3 patient information, support and community strategic priorities, connecting patient to patient (26) and patient to specialist (26) tied as the top two priorities. The next two priorities included identifying new patients early in the diagnosis (20), as well as developing educational tools or programs (19) for families. In the other category, Rares noted expanding skills of parents/caregivers to advocate for and access appropriate educational services to improve QOL.



Biggest Challenges. Among the biggest challenges developing/delivering services to disparate patients and providing specialized support for patients with a broad spectrum of disorders were ranked 11 and 9 respectively, followed by lack of collaboration (6). However, a majority of orgs denoted "other "(15) and the biggest challenges they reported included:

- Lack of collaboration among researchers and doctors to avoid duplicated efforts
- Newness of the disease
- Lack of doctor awareness of the disease.
- Lack of families' willingness to contact organizations for privacy or other reasons
- Abundance of issues/staff being overwhelmed/lack of capacity
- Formalizing the organization structure as a 501c3
- Translation of information from Patient Advocacy Group (PAG) to patient

Patient/Caregiver Discovery of Rare. The most predominant way rare patients and caregivers find Rare organizations is via the Internet (41). Referrals from doctors or health professionals (20) had the next highest rating. Additionally, FB support groups, social media, community events and referrals from other groups, individuals and organizations were mentioned as well. KCNMA1 reported that a recent Netflix series led to patient referrals: Netflix Diagnosis series, Episode #4 'It takes a village'. Referrals from NORD/Global Genes (5), general epilepsy groups like AES, EF, REN (4) and NINDS (3) was perceived to be very low.

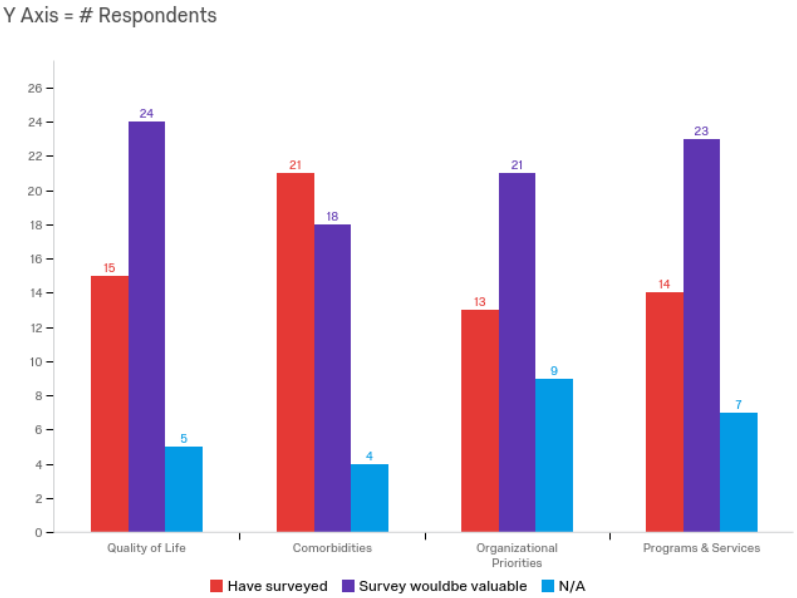
Racial & Economic Diversity in Rare Diagnoses. Most groups reported that their patient population is both racially and economically diversified (33). However, some groups reported economic but not racially diversified (5); other groups were not sure (2); and one group felt it was neither racially nor economically diversified. In "other", groups commented that "because we're internet-based, we do require literate parents who have access to the Internet (have computers, etc.)" which suggests there may be a digital divide. Another group reported that despite their racial/economic diversity "there is not a balance as access to healthcare and genetic testing is not easy to access" raising important concerns about access to care for all.

Programs & Service Priorities. In regard to Programs and Services priorities, response are divided into what Rares currently have, what they want and what is not a priority. This insight could be used to align organizations that have a shared want with organizations that have a resource. The "wants" include areas for potential large scale collaborations. Even within "the haves" and those items that are deemed "not a priority" there are wants for some organizations.

Summary of Programs & Service Priorities:

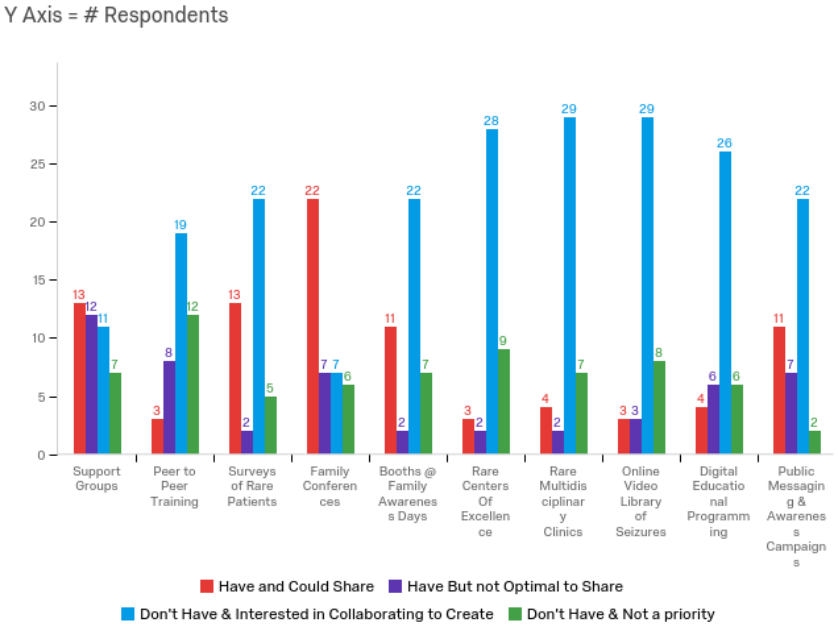
Have	Want	Not a Priority
• Websites (43) • Family Conferences (29) • Facebook Helpline (28) • Newsletter (28) • Registries (27); 12 want • Fact Sheets, Brochures (26) • Support Groups (23) • Email Helpline (21)	• Clinical Trials or studies (26) • Translation of websites (25); services (23); digital and other content into other languages (22) • Biosample repositories (24) • Legal guidance re: education and IEPS (22) • Specialized Clinical/Treatment Centers (21); 17 have • Digital Programming (20); 19 have • Peer to Peer Counseling (19); 15 have	• Malpractice (39) • Legal Guidance re workplace (35) • Camps (34) • Professional Counseling (32) • Crisis Intervention (32) • Hospice Care (32); 10 want • Insurance (31) • Rehab Services (30) • Transportation (30) • Grief Counseling (28) • Respite Care (28); 14 want • Institutional Placement (28) • Telephone Helpline (26) • Referrals (24) • Home Modification (23)

Rare Surveys. Rares expressed value for constituent and stakeholder surveys on topics including Quality of Life, Organizational priorities, and Programs and Surveys. A significant number of organizations have conducted surveys on these topics that may provide resources/templates. In "other" some Rares shared that although they have not undertaken formal surveys, they have obtained informal feedback during breakouts during conferences on topics to gather feedback.



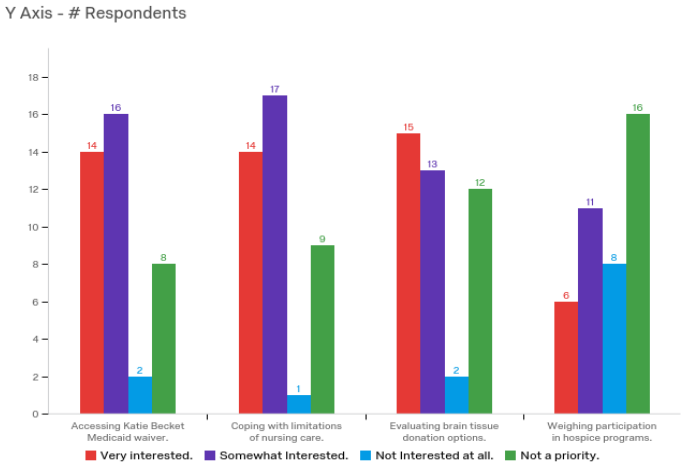
Rare Care Via Clinics & Specialty Centers. Less than half of respondents (17) reported the availability of either a specialty disease clinic (9) or hospital with specialized center (8). In addition to Clinics and Centers, some Rares described consortiums including multiple Rares and/or hospitals. Several Rares commented that while they may be aware of centers with expertise and capacity to treat all aspects of patient concerns, the organizations do not use a vetting/certification process. The majority of organizations responded other to this question and shared in many instances there are a handful of doctors that have seen multiple patients with any given disorder and have become experts e.g., Tess, CureGRIN. Several Rares reported this was a priority and in development e.g., Brain Recovery wants to create a list of what surgeries are performed where plus level of experience.

Clinics	Centers	Consortiums
1. CDKL5 Centers of Excellence 2. Bridge the Gap – Specialty Disease Clinics 3. CureSHANK: Clinics at Seaver Autism Center, Texas Children's Hospital, Mass General, Miami 4. 15q Clinical Research Network 5. CFC International 6. SLC6A1 Connect 7. TS Alliance	1. Hope for HH Treatment Facilities 2. Batten Centers of Excellence 3. Cute Syndrome – Children's National Hospital – John Schreiber 4. Mickie's Miracles: CHOC Children's Neuroscience Institute 5. Chelsea's Hope: UT Southwestern & UCLA 6. Dravet – Centers that treat all aspects of the disease 7. BPAN: OHSU, http://nbiacure.org/nbia-clinic/nbia-center-of-excellence/ has an NBIA Centers of Excellence (BPAN is 1 of now 15 NBIA conditions) 8. SCN2A: ENGIN @ CHOP 9. KIF1A: Many patients make clinical appointment with our primary research lab (which includes PH.D/MD experts) 10. PVNH (Hospitals with expertise in Netherlands, UK, US)	1. Phelan: Rare Disease Clinical Research Network Developmental Synaptopathies Consortium (with Tuberous Sclerosis and PTEN) 2. NORSE: Clinicians who are members of the Critical Care EEG Monitoring Research Consortium, all neurophysiologists specializing in EEG monitoring, are familiar with NORSE. The ongoing prospective observational study of NORSE patients is being conducted through their membership.



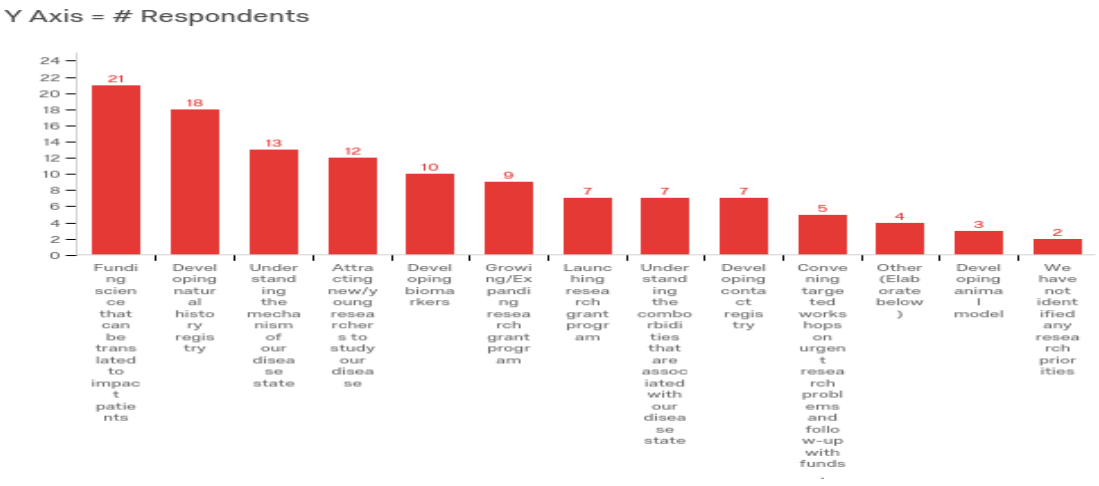
Sharing Opportunities. Many opportunities were identified for sharing across programs and services with the highest interest in Rare Multi-disciplinary clinics (29) and online video of Library of Seizures (29) followed by Rare Centers of Excellence (28), Digital education programming (26), and public messaging and surveys (22). Other potential patient/caregiver support initiatives included: online patient portal searchable by caregivers with meaningful exchanges protected, roadmap for strategies, getting researchers to work with other similar disorders. Family conferences was an area where a large number of Rares had developed expertise and were willing to share. Some groups reported the same for Support Groups (13) and Public Messaging & Awareness Campaigns (11).

