2021 Annual Report

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Overview of This Report

The HI Global Registry (HIGR), launched on October 8, 2018, is the first global patient-powered congenital hyperinsulinism (HI) patient registry. Annually, the HIGR investigators have published a report consisting of descriptive data across key surveys to provide insights for those who share their data and other members of the HI community. This year's report includes information provided by HIGR participants from launch through September 2021. The intended audience is the HI community: people living with HI, their families, and all those interested in HI and its related research.

The registry consists of thirteen surveys made up of questions about the patient's experience with HI over their lifetime. These surveys include questions about contact details and demographics (such as age, sex, and country of birth), as well as questions about diagnosis, medication management, diet and feeding, surgical procedures, other diagnoses, development, and quality of life for the parent/guardian and participant (patient). Some surveys may be updated by the participant to allow data collection over time to study the natural history of HI. These updates are made at the respondent's discretion when there is a notable change in the participant's status, such as a new address, a change in treatment, or a newly diagnosed health condition. Other surveys are meant to be completed at specific time intervals. Only two surveys (Pregnancy and Birth) are final after the initial submission. The survey questions were carefully developed by an international team of HI experts, including family members of children with HI, advocates, clinicians, and researchers.

HIGR data is stored on the secure cloud-based IAMRARE™ Platform developed and hosted by the National Organization for Rare Disorders (NORD). The IAMRARE™ Platform was created with input from patients, caregivers, and government stakeholders to ensure a safe and user-friendly system for study participation. HIGR is sponsored by Congenital Hyperinsulinism International (CHI) and governed by internationally recognized HI patient advocates and experts who are members of the HI Global Registry Steering Committee.

This report includes similar, high-level data elements as well as a new section on patient self-reported quality of life. At this time, any year-to-year comparisons would focus on the increased number of observations. Although this change is valuable, reporting on longitudinal (or repeated observations over time) in subsequent reports and publications will be more meaningful in informing the natural history of the disease.

Each report includes the number of participants who provided information related to each specific element. The variation in the number of individual responses is the result of three factors: 1) the majority of surveys and questions are optional, 2) the finite set of questions to which each participant/respondent has an opportunity to respond is based on the individual's unique natural history, and 3) participants/respondents complete surveys at their own pace. For each element reported, the number of participants is listed as "n" followed by an equal (=) sign and the count of participants in that report. This year's report remains observational with the intent to provide a factual synopsis of key or commonly requested data elements as HIGR participants have reported them.

The investigators carefully consider the sample size and acknowledge that less than 30 participants is a small sample size. In small samples, the results may not be representative of all those with the

same condition. For that reason, readers are cautioned not to draw overarching conclusions about HI in smaller subgroup (less than 30 participants) reports. Data analysis of participant subgroups of 30 or more is presented with greater confidence. Due to the expressed interest in particular data points, some smaller subgroup data has been included with a notice of caution stated for those topics.

This annual report is meant to foster an active dialogue with the larger community of researchers, physicians, those with HI and their family members, regulators, drug developers, and other community stakeholders about the data. The investigators openly invite comments and questions about the report and welcome ideas for engaging all key HI stakeholders. Broad and robust participation from all members of the HI community will certainly serve to strengthen HIGR. The HIGR team can be contacted at info@higlobalregistry.org.

Note from CHI's Executive Director

We launched HIGR in 2018 because we believed the family and patient experience of living with HI is critical to better understanding the condition to advance better treatments, potential cures, and more timely and accurate diagnoses. Three years later, it is thrilling to see the interest build under the direction of CHI's Principal Investigator, Dr. Tai Pasquini.

Since launching:

- 437 people have registered with HIGR
- Over 2,000 surveys have been completed.
- People from 46 countries have participated.
- Hundreds of families have access to graphic representations describing the HI community across topics of great importance to them.
- Four biotechs are utilizing de-identified aggregate data for the development of new treatments.
- Yearly reports are available on our website.
- HIGR is contributing to combined de-identified aggregate rare disease data through our partnerships with the National Organization for Rare Disorders (NORD) and the Critical Path Institute (C-Path)
- HIGR data supports CHI programming to better support families, improve access to excellent care, research new and better treatments, and to raise awareness of HI to end preventable brain damage and death.

This work and progress are the result of the dedication of the HI community as a whole. The community includes dedicated parents of children with HI who have registered and completed surveys and adults living with the condition who delve into their past to provide retrospective data. The clinicians who share HIGR information with their patient families are also vital to the success of HIGR, as are the researchers who see value in patient-reported data.

During the three years since we have launched HIGR, CHI has been able to grow through the generosity of CHI sponsors, donors, and volunteers. We now have a staff of five, with two full-time researchers and a full-time communications specialist. These additional staff members will help us significantly increase our productivity and outreach. Outreach is vitally important because increased participation is still needed to characterize the condition in all its complexity.

