GRIN Genes Roundtable Summary

March 4, 2021

CureGRIN

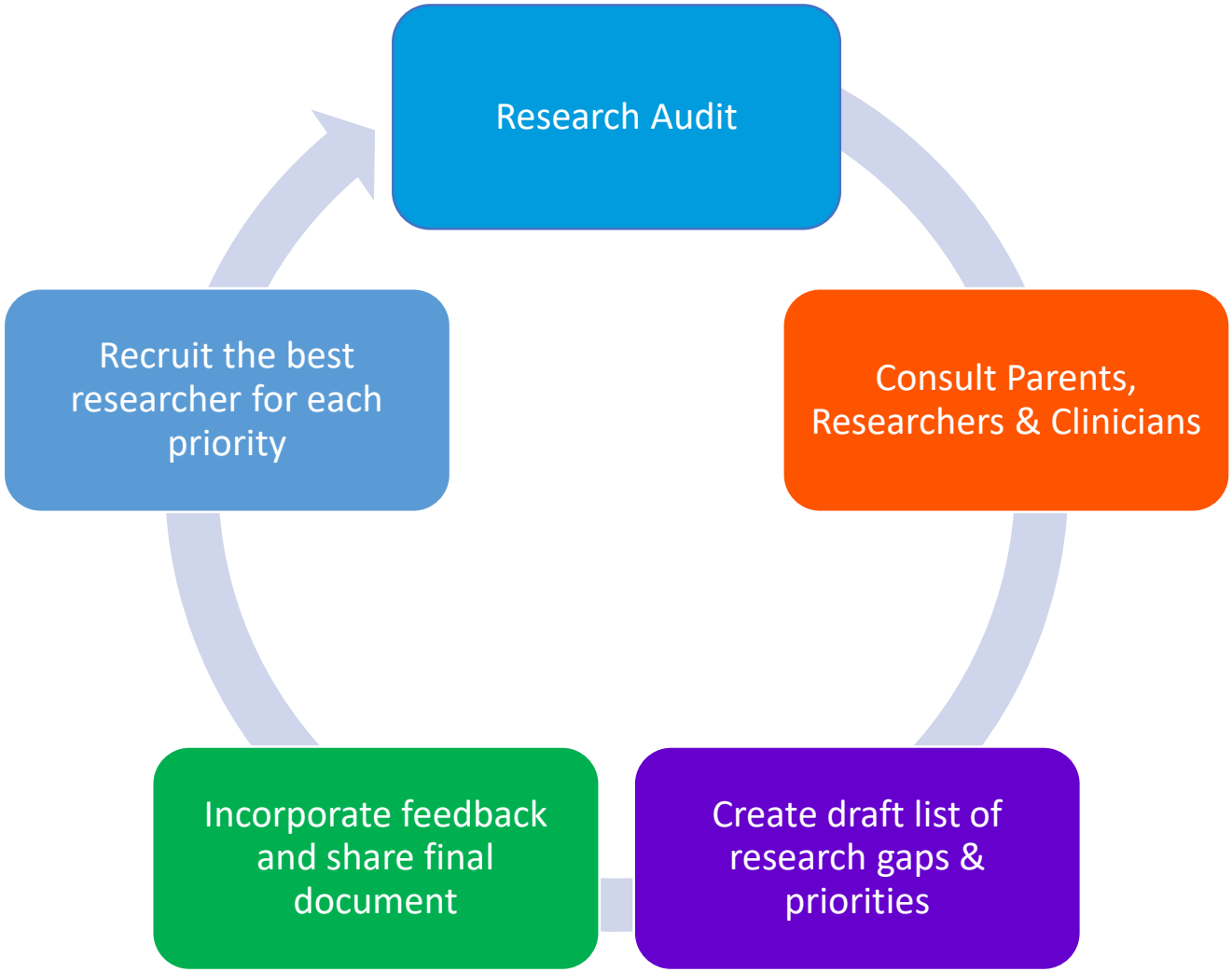
Funding Research for GRIN Disorder

CureGRIN Foundation hosted our fifth GRIN Genes Roundtable on March 4, 2021. Our goal is to **promote collaboration so that we can accelerate the path to treatments and cures for GRIN Disorder.**

We brought together researchers and clinicians studying GRIN Disorder, GRIN genes, NMDA receptors, and other ionotropic receptors to discuss and exchange ideas on identifying GRIN research priorities. There were 37 participants present for the meeting.