A BONUS Question. was included by Wishes for Elliott asking specifically about resources needed for the most severely affected children. 14-15 Rares were very interested and 13-17 Rares were somewhat interested in Accessing Katie Becket Medicaid waivers, Coping with limitations of nursing and evaluating brain tissue. For other organizations, this was either not an interest or a priority which suggests even among the Rares, there is a spectrum of needs and interests. Other areas requested by families included: respite care, education and transitioning into adult life, caregiver training, free/low-cost transportation services for patients to use for employment or non-medical needs, diagnostic testing criteria education for families. Regarding Katie Beckett, RASopathies shared resources: State-by-State, and Family Voices and Parent2Parent USA for state-specific information, resources and advocacy. Also, respondent Lisa Schroyer – shared, "Through my salaried jobs (for the County of Los Angeles), I participated in California's Pediatric Palliative Care Home and Community-based Services (HCBS) Medicaid waiver, and the accompanying information needed to provide informed advocacy. I'm happy to be tapped individually." Also, K1F1A noted they have established brain tissue donation and Christianson Syndrome Association is in the process of setting up a brain bank.



E. RESEARCH PRIORITIES AND CHALLENGES

Research Priorities. Top three priorities for research were funding science that can be translated to impact patients (21); developing natural history registry (18) and understanding the mechanism of disease state (13), followed closely by attracting new/young researchers to study the disease (12).



Research Challenges. 12 Rares reported their biggest challenge is difficulty connecting researchers to seed collaborations. Connecting to commercial therapy developers received 7 counts. In "other" groups reported,

- Limited access to funding – grants, NIH, biotech, etc.
- Acquiring sufficient patient data to inform clinical trials
- Sustainability of collaborative research initiatives
- Lack of resource/process to enable efficient PAG-Researcher collaborations.
- Shortage of patient diagnosis/identification to increase sample sizes
- Lack of clinician awareness and possibility of underdiagnosis of diseases
- Lack of research strategic planning
- High cost/long term investment required to conduct clinical studies in key areas e.g. comorbidities; develop clinical outcome measurements; and launch natural history studies

Developing a Rare Research Program. Stories describing how Rares developed their research programs are included at Appendix G. When asked to list the first three steps a new Rare should take to advance research, Rares replied below. Find individual advice in Appendix H.

1. Establish a patient registry (9)
2. Organize a Stakeholder conference (7)
3. Coordinate a natural history study (6)
4. Develop a 3 year strategic plan (3)
5. Seed small grants (3)
6. Understand the mechanism of your disease and any related diseases (3)
7. Identify researcher/institution interested in your disease or related diseases. (3)
8. Develop a strong Scientific Advisory Board (SAB) (3)
9. Establish a clearly defined grant program with a thorough grant review process (2)
10. Support a consensus paper on the "State of Science" to identify gaps & priorities. (2)
11. Share your story with researchers and assure them you have data and clinical trial capacity (2)
12. Identify "research clinicians" or person who can translate between patients and scientists (2)
13. Develop Centers of Excellence (1)
14. Work collaboratively; learn from other PAGS (1)
15. Attend conferences to represent disease (1)
16. Develop Animal model (1)
17. Develop a biobank (1)
18. Identify biomarkers (1)
19. Understand drug development and critical bottlenecks (1)
20. Engage NIH program officer (1)
21. Create a master resource library/repository. (1)
22. Disseminate results (1)

RARE INSIGHT.

"Know who your patients are and build a tight-knit community. Our community is our biggest asset. Not only is it the source of our fundraising, but our parents volunteer considerable time and resources, spread awareness and are motivated to travel to participate in studies."

"Commit to funding early investigators annually; not only build knowledge but nurture the development of a growing pipeline of new investigators dedicated to research related to your disease."

"Locate researchers in your disease and related disease. Let them know you have organized the patient community and that you will help them in collecting data and recruitment."

"Support (facilitate/fund) publication by gathered scientists on a consensus paper on the " state of the science" in your disease area including critical gaps and emerging priorities."

"Recognize that it is not uncommon, even in rare diseases, for there to be multiple organizations that are supporting a single rare disease. Egos need to be pushed to the side and the patient leaders need to work with one another collaboratively if they hope to make headway. There is no benefit to divisive or duplicate efforts when there are limited resources - both financial and patient families."

"Constantly ask yourself the question, "what would I do if $1 million for research dropped in my lap tomorrow?" Even if it seems like a dream, you need to be ready. When the funding comes, you have to know what you're going to do with it immediately."

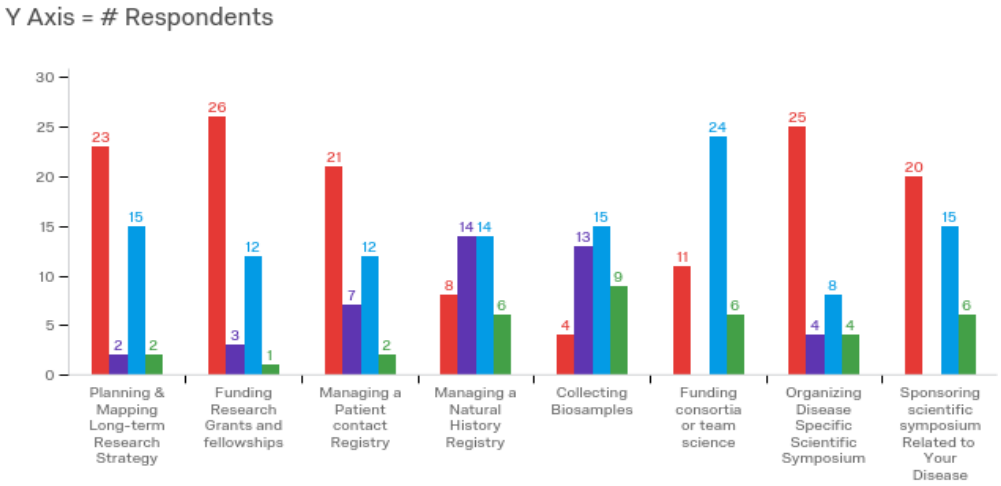
"Find someone passionate about your syndrome who speaks science. You have to have a bridge between the families and the science; someone who can speak to both groups."

"Identify all of the researchers currently working on some aspect of the disease and find a way to bring them together. In the field of LD research, the synergies discovered at the first workshop were astonishing and it was a profound catalyst to research progress."

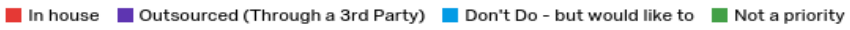
Research Strategic Planning, Decision Making & Grant Review. For 13 Rares, Research strategic planning is driven by the Board of Directors/Leadership. 6 Rares relied on staff; 5 relied on Chief Scientific Officer; and 7 relied on Scientific Advisory Board. Similarly for research decision-making, 12 Rares rely on their Board/Leadership; 7 rely on staff; 3 have CSO; 9 rely on SAB. For Grant review, 17 organizations reported decisions were made by either MAB, SAB or scientifically trained person with 9 reporting decisions were made by either Staff or leadership. The question could have been improved to clarify whether staff had science experience. In Other, Rares reported reliance on external grant review e.g. AES & NORD.

Rare Participation in Professional Meetings. 24 Rares reported attending AES at least once in the last 3 years; 10 attended Child Neurology Society; 8 for American Academy for Neurology (AAN); 6 for Society of Neuroscience and 4 for American Academy of Pediatrics. Other specialty meetings attended included: American Congress of Rehabilitation Medicine; American College of Medical Genetics (ACMG); National Society of Genetic Counselors; Global Genes; Epilepsy Precision Medicine; NORD; So. Cal Rare Disease Genetics Meeting; International League Against Epilepsy (ILAE); European Conferences; and Disease specialty meetings.

RARE INSIGHT. *"We have not yet funded research. Our current research program and strategic plan is primarily patient driven, allowing the patient and foundation leadership to assess the research projects that are most essential for our community. Rather than have open calls for grants we are actively identifying researchers best equipped to complete the research projects most essential to our current strategic plan. Once identified, the projects will be funded. We are choosing to eliminate the standard grant review cycle in lieu of a more expeditious project specific funding strategy to allow very urgent research to be completed very quickly. All the research, grant structure, contracts will be reviewed by foundation leadership and scientific advisory board (which is also concurrently under development). We recognized that we had to do many things in parallel as we are limited in time and our children cannot afford to do things in a linear pattern."*

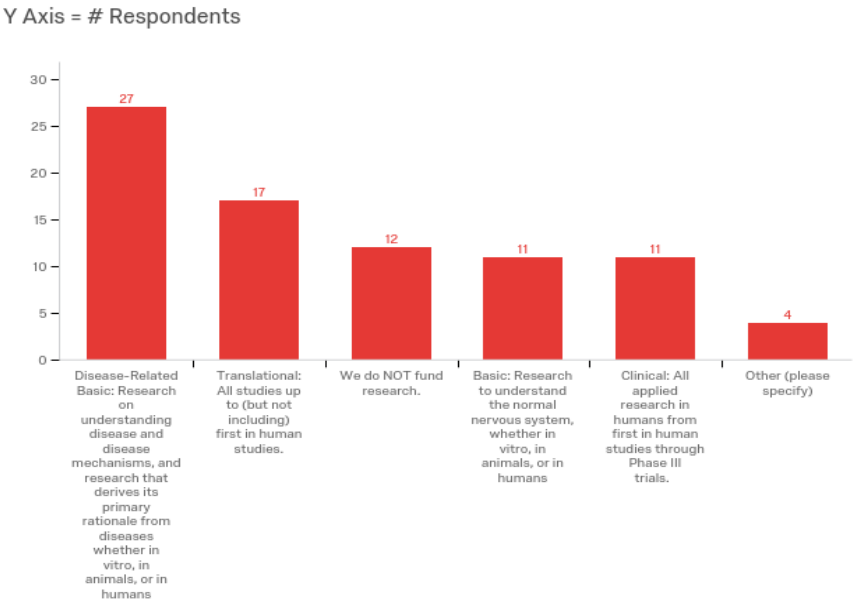


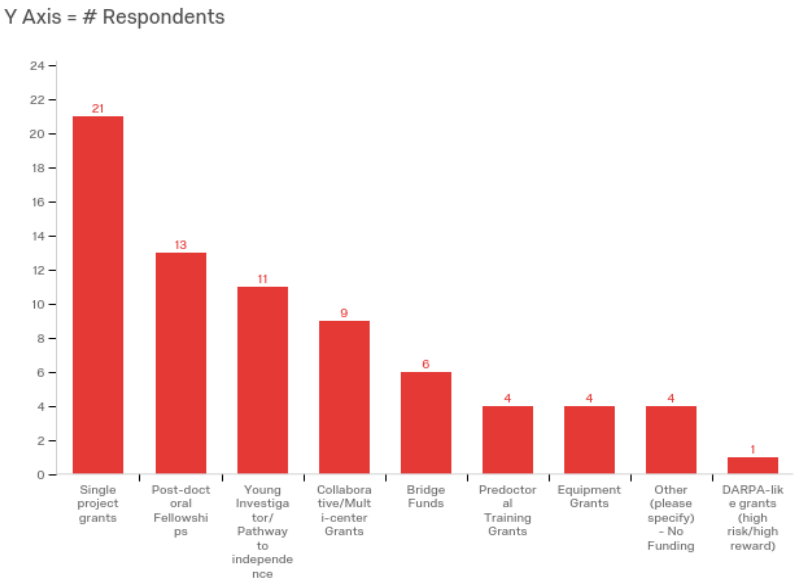
Collaboration & Shared Learning. Opportunities for collaboration and/or shared learning include: funding consortia or team science (24), collecting biosamples (15), managing a natural history registry (14), sponsoring disease symposium (15) and mapping research strategy (15). 50% of organizations have experience planning/mapping research strategy (23), funding grants (26), managing patient registries (21), and organizing disease specific symposium (25) that could be leveraged to educate newer organizations how to do the same.



Research Grant Focus. A majority of groups are funding disease-related basic research followed by translational. 12 groups are not funding research at all. In Other, several Rares reported that they have not launched a research program but plan to, others reported that they want to fund translational and clinical, but the science isn't there yet and others reported they are providing small stipends but not funding large projects.

Current preclinical research is focused on understanding the mechanism of disease (23) and identifying targets for drug development (19). In Other, Rares reported: understanding gene function, biomarker and measurable outcome studies, and collection of data into international registry to disseminate data to researchers and industry plus recruit for studies.

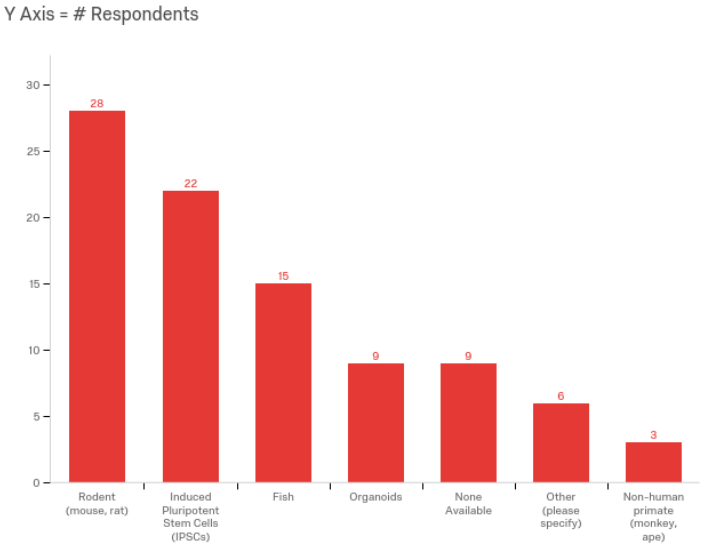




Research Grantees. 21 Rares are funding single project, 13 focus on post-doctoral fellowships, 11 on Young Investigators, 9 on multi-center grants, and 6 on bridge funds. 4 each focus on predoctoral and equipment grants. 4 organizations do not give any funding and only one funded DARPA-like high risk/high reward grants.

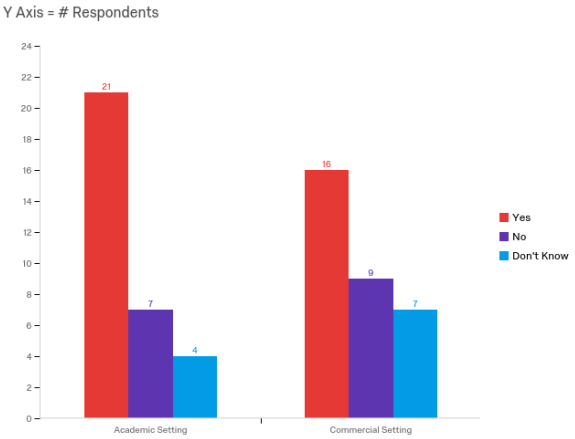
Contact Registries & Natural History Studies. Rares were polled on contact registries as well as natural history registries. There was great variability among responses, but a few trends include contact registries date back to 1989 whereas natural history registries were primarily established 2006 to present. Of the 25 that had contact registries, 16 had natural history registries as well. 3 organizations reported natural history registries but no contact registry. While most operated separate platforms, 4 organizations appeared to either use the same platform and/or host. For more detailed information on registries, contact author.

	Contact Registry	Natural History
	25 registries; 1 launching soon	20 natural history registries
Year Launched	1989 through the present.	2006-present
Housed	Registries ranged from those that were housed in house or in the cloud/online to housed at Invitae, NORD, and a handful of Universities and Foundations including Sanford Research, Columbia, Simons Foundation, Simons Searchlight, U. of AZ, U. MI, UT Southwestern, Western University (Canada) and Freidrich Baur Institute.	The registries are housed inhouse and at Universities including Columbia, Cincinnati, NORD, Telepath Kids/Orphan Disease Center (Australia), Warren Alpert medical School, University of Arizona, University of MN, University of Rochester, UT-Southwestern, Washington University.
Platform	Excel, Google sheets, Etapestry/Blackbaud, Airtable, Invitae, Mailchimp, NORD, Network for good, private, redcap (5), Salesforce, Simon's searchlight and Square space	Pharm-Olam, NIH Data Coordinating Center, NORD, ODC-Pulse, Red-Cap (3) StudyTRAX, Custom.
Enrollees	25 to 5000	20 to 2200
Marketing/ Recruitment	Email, Facebook, website, newsletters, and word of mouth.	Online, Facebook including ads, website, conferences, social media, support groups, coordination with center who houses the registry
Costs	Free and <$1000 to $10000 annually. One organization made a $20,000 initiate set up grant	$3500 at the lower end to upwards of $5M (RDCRN over 5 years, 3 conditions, 10 sites). Other costs include $30k for 100 enrollees, $60k (20 enrollees), $102K (100 enrollees); $200K (2223 enrollees).
Funding Source	Primarily donations; Some Rares listed grants, PCORI (expired), and FDA/NORD.	FDA/NORD; foundation grants, individual donation; industry/biotech partners, NIH.
Sustainability	16 organizations with costs between $1000-$10,000 reported it is sustainable. 7 organizations with costs between $1k-$14,000 reported it was not sustainable	Mixed feedback from those that recognized they will need to reapply every 5 years to others that are driving pilots. Some reported the registries were not sustainable or they did not know.
Value/Impact/ Challenges	• Collecting phenotype and genotype data for better characterization of disease. • Recruitment to studies and clinical trials • Ability to recontact patients for studies based on symptoms, geography or genetics. • Continuous analysis of data resulting in frequent unique data-based presentations and peer reviewed published studies. • Identify prevalence, trends, symptoms and priorities • Several replied either they were not using their contact registry or not sure how to use it most effectively; others are rethinking how to globalize the resource • Attracting interest from disparate disciplines to use data • Publishing open-access analysis papers, will investigate specific questions • Used in translational science to find mechanisms	• Continuous analyses, formal presentations and published studies • Determine seizure outcomes; • Support natural history studies, • Used for inhouse research; genotype/phenotype studies; drug companies in their applications to the FDA for clinical trials • Sharing clinical data along with biosamples collected from participants to gain better understanding • The data collected across the site will be included in publications. • The teams at each site are becoming experts in the condition. Each site is set up for future clinical trials.



Animal & Other Models. Rares reported a predominance of Rodent models (29). 9 organizations reported no animal model. Other models reported included fruit fly (drosophila), large animal nonprimate (dogs, sheep, cows and pigs) as well as animal models in development. See Appendix I for stories regarding the value of animal models for specific Rares.

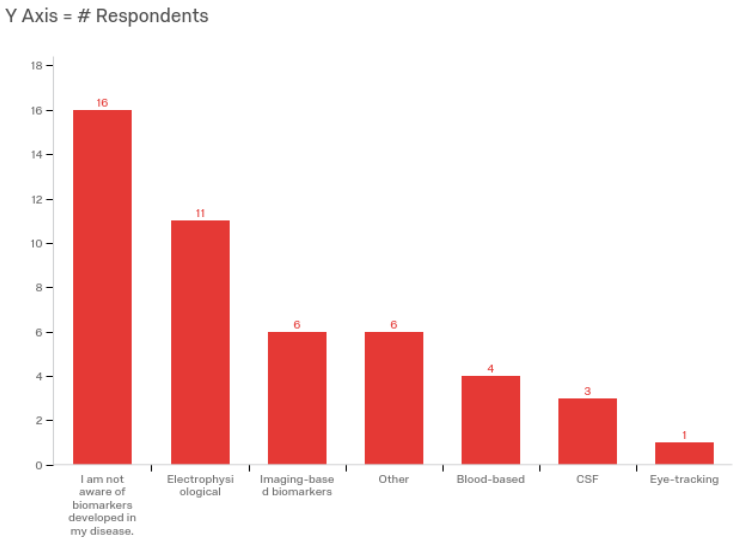
> ***RARE INSIGHT:*** *"The value of animal models is increased understanding of disease mechanism leading to preclinical studies and ultimately the testing of treatments."*
>
> *"Discovering a naturally occurring dog model for one of our forms has allowed many preclinical studies to be done that eventually led to the current treatment. The challenges were making sure they were available to other researchers (outside the home institution)."*



Drug Screening. 21 organizations reported drug screening in an academic setting and 16 reported the same in a commercial setting. 16 reported no screening in either academia or commercial settings. 11 organizations were not sure. BPAN warriors shared, "Dr Apostolos Papandreou of University College London co-funded by Action Medical Research and the BPNA (British Paediatric Neurology Association)." DNM1 Dynamos shared, "a zebrafish model is being used to screen for drugs at Translational Genomics Research Institute (TGEN) in Arizona A mice model is being used at Columbia to screen for drugs and studying the impact of viral therapies." NORSE explained, "Drug screens done in ER and ICU to exclude drugs and toxins."

Biosample Collections. 10 organizations reported they were not aware of biosample collections in their disease. 20 reported that researchers operate a biorepository or samples were housed in larger biobanks like NIH NeuroBioBank or Autism Brainnet.3 organizations reported they operated a biorepository. For those that identified repositories for specific diagnoses See Appendix J. Several groups were working with the Corielle Institute for Medical Research.

The vast majority of Rares reported Blood or DNA biosamples (26), followed by IPSCs (21) and brain tissue (14). Some Rares were not aware of biosamples in their disease (6). Others reported the collection of cerebrospinal fluid, serum, buccal cells, remnant surgical tissue, teeth, and skin fibroblasts.



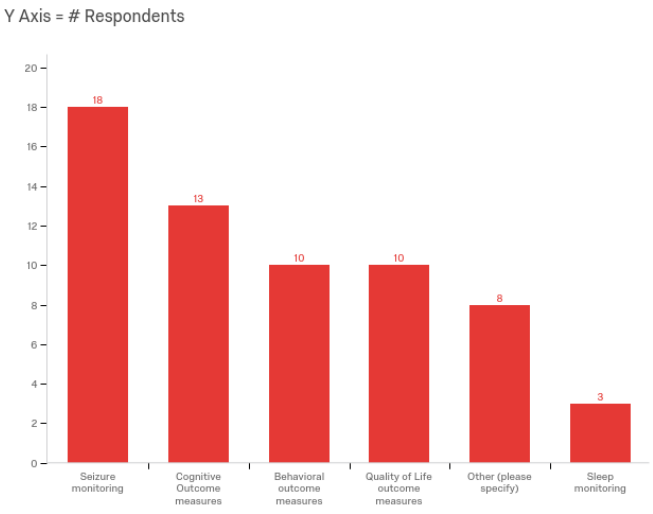
Biomarkers & Validations. 16 Rares reported they were not aware of biomarkers (an indicator of a particular disease) developed in their disease. 11 groups reported electrophysiological biomarkers, followed by imaging (6), other (6), blood-based, (4) CSF (3), and eye-tracking (1). In OTHER, it was reported SCN1A may be a biomarker for SUDEP. Other groups reported they were still trying to identify, develop and determine the efficacy of biomarkers.

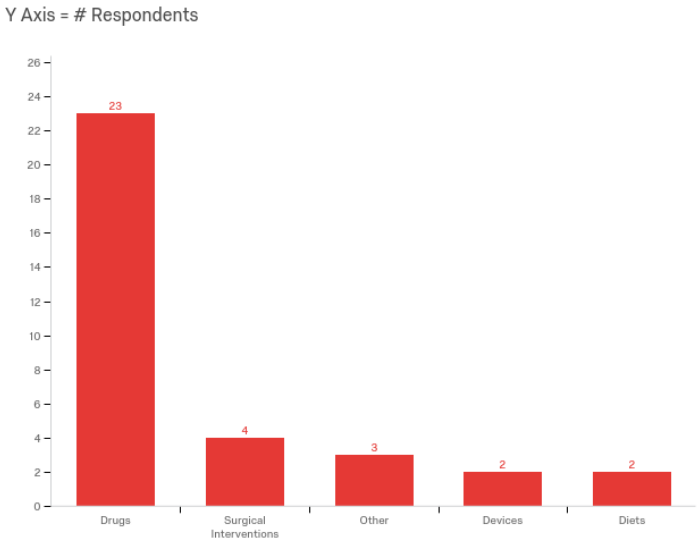
In 8 Rares, biomarkers were validated for diagnosing patients. 7 replied they were not aware of any biomarker validations. Smaller numbers reported using biomarkers as surrogate outcome measure in clinical trials (3), to predict drug responses or side effects (3) and to stratify patients (1).