Keith McArthur (CureGRIN, CEO/Head of Science) presented the results of the GRIN Family Survey and Researcher/Clinician Survey. Meagan Collins (CureGRIN, Research Coordinator) presented on the most important research questions from the results of the Researcher/Clinician Survey. Following the presentations, we also had an open discussion on this topic. This document summarizes these presentations and the group discussion.

Identifying GRIN Research Priorities: Research Roadmap



Identifying GRIN Research Priorities: GRIN Family Survey

What symptoms does your child have? Please include all symptoms even if their connection to GRIN Disorder is unknown.

All GRIN (n=196)

1. **Intellectual Disability (94%)**
2. **Speech (81%)**
3. **Low Muscle Tone (73%)**
4. **Sleep Challenges (67%)**
5. **Mood / Behavior (53%)**
6. **Epilepsy / Seizures (51%)**
7. **Mobility Impairment (50%)**
8. **Constipation (50%)**
9. **Visual Impairment (45%)**
10. **Digestive (38%)**
11. **Neurostorms (33%)**
12. **Feeding Tube (21%)**
13. **Hearing Impairment (5%)**

GRIN1 (n=71)

1. ID (94%)
2. Speech (86%)
3. Sleep (74%)
4. Mobility (73%)
5. Low Muscle Tone (71%)
6. Epilepsy (59%)
7. Constipation (58%)
8. Visual Impairment (53%)

GRIN2B (n=80)

1. ID (98%)
2. Speech (85%)
3. Low Muscle Tone (75%)
4. Mood / Behavior (67%)
5. Sleep (63%)

GRIN2A (n=36)

1. ID (72%)
2. Epilepsy (69%)
3. Speech (68%)
4. Low Muscle Tone (60%)
5. Sleep (60%)

GRIN2D (n=9)

1. Low Muscle Tone (89%)
2. ID (89%)
3. Epilepsy (89%)
4. Visual Impairment (78%)
5. Sleep (56%)
6. Speech (67%)

* Responses >50% included here

Identifying GRIN Research Priorities: GRIN Family Survey

Of these symptoms, which is the most important for you for CureGRIN to prioritize in our funding of research and work with researchers and physicians?

All GRIN

1. **Intellectual Disability (34%)**
2. **Epilepsy (22%)**
3. **Speech (10%)**
4. **Mood / Behavior (9%)**
5. **Neurostorms (7%)**
6. **Mobility (5%)**
7. **Sleep issues (4%)**
8. **Feeding require feeding tube (3%)**
9. **Breathing (2%)**
10. **Low Muscle Tone (2%)**
11. **Constipation (1%)**
12. **Digestive (1%)**
13. **Visual impairment (<1%)**
14. **Hearing Impairment (<1%)**