Development Pipeline. Rares reported that the development pipeline was weighted toward drugs (23); 4 reported surgical interventions, 2 devices and diets each. When asked what is in development and by whom replies included:

- Epidiolex – FDA approval 2018
- Fintepla – FDA approval pending Q1 2020
- Clemizole –Epygenix
- TAK-935 –Ovid/Takeda
- Zygel (ZYN-002) - Zynerba
- A state of the art in NORSE and FIRES article with authors and links is here
- TANGO technology – Stoke Therapeutics
- ASO Technology – Encoded Therapeutics
- Focused Ultrasound Neurosurgery
- Xenon, Praxis, Meisler
- MEK Inhibitor usage
- Gene Therapy
- Deferiprone – in clinical trial for another NBIA and used in multitude of applicaions for iron related disorders. The drug is an iron chelator and the trial is not for BPAN. Its been used on a few patients (varying ages) with little positive benefit and side effects.
- Q State Bioscience – Drug Screen on stem cells derived from a single patient
- PREVeNT study – Preventative study to prevent onset of epilepsy in infants by TSC Clinical Consortium led by Martina Bebin, MD, MPA.
- IGF-1 https://clinicaltrials.gov/ct2/show/NCT01525901?cond=shank3
- Seaver Autism Center Growth Hormone
- Ras-ERK Inhibitor for epilepsy
- Intranasal Oxytocis Seaver Autism Center

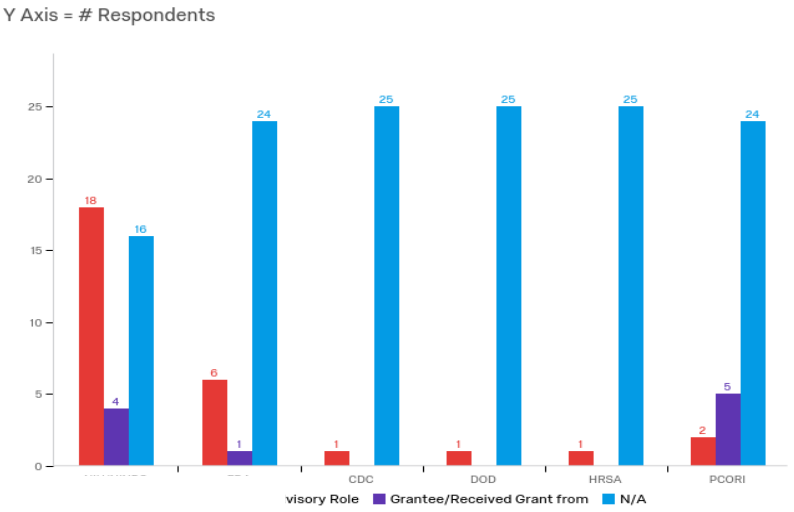
Clinical Trials. 18 Rares support clinical trial recruitment/patient education; 9 reported they do not; and 3 Rares fund or co-fund clinical trials. In Other, Rares reported that they are ready, willing and eager to support them once the opportunity arises. 1 organization reported they provide start-up funding for NIH supported clinical trials to cover coordinator salary and/or to launch the study.

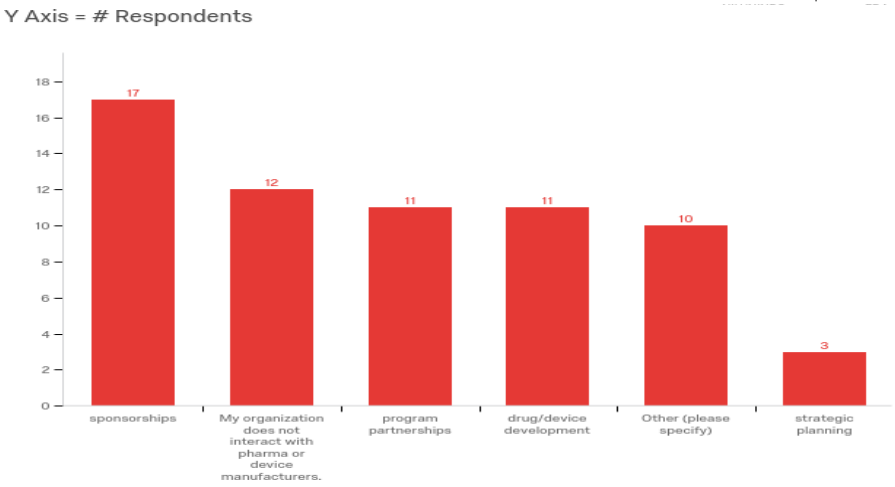




Outcome Measures in Clinical Trials. In measuring outcomes for clinical trials, 18 use seizure monitoring, 13 report cognitive outcomes, 10 report behavior and quality of life, and 3 report sleep. For other, one group shared mobility was another outcome measurement. Another reported, "The tools to measure QOL, sleep, cognition, behavior seem to be insufficient and the data is nto always shared b pharma when they do track it as a second endpoint. Another group shared they are working on validating those areas and "currently there are two trials with co-primary outcome measures as we search for better ways to measure improvement."

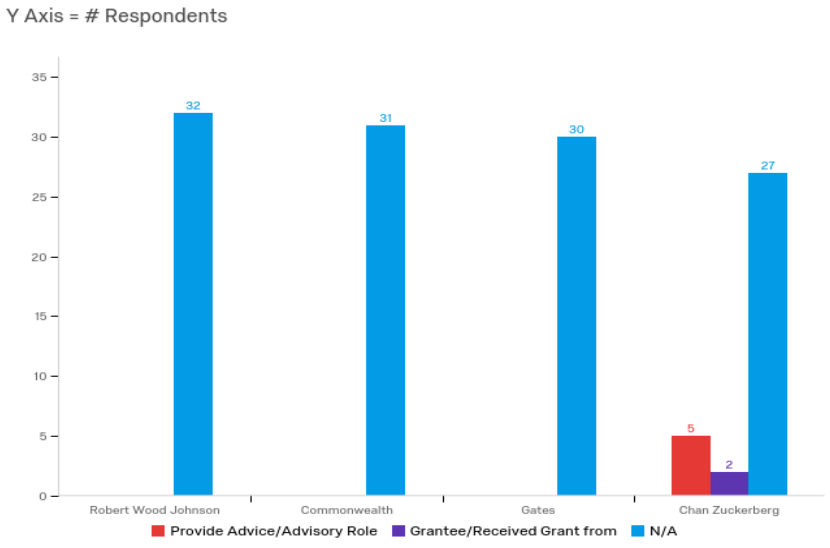
Rare & Government Advisory Roles and Funding. 18 Rares reported providing advice or serving as an advisor to NIH/NINDS. Only 10 groups reported receiving grants from NIH (Christianson, Bridge the Gap, RASopathies, Brain Recovery), FDA (Bridge the Gap) and PCORI (KIF1A, Phelan, Glut1, Dravet, Brain Recovery). It is striking how little interaction the Rares collectively have had with other relevant federal agencies as both advisor and grantee. When asked if Rares interacted with other government agencies, groups mentioned seeking intramural researchers to pursue focused initiatives and working with program officers. National Cancer Institute was also mentioned.



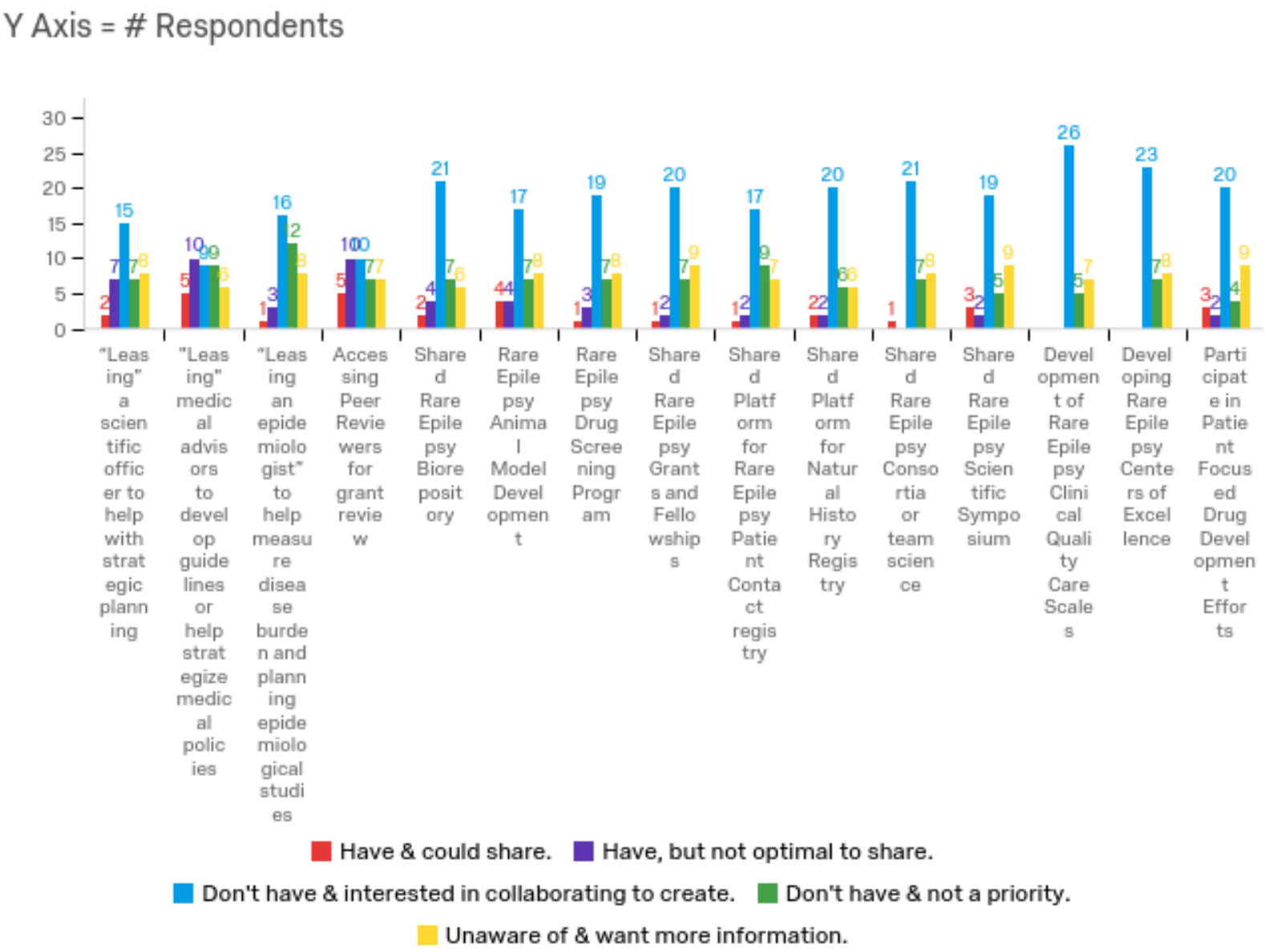


Pharma & Rare Partnerships. 17 Rares partner with Pharmaceutical, Biotech, and manufacturing companies to secure sponsorships (primarily for symposia ad conferences). 12 Rares reported no interactions. Other Rares reported interacting around program partnerships (11) and drug/device development (11). Only 3 listed strategic planning as a partnerships strategy. In Other, patient advocacy, obtaining family interviews/perspectives were mentioned.

Rares & Health Focused Foundations. The majority of Rares reported a minimum of interactions as either advisor or grantee with large scale health focused foundations including Gates, Robert Wood Johnson and Commonwealth. 5 organizations were providing advice to Chan Zuckerberg and 2 were finalists/had received grants. When asked regarding other foundations Rares interact with, also mentioned was the Charlie Foundation for Ketogenic Dietary Therapies, as well as Global Genes, Eurordis, CORD, Genetic Alliance UK, Rare Disease Foundation and Orpha.net. Integra Foundation, SFARI (Simons Foundation) Autism Speaks Autism Science Foundation were also mentioned as was University of Pennsylvania Orphan Disease Center.



Research Collaborations. The interest in collaborating across key research areas is evident from the preponderance of blue lines below. Shared Development of Rare Epilepsy Clinical Quality of Care Scales and Developing Rare Epilepsy Centers of Excellence ranked as two areas of significant interest without existing efforts underway in those spaces. Moreover, in many instances, groups in red had developed areas of expertise that they were willing to share and help others. The green lines represent areas that were not priorities for organizations. The yellow lines demonstrate that across the board upwards of 5-10 Rares would like more information about opportunities. In regard to some items that are not optimal to share e.g. contact registry, could explore the use of shared platforms, training resources, group discounts etc.



Groups with expertise or resources they are willing to share:

- Leasing Scientific Officer to help with strategic planning: LGS, Lissencephaly
- Leasing medical advisors to develop Guidelines: CFC, Grin2B, LGS, CDKL5, RASopathies,
- Leasing an Epidemiologist: LGS
- Accessing Peer Reviewers: BPAN, Cute, TS ALLIANCE, RASopathies, LGS
- Shared Biorepository: Hope for Harper, TS ALLIANCE
- Shared Animal Model Development: Cute, Tess, Hope for Harper, TS ALLIANCE
- Shared Drug Screening: TS ALLIANCE
- Shared Grants/Fellowships: TS ALLIANCE
- Shared Contact Registry: PMSF
- Shared Natural History Registry: TS ALLIANCE, LGS
- Shared Consortium/Team Science: TS ALLIANCE
- Shared Scientific Symposium: Cute, LGS, TS
- Patient Focused Drug Development: LGS, TS ALLIANCE, CDKL5
- Other: Education, transitioning to adult care, QOL, comorbidities: Brain Recovery

F. PROFESSIONAL EDUCATION PRIORITES & CHALLENGES

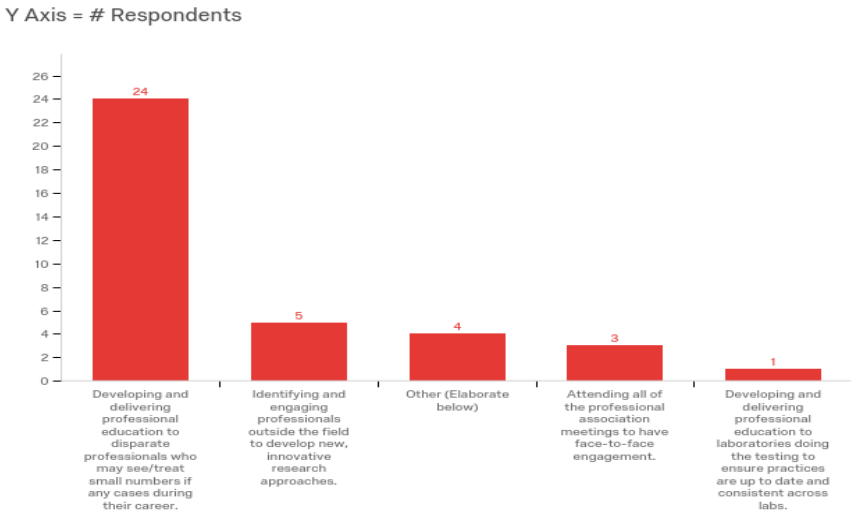
Professional Education Priorities. The top 3 professional education priorities included educating professionals to detect/diagnose the disease (24); educating professionals on the best diagnosis, treatment and management practices (24); and connecting professionals with each other to seed collaborations among institutes and disciplines (22). Other priorities included:

- Update researcher thinking on rare conditions e.g., LGS
- Empowering families to educate professionals

- Liaising for two way dialogue between professionals and families to share lessons learned.
- Funding clinical consensus guidelines.
- Getting clinicians and scientists to communicate with each other and coordinate research model and biosample protocols.

Professional Education Challenge. Educating disparate professionals who treat small number of patients was above and beyond the most pressing challenge (24). Other challenges expressed included:

- Unwillingness to learn beyond scope of practice from medical professionals like primary care physicians.
- Doctors who know everything already.
- Communication between clinicians and scientists is poor.
- Managing growth as disease interest increases
- Influence of Parents to parent conversations - via social



Recruiting Professionals. Rares reported their most effective tactics for recruiting professionals include:

- Peer to Peer interactions and professionals educating professionals – identifying a disease ambassador.
- Inviting professionals to family conferences to interact with families.
- Inviting patients to professional conferences to share their journey.
- Staffing booths at professional conferences like AES, CNF, NSGC.
- Contacting researchers published in the field.
- Sharing data with professionals

RARE INSIGHT: *Inviting them to the biennial International Family Conference and having them interact with families in an organized program (McPosium). We did this in 2016 and 2018. This is a link to the videos and white papers from 2016. https://www.pmsf.org/research/mcposium-sessions-2016/*

Twice over the past 10 years we have had a story telling contest for families and the best 10 were put in a book that was disseminated to the research community. https://www.pmsf.org/about_pms/stories/

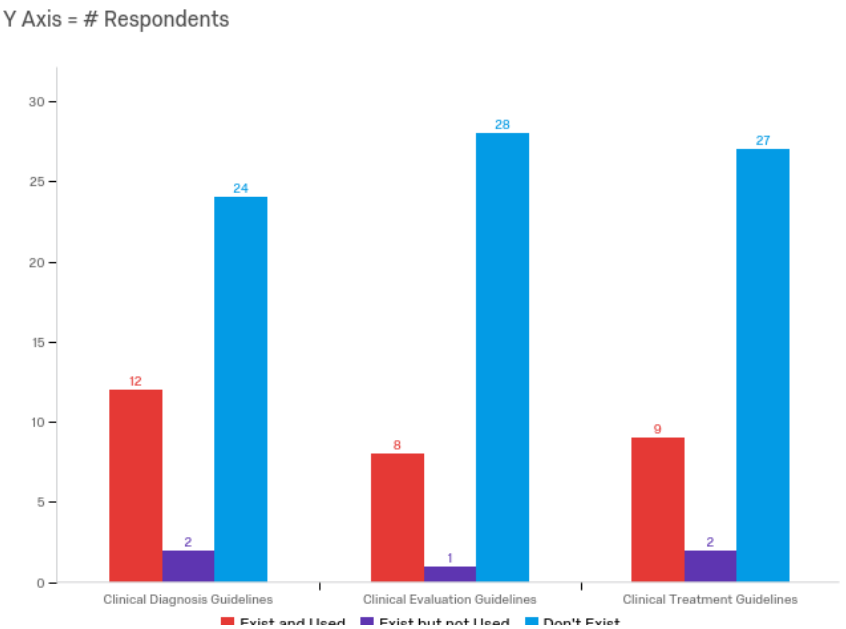
Top Professional Targets. Neurologists are the top targets (37), followed by pediatricians (23); Nurse Practitioners (6); Neuropsychiatrists (4) and Neuropsychologists (2). Outreach to Geneticists by far were top of the Rares list in other. Other professional targets also included: Psychiatrists; Cardiologists; Epileptologists; Movement disorder specialists; Immunologists; Endocrinologists; GI/motility specialists; and ICU intensivists. Complete messages are in Appendix K.
Priority messages to target professionals included:

- Sharing updates and new information with the Rare organizations so they can share that with the families and not to rely exclusively on publications for dissemination and practice changes
- Encouraging professionals to listen to patients and consider each individual's unique circumstances
- Being alert to symptoms/signs of Rares
- Continuing professional education by doing literature searches, following research,
- Engaging and sharing their insights to help advance knowledge and best practices.
- Considering both traditional and non-traditional interventions
- Not dismissing comorbidities of each disease if the seizures themselves are refractory
- Increasing discussion regarding organ donation and CBD.

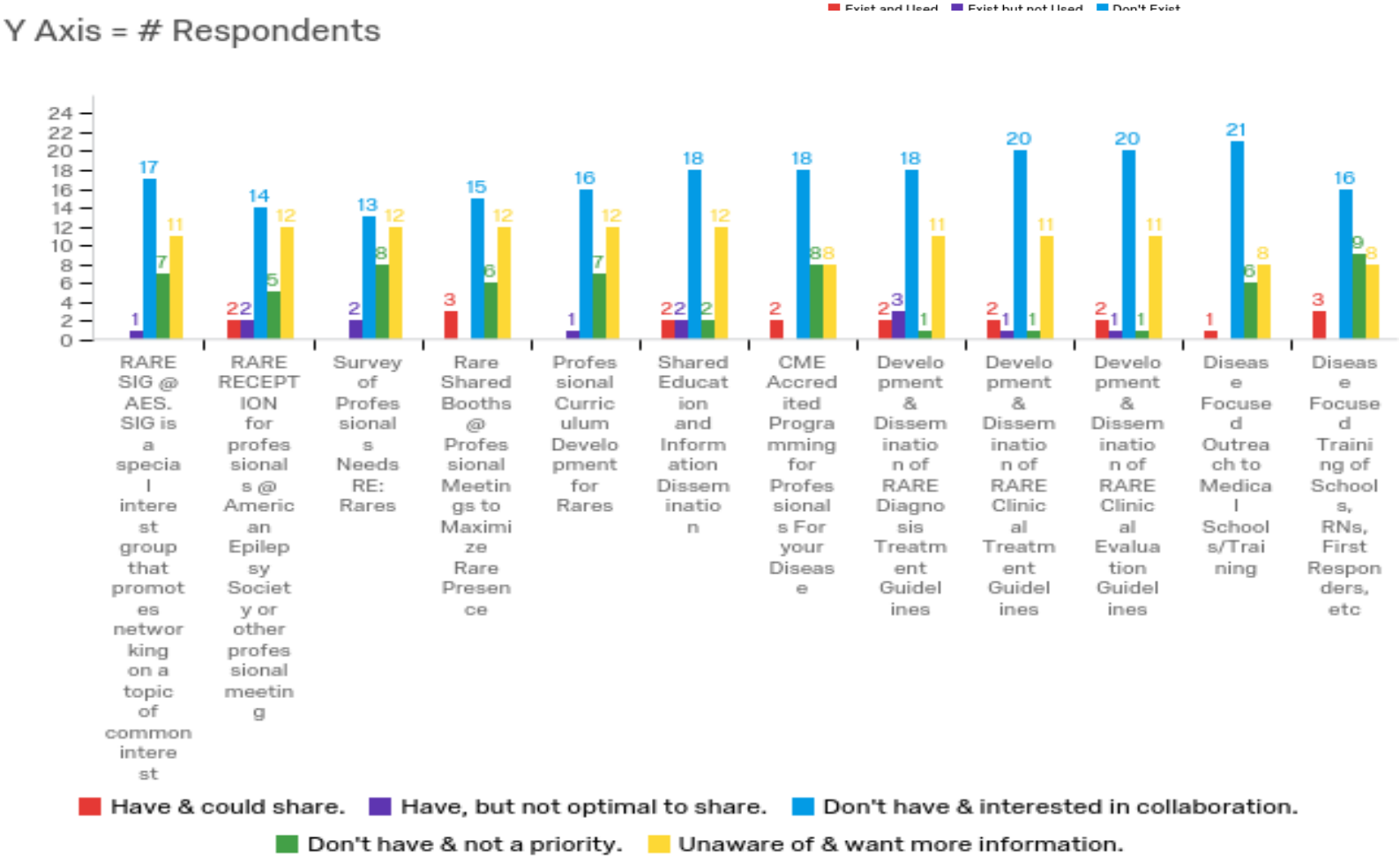
RARE INSIGHT: *"Symptoms should not simply be dismissed because of [rare] diagnosis. Although treatments/therapies are not available currently, this does not mean that underlying issues such as hormone imbalances, vitamin deficiencies, endocrine issues, metabolic dysfunction, GI issues, irregular sleep, etc. cannot be addressed. Listen to your patients/caregivers and recognize that they have insights to the disease and symptoms. They may not know the diagnostic path to address some of the seemingly "odd" or unrelated issues, however it is your duty to provide critical guidance to families who are just doing their best to survive. Please do not dismiss, doubt, shame, or second guess, patient caregivers when so little is known. We are learning as we go and need support from professionals not push back."*

Educational Curriculum. The Rares themselves are in large part developing curriculum to educate professionals about their disease. Other sources for resource development included: European Brain Consortium, Individual doctors or labs; international affiliates; Child Neurology Foundation; and collaboration between RDCRN PIs and the patient advocacy group.