GRIN1

1. ID (36%)
2. Epilepsy (21%)
3. Neurostorms (10%)
4. Speech (9%)
5. Mobility (6%)

GRIN2B

1. ID (41%)
2. Mood / Behavior (14%)
3. Speech (15%)
4. Epilepsy (10%)
5. Neurostorms (5%)
6. Feeding (5%)

GRIN2A

1. Epilepsy (44%)
2. ID (17%)
3. Mood / Behavior (11%)
4. Neurostorms (7%)
5. Mobility (6%)
6. Speech (6%)

GRIN2D

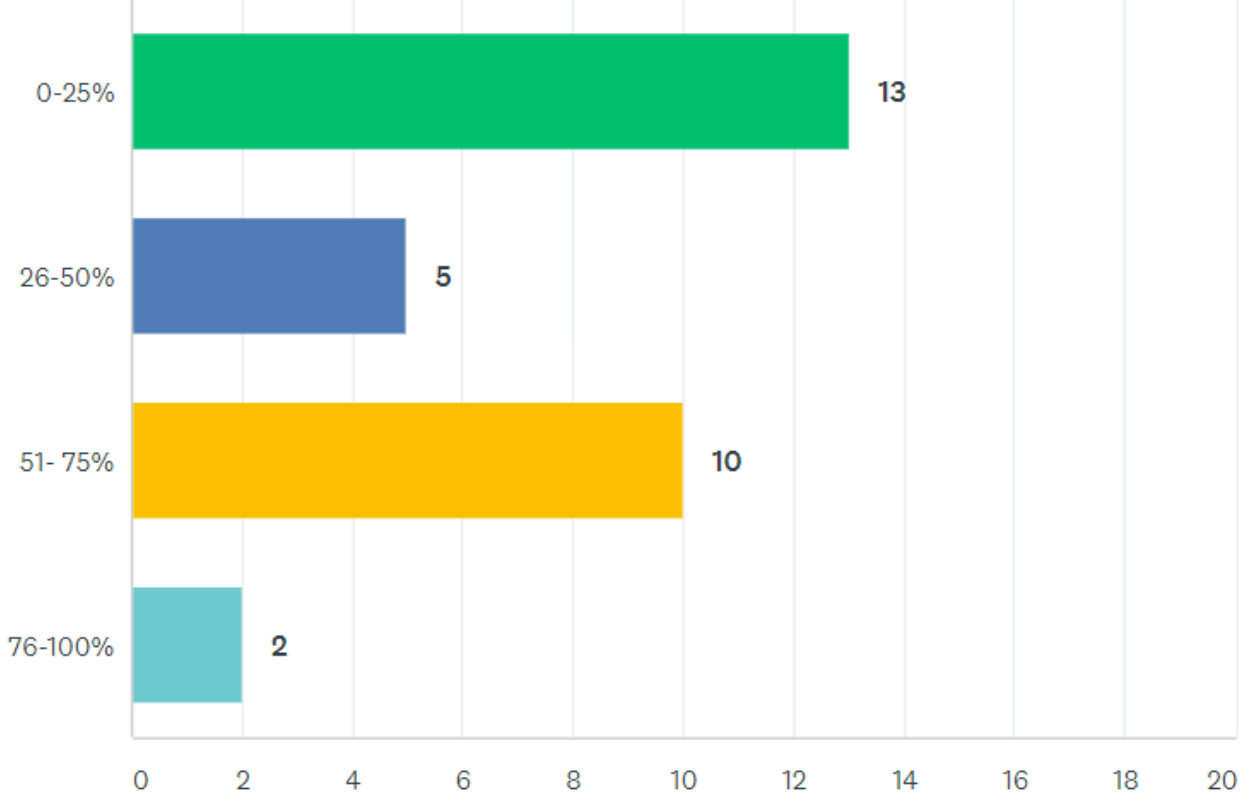
1. Epilepsy (56%)
2. ID (34%)
3. Mobility (11%)

Identifying GRIN Research Priorities: Researcher/Clinician Survey

Time Spent on NMDARs / GRIN

How much of your work week do you spend on research / medicine related to NMDA receptors, GRIN Genes or GRIN Disorder?