Diagnosis, Evaluation and Treatment Guidelines for Rares. There is dearth of guidelines for diagnosis, evaluation and treatment across Rares. Some exist and aren't used. The Rares that have guidelines that are in use could be instructive for those that don't. See Appendix L for a complete list of Guidelines by Rares.

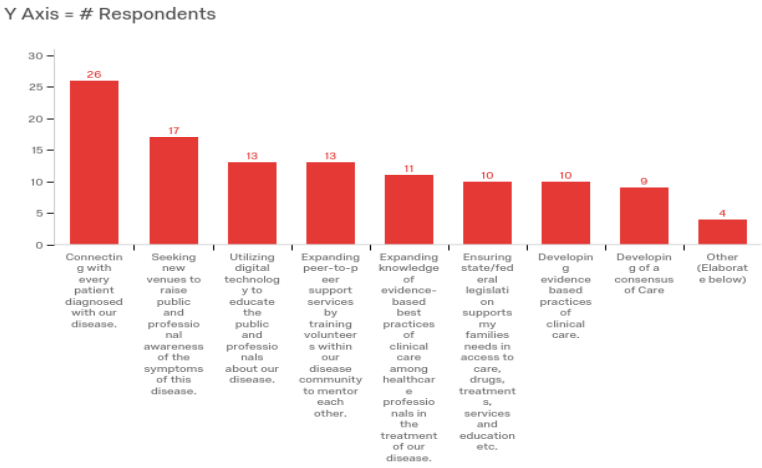


Collaboration across Professional Education. Professional Education highlights another abundance of areas where Rares either would like to collaborate to develop resources (blue) or are unaware of resources and seek more information (yellow). Disease focused outreach to medical schools ranked highest followed by Rare clinical treatment, evaluation and diagnostic guidelines. Other examples of priorities where there are no efforts include a Rare SIG, Survey of Professionals re: Rares, and Development of Professional Curriculum.



G. ADVOCACY & AWARENESS PRIORITES & CHALLENGES

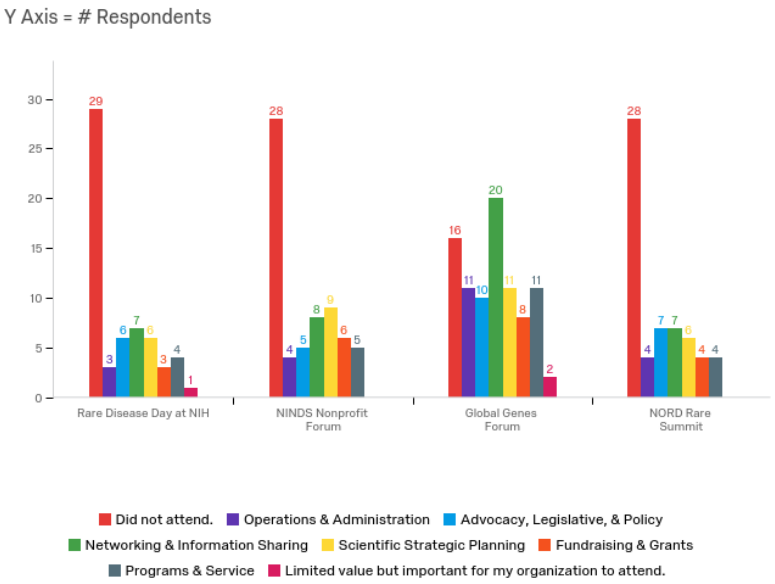
Advocacy & Awareness Priorities. Top advocacy goals include connecting with patients diagnosed and seeking new venues to raise awareness. Other goals included: Securing more funding for ABA therapy and Medicaid funding for long term care and waiver programs; securing DOD funding for TSC; expanding testing to increase diagnoses; and promoting the collaboration of cross-disease research (AGENDA, REN) to solve shared challenges and move research (registries, biomarkers, clinical trials) forward faster and more effectively across diseases.



RARE INSIGHT: *"We are a small organization and limited in resources. With such little consensus on our disease medically and scientifically we are starting from scratch. Staying focused while connecting to our patient community is a 2/4/7 task which requires constant upkeep. Our patient community is also very limited in their understanding of the disease. This has pressed our organization to its limits as we attempt to perform multiple tasks in parallel."*

Advocacy & Awareness Challenges. The challenges standing in the way include lack public awareness of the conditions and PR/marketing deficiencies in outreach and maintaining websites and social media channels. Other common replies included lack of time, money, and trained staff, as well as lack of patient participation. Rapid growth of diseases with limited staff was also cited.

Value of Participating in Patient Advocacy Forums/Days. Global Genes is fairly well attended by the Rares and valued for networking/information sharing, as well as programs & services, operations and admin and scientific and strategic planning. Only a small number participated in Rare Disease day at NIH, NINDS Nonprofit Forum, and NORD. Those that did valued networking and information sharing, followed by scientific strategic planning and advocacy legislative and policy. Some groups reported being unaware of meetings but interested in joining mailing lists for future meetings. Other patient advocacy meetings attended included: Global Genes Data DYI, Genetic Alliance, CBIA Rare Disease Summit, DIA Congress, World Orphan Drug Congress, Canadian Organization for Rare Diseases (CORD), BIO Patient & Health Advocacy Summit; ASENT.

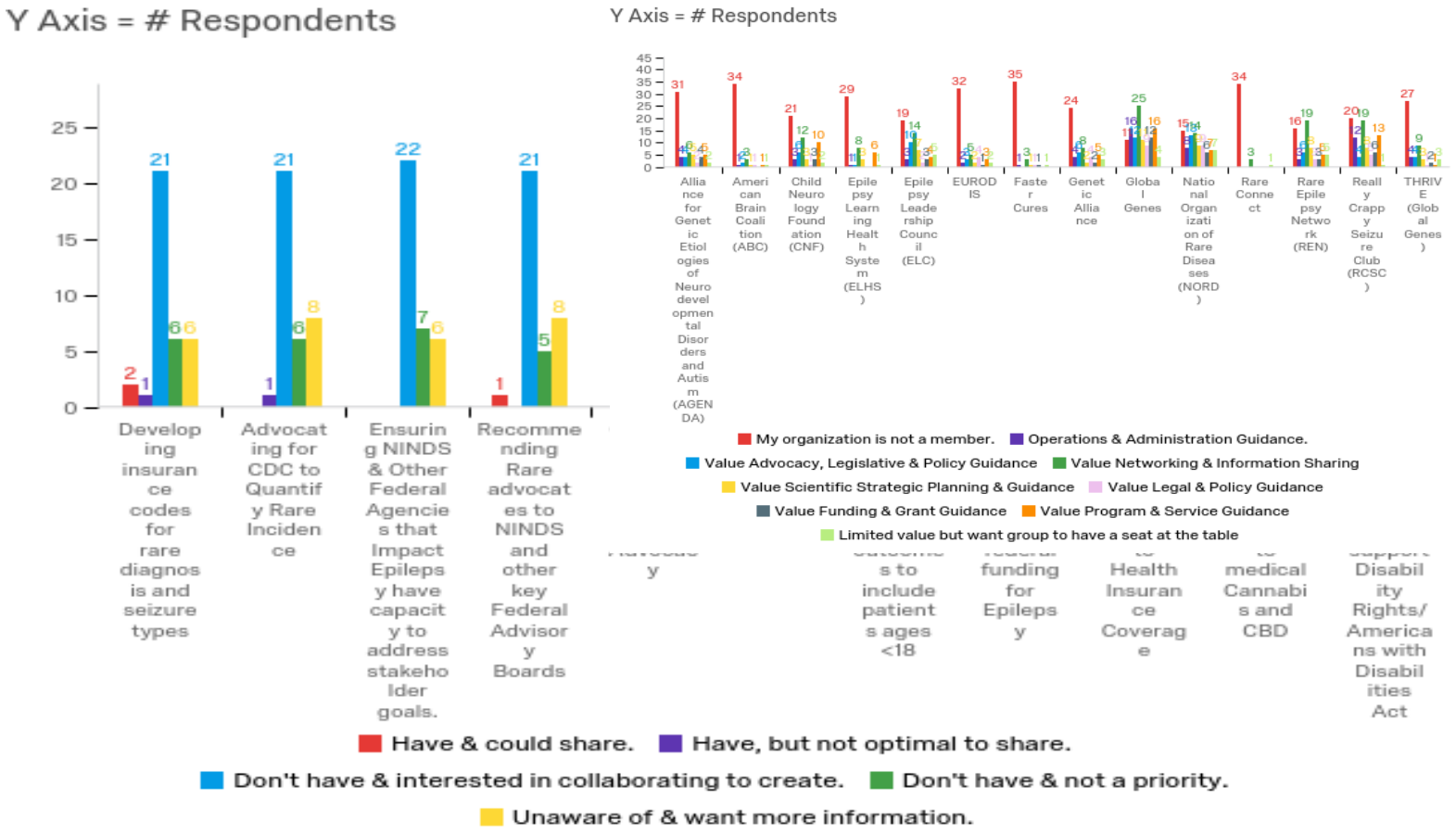


Curing Epilepsy & Epilepsy Across the Spectrum. The majority of Rares were unaware of the Curing Epilepsy Meeting, both past and present. Just 10 organizations reported intent to participate in the upcoming 2020 meeting. 6 organizations reported participating in the 2013 meeting and 5 reported it added value to their rare disease community. Rares advocated that accountability and a plan should be built into the upcoming meeting. Similarly, a large number of Rare organizations were unaware of the Institute of Medicine (IOM) initiative and subsequent report. 13 were aware, but only 3 reported having participated. 8 reported value and 7 advocated for another meeting.

Legislative & Regulatory Activity of Rares. The majority of Rares do not engage in legislative or regulatory activities. Those that do, participate through coalitions or efforts led by others. A smaller number engage directly in state (9) and federal (8) activities. Only 4 thought they currently got good advice and just 2 retain a lobbyist. In other, Rares mentioned they participate in Everylife, NORD and ELC advocacy efforts. Several do not participate presently but would if opportunities related to drug development arose.

Influencing Research. 28 groups reported they work with the research community to ensure patient/caregiver views are included. Others reported working with the research community to design/implement studies. Only 7 reported working with their NIH program officer to strategize research and only 4 co-fund NIH research projects. In other, most replies were N/A.

Advocacy Collaborations. Advocacy was another area where the blue lines signal an interest in collaboration among Rares. There was high interest across all areas especially coordinating advocacy to increase federal funding for epilepsy (24) as well as addressing capacity at federal agencies (22), ensuring enforcement of the Disability Rights Act, influencing CDC policies (21), recommending advocates to key Boards (21). While some groups did not prioritize these initiatives, quite a few sought more information. In other, groups reported newness and size has limited their ability to engage on advocacy. Other topic raised was making seizure / service dogs available to those on Medicaid and other health plans. The Arc was cited as an example of an organization doing good work in disability rights and access to health insurance.



Rare Coalition Participation. Rare participation was highest in REN, RCSC, Global Genes, ELC, NORD and CNF. The value derived from the majority of coalitions was networking and information sharing, followed by program and service guidance; advocacy, legislative and policy advice; scientific strategic planning, and operations and admin. Benefits and providers follow below:

1. Networking & Information Sharing: GG, REN/RCSC, ELC/NORD
2. Programs & Services: GG, RCSC, CNF
3. Advocacy, Legislative & Policy: NORD, GG, ELC
4. 4 Scientific Strategic Planning: GG, NORD, REN/RCSC
5. Ops & Admin: GG, RCSC
6. Fundraising: GG
7. Legal: NORD/GG

H. FINANCIALS & FUNDRAISING PRIORITIES & CHALLENGES

Fundraising Priorities. For fundraising, 21 groups prioritized developing a major donor strategy (21) followed by a fundraising strategy (19); improving donor cultivation (18) and grants (17). In Other, groups noted developing consistency for sustainability, empowering and activating families to do local fundraising, more deeply connect with and grow followers to convert to donors and lead to more corporate donations; and identify families with the condition depends on increasing professional education.

Fundraising Challenges. 12 groups identified families in crisis/survival mode who don't have capacity to donate. 11 groups identified encouraging donations from non-impacted donors and 8 listed skilled fundraising expertise. In other, groups reported the challenge of donor fatigue (active but small community carrying the weight for the masses); and converting loyalty grants into passion and extraordinary gifts.

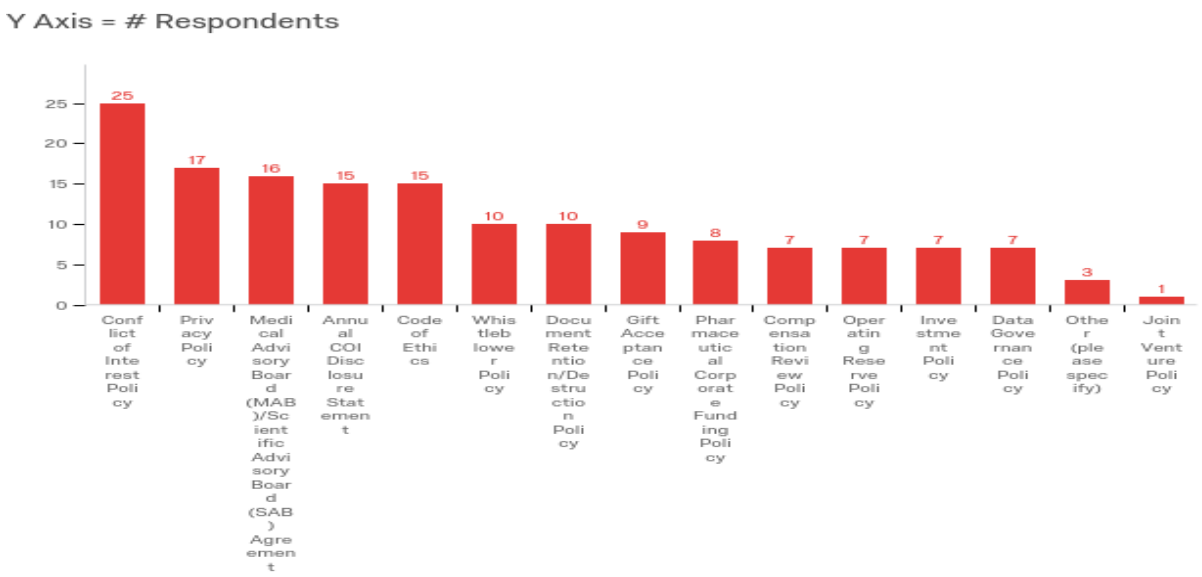
Tax Filings, Audits & Annual Reports. 36 Rares are 501c3s. 2 are 501c3 pending. 4 are non-incorporated support, Facebook, or other groups. 13 Rares filed gross receipts >$200k or total assets >$500K including one that selected other and another that did not meet the financial requirements but elected to 'file up." 7 Rares filed 990 EZ with gross receipts >$50k and assets between $200-500K; 8 Rares filed 990-N (< $50,000 gross receipts). 10 groups declined to answer.

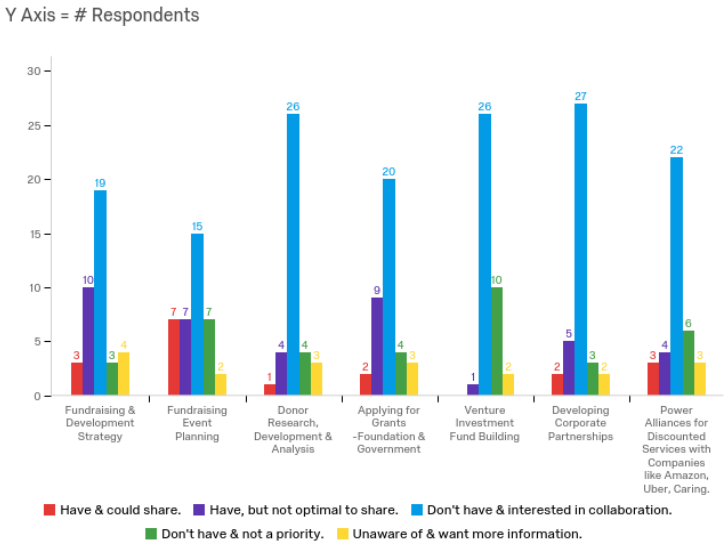
Research & Patient Support Expenditures. Monies spent on research programs varied from $0 to $2.4M. Highest reported expenditures were for TSA ($2.4M); Dravet ($426k); and Batten ($270k). Norse, Dup15q, and Bow all spent in the $100K range. 6 other groups combined spent $162,783. 14 groups reported collective expenditures on research in Rares was $3.6M. Also, 14 groups reported expenditures on patient support ranging from $1,153 to upwards of $1.8M. Upwards of $3.1M was spent by the 14 organizations for the period reported. In all but one instance, revenue exceeded expenses. Moreover, 16 Rares reported funding surpluses in 2018; 10 in 2017 and 13 in 2016 suggesting Rares were stockpiling funds. Additionally, net assets reported for 10 organizations suggest the organizations are financially stable.

	Rares	Independent Audit	Annual Report
>$200K or total assets > $500K	13	7	7
990 EZ (gross receipts > $50,000 and < $200,000 and total assets < $500,000)	7	0	1
990-N	8		

Sources of Revenue. Only 16 responders as follows. Newer organizations were less diversified and trended more toward individual donations. 3 organizations relied heavily on Corporate sponsors for > 50% of their funding. 1 organization relied on > 80% for fees for service. Foundation grants accounted for < 30% across 8 organizations. 4 organizations kept corporate sponsors to < 30%.

Policies. 25 Rares had a conflict of interest policy, 17 had a privacy policy and 16 had MAB/SAB agreements. 7 or less organizations had policies for compensation review, operating reserve, investment, data governance, and joint ventures. In other, NDA was mentioned.





Fundraising Collaborations. In Fundraising, there was also high interest in sharing resources especially in developing corporate partnerships (27), venture investment fund building (26), donor research and development analysis (26), and power alliances (22) among others. Less than 10 organizations either had this expertise and were willing to share or possessed this expertise even if not optimal to share. In other, responders mentioned the strategies in practice but the lack of formalized strategies as well as matching grants chosen by donors.

I. MANAGEMENT ACROSS RARES & OPPORTUNITIES FOR COLLABORATION

Management Resources. A common theme was the reliance on "other foundation leaders" for advice and resources. Several organizations were specifically mentioned including LGS, TS ALLIANCE, CNF, and Dravet as gracious in their giving of advice and sharing templates and resources. BPAN Warries mentioned CDKL5, Angelman, Rett Syndrome, Reverserett and epilepsy.com as relied upon resources. Additionally, the following resources were mentioned:

> ***RARE INSIGHT**: "Our organization is not the first rare disease organization. Many others came before us and rather than re-inventing the wheel, we simply take the templates others have set forth and use those templates to guide our organization. Sometimes, we literally just copy what others have done. In addition, we have developed wonderful working, collaborative relationships with other rare disease organizations such as FoxG1, CDKL5 and SATB2. These organizations have helped us and we have in turn helped them. We all work together to develop clear pathways forward in our organizations."*

Organizations	• Epilepsy Foundation/Brandy Fureman • REN • AES for partnering on early career grants • NORD, CORD • EURORDIS • Genetic Alliance
Government	• NINDS staff and forums • PubMed
Nonprofit Fundraising Leadership	• The Nonprofit Leadership Center • Board Source • Foundation Center/Candid trainings • Network for Good • Vistage
Books	• Five Dysfunctions of a Team (book) • The One Thing (book) • The Patient Group Handbook: A Practical Guide for Research and Drug Development, Anthony Hall and Nicolas Sireau • Global Genes (Guidebooks)

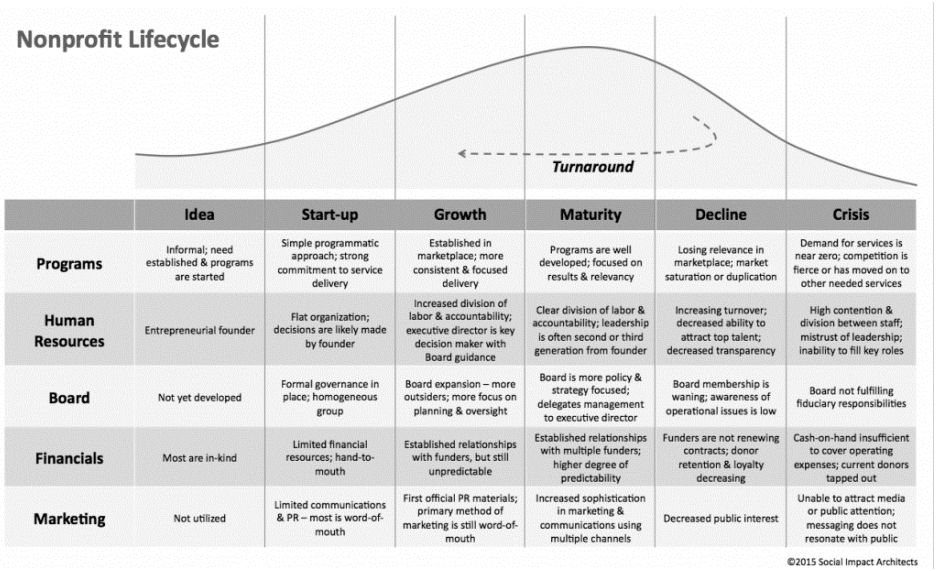
Rare Staffing & Leadership. 38 groups had a person dedicated to the role of CEO and ED. Also, 28 groups had a CFO, Comptroller or bookkeeper. Approximately half had someone dedicated to communications and marketing. Fewer than half the groups had someone dedicated to development, science, operations, programs/services and advocacy or government relations. In some instances, the same person or a small group of people served in all key roles. Other groups also had a secretary/admin and registry coordinator/genetic counselor. Some groups had none of the above.

- 20 groups reported no FTE, PTE, or Independent Contractors and exclusively relied on Volunteers or Board members to staff operations, programs and services.
- 13 Rares had 1 FTEs: 9 Rares had just 1 FTE; 4 additional Rares had 2 FTE, 4 FTE, 5.5 FTE and 19 FTE

- 3 Rares rely on PTEs
- 5 Rares rely on Independent contractors

Boards, Term Limits, & Roles. Boards varied in size – 16 Rares had boards with 3 or 5 members. 7 Rares had 6 member boards. 6 organizations had 10+ member Boards. 2 organizations had less than 3 member Boards and 2 Rares had no Board of Directors. 20 organizations had no term limits and boards can serve indefinitely. Whereas 2 groups limited Board service to 1-2 years; 6 to 3-4 years; 4 groups to 5-7 years and 1 group to 8-10 years. 23 organizations reported Board members were only serving in advisory capacity regarding governance and policy. 18 reported Board members were serving as staff. 10 reported Board members lead committees. 6 reported Board are no longer involved. Several Rares were working on succession and some reported founding board member who had transitioned to Executive Director.