Answered: 30 Skipped: 0

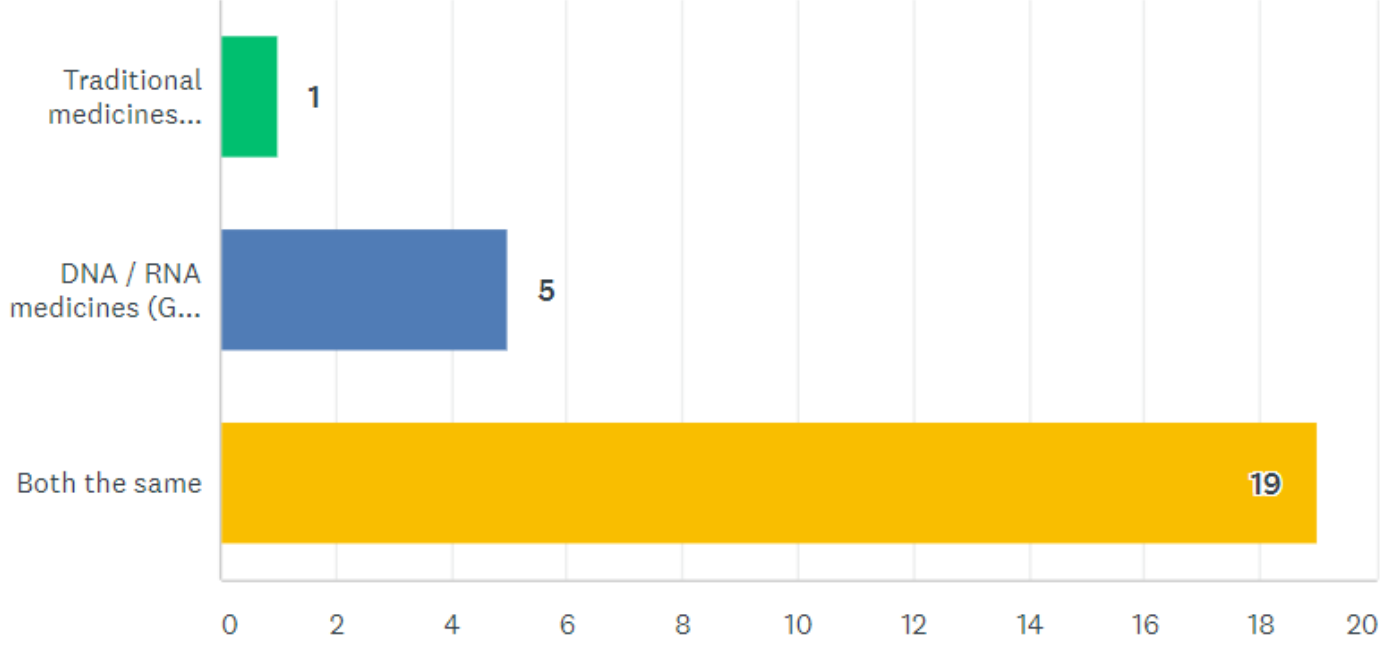


Identifying GRIN Research Priorities: Researcher/Clinician Survey

Traditional vs. RNA / DNA

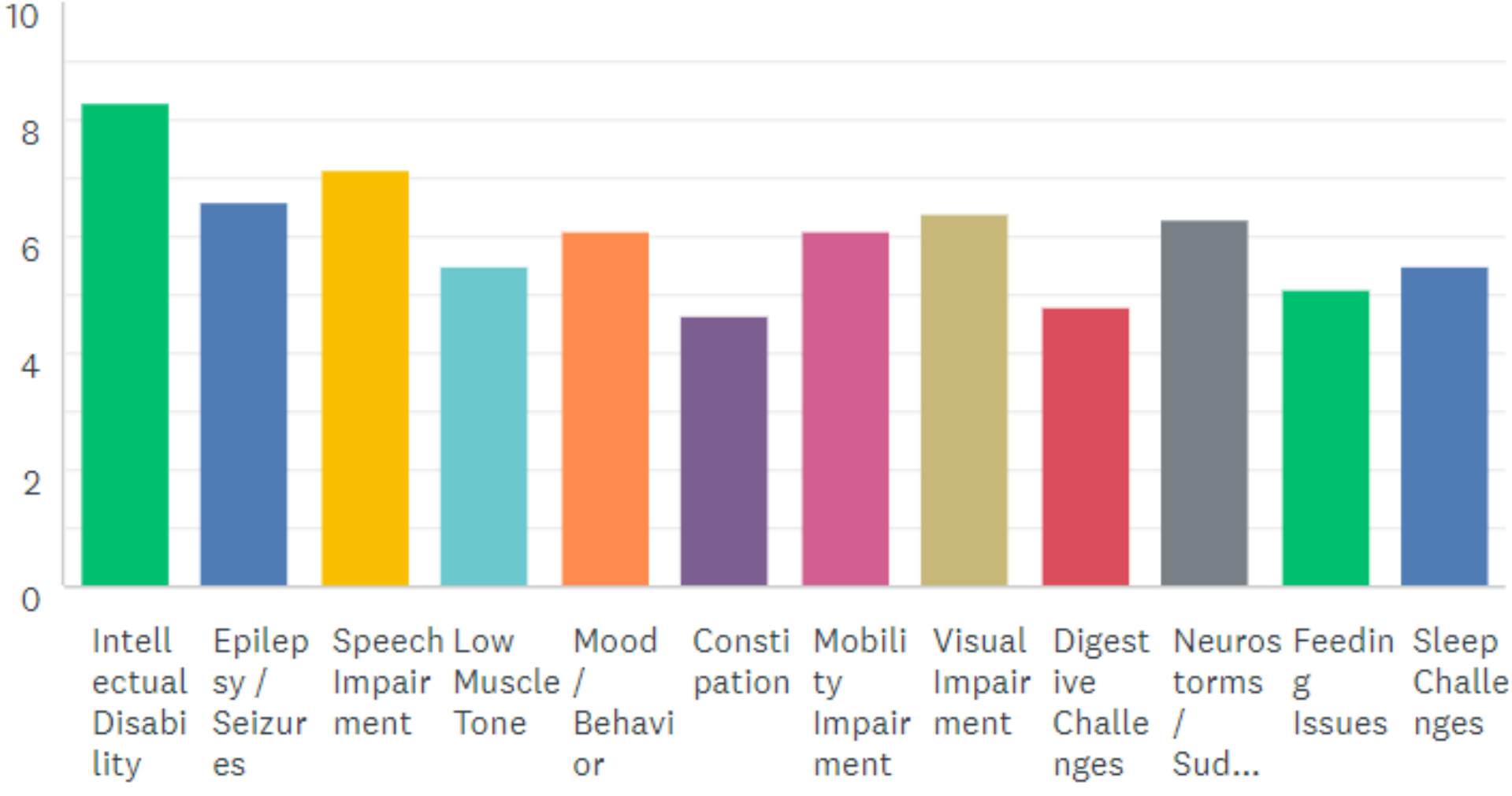
In order to find cures and treatments for people living with GRIN Disorder, how do you think we should balance our efforts between traditional medicines and DNA/RNA-based medicines?