> ***RARE INSIGHT**: "We are a small group and rotate out every 3 years. some folks stay longer but tends to be burnout from doing all the work. Fundraising has become very challenging. Our family reunions are wonderful but not sure how long we can do this without donations to the network."*

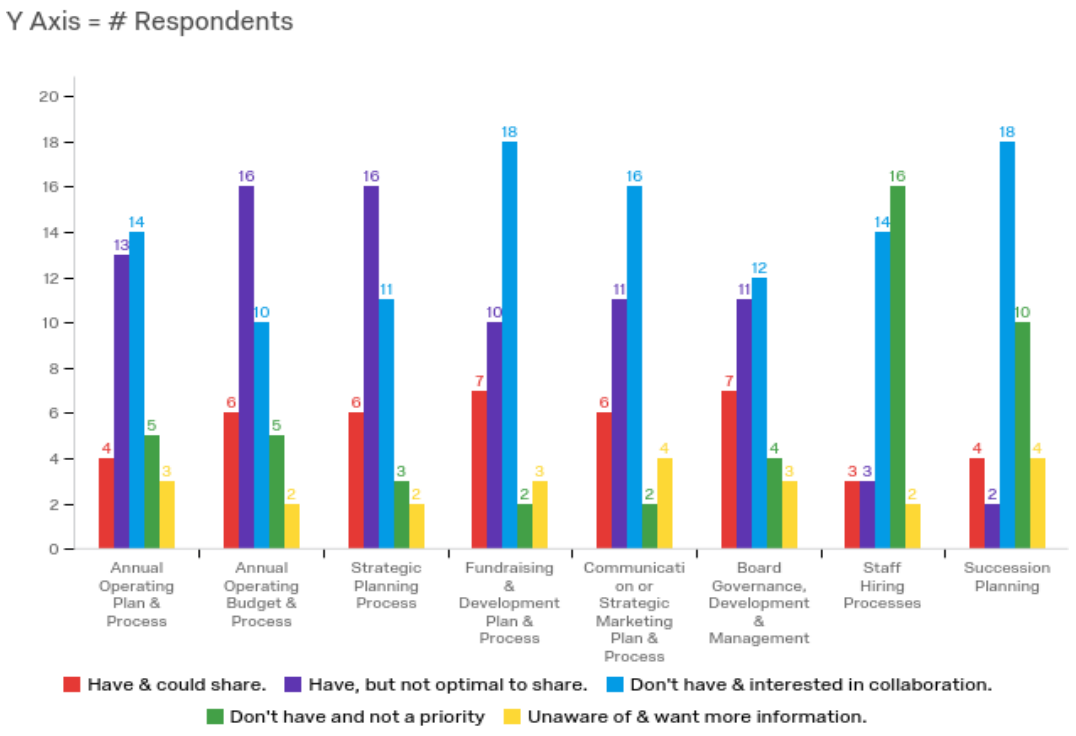


	Idea	Start-up	Growth	Maturity	Decline	Crisis
Programs	Informal; need established & programs are started	Simple programmatic approach; strong commitment to service delivery	Established in marketplace; more consistent & focused delivery	Programs are well developed; focused on results & relevancy	Losing relevance in marketplace; market saturation or duplication	Demand for services is near zero; competition is fierce or has moved on to other needed services
Human Resources	Entrepreneurial founder	Flat organization; decisions are likely made by founder	Increased division of labor & accountability; executive director is key decision maker with Board guidance	Clear division of labor & accountability; leadership is often second or third generation from founder	Increasing turnover; decreased ability to attract top talent; decreased transparency	High contention & division between staff; mistrust of leadership; inability to fill key roles
Board	Not yet developed	Formal governance in place; homogeneous group	Board expansion – more outsiders; more focus on planning & oversight	Board is more policy & strategy focused; delegates management to executive director	Board membership is waning; awareness of operational issues is low	Board not fulfilling fiduciary responsibilities
Financials	Most are in-kind	Limited financial resources; hand-to-mouth	Established relationships with funders, but still unpredictable	Established relationships with multiple funders; higher degree of predictability	Funders are not renewing contracts; donor retention & loyalty decreasing	Cash-on-hand insufficient to cover operating expenses; current donors tapped out
Marketing	Not utilized	Limited communications & PR – most is word-of-mouth	First official PR materials; primary method of marketing is still word-of-mouth	Increased sophistication in marketing & communications using multiple channels	Decreased public interest	Unable to attract media or public attention; messaging does not resonate with public

Nonprofit Lifecycle. On the Nonprofit Life cycle, most Rares characterized themselves as in Start Up or Growth mode. 1 was in idea mode; 4 self-identified as maturity and 3 in decline with 1 in crisis. For other, several felt they were somewhere between start up and growth mode.

Strategic Planning. 13 organizations were revisiting their strategic plan annually. 12 organizations reported having no planning process. 11 organizations undertook a strategic planning process every 3-5 years. In other, some groups were just starting this process.

Management Collaboration. There was high interest in sharing fundraising/development planning (18) and succession processes (18), as well as communication/strategic marketing (16) followed by Annual operating planning (14) and staff hiring (14). Roughly 7 organizations had this expertise and were willing to share. A large number indicated these were not optimal to share. Staff hiring was not a priority for 16 organizations and 10 did not prioritize succession planning. 4 or fewer organizations wanted more information about these tasks.



J. RESOURCES ACROSS RARES

Contact Database. 29 groups maintain a contact database that includes patients and donors. 17 noted their contact database and registry are the same; 13 noted their contact database is separate from their registry. 3 do not maintain any kind of contact database or registry. In other, groups listed that their databases also included contacts for researchers, press, and legislatures. One reported their database was exclusive to families diagnosed. Another reported they maintained an email list plus a retrospective and prospective natural history registry.

Constituents. Databases ranged from as few as 20 constituents to as many as 12,000. 7 Rares had 100 or fewer; 3 had 200-499; 6 had 500-999, 5 had 1000-2999; 6 had 3000-4999; 1 had 5300 and 1 had 12000. Wide range of how many rare patients/caregivers comprised each database. Some were as few as 2% all the way to 100%. 14 organizations had < 50%; 10 organizations had 50% or more; 4 organizations did not know; 2 groups had 0.

Websites. Most sites are managed by volunteers with 12 managed by staff and 7 by consultant or third parties. Several sites are managed by the founders/Presidents/Executive Directors. 13 Rares shared insights from Google Analytics. There was great variability in monthly visitors from as few as 30 to as many as 35,000. New visitors ranged from 12 to 6,200. Visitors are spending on average 1-2 minutes on most websites. Two organizations reported visitors spending 6-11 minutes on site.

Social Media Platforms. Looking across social media platforms:

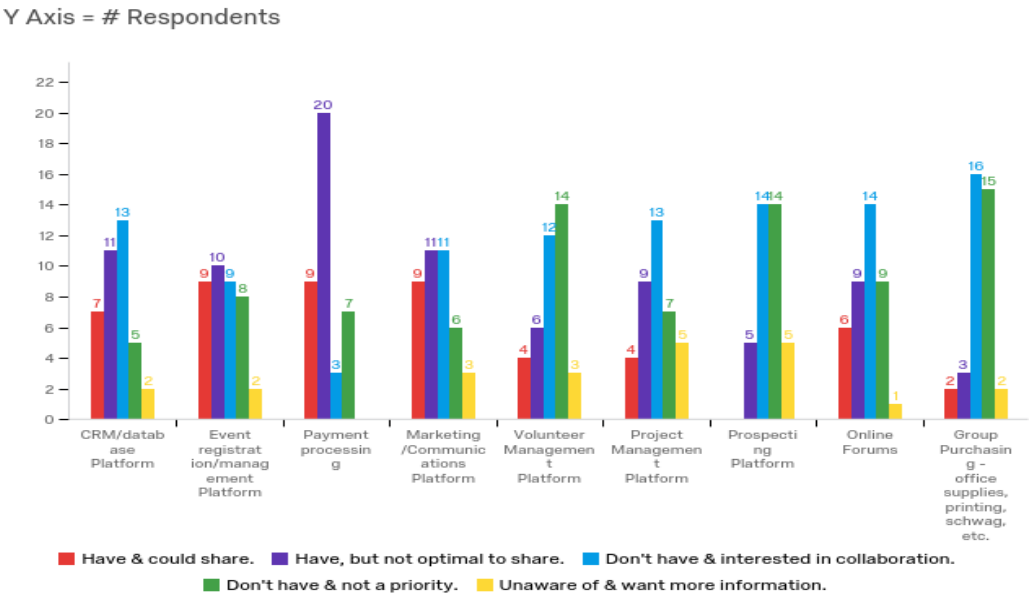
- Facebook: 2 groups did not have. 20 post 1-3x a week and 29 reported constituents were highly engaged.
- Twitter: 13 groups did not have. 19 post 1-3x a week. 18 felt constituents were somewhat engaged.
- Instagram: 11 groups did not have. 18 post 1-3x a week. 23 reported constituents were either highly or somewhat engaged.
- YouTube: 15 groups did not have. 13 post 1-3x a week. 10 reported constituents were somewhat engaged.
- Linked In: 17 groups did not have. 13 post 1-3x a week. 13 reported constituents were not engaged.

***RARE INSIGHT**: Check out the Celebrating Rare The GRIN2B Podcast*

Software Platform Usage Across Rares.

Customer Relationship Management (CRM)	**Enewsletter/Marketing Messaging**	**Online Payment Processing**
16 Excel. 6 none 4 Etapestry/Blackbaud 2 Salesforce; Zoho; Aplos; Salsa 1 each Kindful, Network for Good, Custom, Neon, Mailchimp, Donor Snap, Donor Perfect, Flipcause	19 Mailchimp 10 none 7 constant contact 2 Blackbaud 1 each Vertical Response, Network for Good, Mailerlite, Action Network, Neon, Facebook, Squarespace, Salsa Wix	30 Paypal 15 Network for good and 4 none 8 Stripe 2 Facebook; Blackbuad 1 each Luminate; Donorbox; Auth.net; Flipcause
Event Registration	**Project Management**	**Volunteer Management**
13 Eventbrite 8 none 4 Evite 3 Etapestry 2 Cvent; Givesmart; Custom 1 Network for Good, Wix, Eventzilla, Wired Impact, Facebook, CiviCRM, Luminate, Excel, Everday Hero, myTRS, Salsa, Givergy, Flipcause	22 None 7 Slack 4 Asana 3 Trello 2 Basecamp; Monday.com 1 Google Suites, Doodle; TeamGantt; Drive	29 None 3 Volunteer Match. 1 each Asana, Signup Genius, Basecamp, Blackbaud, Custom/Google Docs, and Flipcause

Resource Collaborations. While many groups noted that they had platforms to operate their organizations, this could be an area to explore group discounts, shared training, and best practices. A few platforms group expressed interest in collaboration included: group purchasing (16); online forums (14); prospecting (14); CRM database (13), volunteer management (12); and marketing/communication (11).



K. FROM THE MOUTHS OF RARES

"Thanks for the opportunity to share. We have only gotten into the area of research recently, therefore this is an exciting opportunity for us to collaborate with other like-minded organizations. We have a lot to learn from well-established organizations and hope that we may re-purpose what they have developed. As has been heard often, we have no desire to reinvent the wheel and only through collaborative efforts with meaningful insights and outcomes, are we able to have a lasting impact on the lives of patients and families who are directly affected … each and every day."

"Thank you for the opportunity to be a part of this. This has reiterated to me where I need to spend time cleaning up my organization so that we can advance and make a bigger impact."

"Just working through this got the juices flowing for either doubling down on our activities and leadership, support or discovering if we are OK with just being online support for caregivers."

ACKNOWLEDGEMENTS

Thanks and appreciation to the grant from Epilepsy Foundation that has made this initiative possible and for the autonomy to undertake a project that hopefully will advance our collective understanding and improve our capacity to tackle common goals in the rare and broader epilepsy community.

Special thanks to Brandy Fureman, Kathleen Farrell, Priscilla Kobi and Sonya Dumanis for their dedication to Rares and support and advice on this project.

The RELA survey has been developed with advice and insights from the Rares themselves. Gratitude for quick replies and insights from the RELA Volunteer Advisory Committee including: Brittany McLarney (PMSF), Jo Anne Nakagawa (TS Alliance); Mary Anne Meskis (Dravet Foundation), Geraldine Bliss (Cure SHANK), Shelley Frappier (The Cute Syndrome), Amber Freed (slc6a1 Connect), Heidi Grabenstatter (Cdkl5), and Jay Etta Hecker & Gabi Conecker (Wishes for Elliott) as well as many members of the Rare and Catastrophic Seizures of Childhood (RCSC).

Inputs from other epilepsy stakeholders were invaluable and included: Phil Gattone, Bob Smith, and the EF Leadership Team; Laura Lubbers at CURE; Amy Brin at CNF; Eileen Murray and Penny Dacks at AES; Vicky Whittemore and Miriam Leenders at NINDS; Rosemarie Kobau at CDC; Meredith Cagle at Global Genes; and Debbie Drell and Allie Crafton at NORD. Appreciate the time and advice of Dr. Jeff Buchhalter, Dr. Steven C. Schachter, John Brothers at T Rowe Price Foundation, Luisa Boyarski at the Center for Public and Nonprofit Leadership at Georgetown University, Michael Gellman at Fiscal Strategies for Nonprofits, Mike Conroy design, and Donna Sprague.

This undertaking had broad input and support from many. Any errors or discrepancies are mine alone. Please report any corrections to: Ilene Miller ilenepennmiller@gmail.com.