Answered: 25 Skipped: 5



Identifying GRIN Research Priorities: Researcher/Clinician Survey

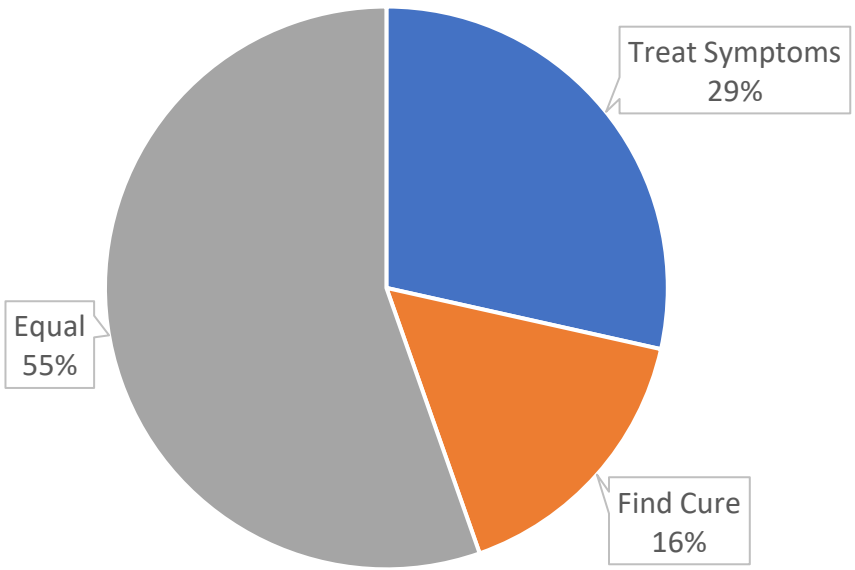
Time / Effort / Resources to find meaningful Treatments



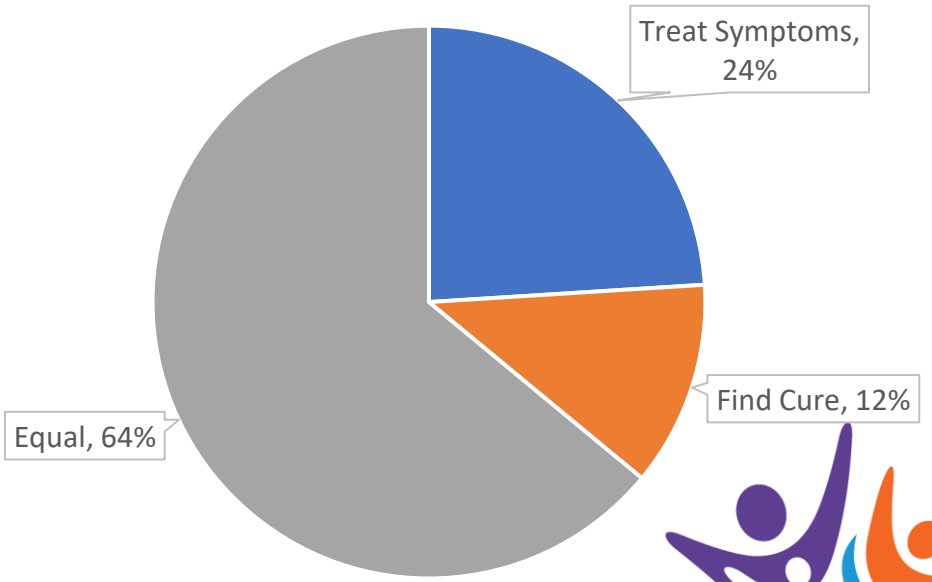
Identifying GRIN Research Priorities: Cures vs. Treatments

It may take years to find a cure. But over the short-term, we may find treatments that can help people living with GRIN Disorder to cope with specific symptoms (related to seizures, vision, sleep, etc.). How do you think CureGRIN should split our resources (time and money) between these two options?

GRIN Family Survey



Researcher/Clinician Survey



Identifying GRIN Research Priorities: Discussion Summary

- Keith McArthur asked a question about the gender split among the patient population (i.e., more females than males) who responded the GRIN Family Survey.
  - A parent representative from another GRIN Patient Advocacy Association commented that, in Europe, a lot of genetic testing is performed in females to confirm the diagnosis of Rett syndrome, autism, and other related disorders. This could possibly contribute to a higher number of GRIN diagnoses being reported in females.
- Keith McArthur asked for researchers' opinions on Traditional vs. RNA/DNA treatments.
  - One researcher noted that she would prefer to balance efforts between the two approaches. She noted that there are already drugs in the pipeline being developed for other disorders that affect the NMDA receptor (i.e., schizophrenia).
  - Another researcher said that he thinks we should focus on DNA/RNA therapies because traditional medicines historically do not always work for genetic disorders.

Identifying GRIN Research Priorities: Discussion Summary

- Keith McArthur asked researchers what their thoughts were about the time/effort/resources required to find meaningful treatments ranking question. He noted that no category was considered “easy” to treat.
  - A researcher responded that she did her rankings based on past results, as scientists have not been very successful at tackling cognitive symptoms and things like vision/speech are difficult to model in animals.
  - Another researcher commented about the bifurcation of early therapies versus later therapies and suggested that it may be difficult to treat some features of GRIN disorder if development has already occurred.
    - A researcher noted that there are critical periods in development for some brain functions, such as vision and speech, where we would need to act early in order to get real improvements.
- Keith McArthur asked researchers what their opinions were about the prospect of inviting biotech/pharma representatives to future meetings.
  - Three researchers responded that they felt that the outside perspectives could be helpful when developing treatments.

Presentation Summaries: Researcher/Clinician Survey

- Most Important Research Questions
  - Questions asked in survey
    - Q11: In your opinion, what is the most important research question we need to answer in order to find meaningful cures and treatments for GRIN Disorder?
    - Q12: What other questions are important to answer in order to find cures and therapies for GRIN Disorder?
- Common Themes of Researcher/Clinician Responses
  - Effects of variants on NMDARs/functional studies
  - Understanding underlying mechanisms
  - Treatments and efficacy
  - Ability to reverse deficits/Timing of treatment
  - Outcome measures

Identifying GRIN Research Priorities: Discussion Summary

- Meagan Collins asked researchers why we need to better understand the effects of variants on NMDARs and perform functional studies.
  - A researcher replied that it is important to stratify patients in order to predict treatments.
  - Another researcher commented that in order to fix something, you need to understand how it is broken, and he elaborated that a detailed functional characterization is needed in order to develop treatments.
  - One other researcher noted that a lot of the variants result in haploinsufficiency and that it would be nice to be able to group these variants together.
- Meagan Collins asked researchers what their thoughts were about the importance of understanding underlying mechanisms/pathways of GRIN disorder.
  - A researcher noted that we need to assess other cell populations in order to address some of the other issues outside of the CNS that GRIN patients experience, such as GI issues.

Identifying GRIN Research Priorities: Discussion Summary

- Meagan Collins asked researchers what their opinions were regarding the ability to reverse deficits/timing of treatments.
  - A researcher noted that once we identify and characterize variants, we could study them in a mouse model to understand neuronal and behavioral deficits, then develop treatments to address these issues.
  - A parent representative from another GRIN Patient Advocacy Association noted that natural history studies are also important.
  - A researcher noted that an early diagnosis is possible for GRIN disorder and that early interventions, like gene therapy, may be more beneficial in infants (due to the timing of immune system development).
- A researcher commented about the need for diagnostic and predictive biomarkers.
  - Several researchers discussed the prospect of collecting CSF and blood lab results in the registries.
- A researcher noted the importance of collaborating with other patient advocacy groups to leverage funding for treatments and therapies.

At our next meeting, we will have an open discussion on the topic of GRIN Research Priorities.

Our next GRIN Genes Research Roundtable is scheduled for:
Thursday, April 15, 2021

If you are a GRIN / NMDAR researcher or clinician, please reach out to meagan@curegrin.org to be added to the next meeting invitation.