We also began partnering with academic institutions to pilot the inclusion of physician-reported data in the registry this year and are piloting an additional quality of life measure. We feel confident we will learn so much from this pilot project called MaxHIGR, which creates a stream of physician-reported data into the registry. Continuing to characterize and hone with data how an HI diagnosis affects a child and family's life is challenging work we are committed to in future reports.

We also launched the Centers of Excellence program this year, and six centers in the US, UK, and Europe have been designated.

The CHI COEs are:

- Congenital Hyperinsulinism Center at the Children's Hospital of Philadelphia, PA, United States
- The Hyperinsulinism Center at Cook Children's Medical Center in Fort Worth, TX, United States

- Great Ormond Street Hospital Congenital Hyperinsulinism Service in London, in the United Kingdom
- Charité – Universitätsmedizin Berlin and the University Children's Hospital Duesseldorf partnership in Germany
- Collaborative Alliance on Congenital Hyperinsulinism headquartered in Magdeburg, Germany
- Northern Congenital Hyperinsulinism Service in Manchester and Liverpool, in the United Kingdom

We hope to find ways to strengthen HIGR through these partnerships.

Affirmation of the centricity of HIGR in future research has come from our Global Collaborative Research Network (CRN). This project funded by the Chan Zuckerberg Initiative Rare As One Project brings together patient families, researchers, and clinicians to create a prioritized research agenda for improving the lives of those born with HI and their families. Dr. Diva D. De León-Crutchlow of the Children's Hospital of Philadelphia is Lead Researcher on this project and Dr. Paul Thornton of Cook Children's is Lead Clinician. In the working groups of this project, the need for natural history is a topic of great significance. Strengthening and growing HIGR while supporting collaborative projects with partner institutions and organizations will pave the way forward for a "future without lows."

Note from HIGR's Principal Investigator

I had the pleasure of taking on the responsibility of HIGR Principal Investigator this past spring. As CHI's Research and Policy Director, I was already familiar with the system and the fantastic potential for data collection, the investigation into new insights on the natural history of HI, and the community's dedication to supporting this effort. This year, we have had the opportunity to share information with the community at two CHI-sponsored virtual research conferences and through posters at virtual Pediatric Endocrine Society (PES) and Global Genes conferences. I am always invigorated by the response from researchers, patients, and families who find the information valuable.

The registry has also been a significant focus in conversations related to the newly launched Congenital Hyperinsulinism Collaborative Research Network (CRN). The CRN is a network of patients and parents, physicians, researchers, and patient organizations working together to accelerate research and cures for HI. Currently, the goal of the CRN is to create a prioritized research agenda or roadmap for research priorities within the community. Participants have discussed the importance and potential of the HIGR to drive progress in better glucose monitoring, diagnosis, genetic discovery, medication management, quality of life for patients and families, and much more!

The power of the registry is apparent, as is the genuine desire to support its growth and potential. Beyond the HI community, the CHI team has relationships with other rare disease organizations through the Chan Zuckerberg Initiative's Rare as One Network and the National Organization for Rare Disorders membership network. These conversations can help guide our efforts to leverage HIGR for a more successful natural history study to support new treatments and cures.

Looking to the year ahead, our team is looking to further leverage the expertise from our HIGR Steering committee. We are also launching a new pilot project, MaxHIGR, funded by the Million Dollar Bike Ride in collaboration with the University of Manchester and global partners in the US, Germany, and Kazakhstan, to include physician data into HIGR. We have also heard that the IAMRARE™ platform is implementing new language capabilities in 2022, which will be critical to expanding the registry. Finally, we commit to further disseminating registry data analysis through increased participation at conferences, publications, and partnerships with researchers interested in using the data for research studies.

To continue to achieve these goals, we need the support of all of you! We hope patients and families will continue to provide updates, join the registry, and share their stories, clinicians will encourage their patients to join, and our donors will continue to support the project. Thank you to everyone for allowing me to serve in this role and working together towards new insights in HI research and a better quality of life for patients.

Protocol Objectives

The HIGR is guided by a research protocol approved by an institutional review board (IRB), also known in some countries as an ethics committee. In 2021, our IRB is the North Star Review Board. An IRB is a group of people who perform independent reviews of research studies. If you have questions, concerns, or complaints that are not being addressed by the research team, you can contact the IRB at info@northstarreviewboard.org, or toll-free at (877) 673-8439.

This protocol was drafted by the HIGR Steering Committee made up of international researchers, clinicians, and advocates. HIGR is designed to function as a natural history study, meaning HIGR will collect specific health-related information over time from its participants to understand how HI develops, how it is treated, and how HI impacts health and life. The objectives (or goals) of HIGR remain unchanged from the previous report and are defined below. The primary objectives are centered around the condition, while the secondary objectives focus on the participants' lives and experiences with HI. The ultimate goal of HIGR is to advance the global understanding of HI and drive research toward better treatments and ultimately a cure.

The primary objectives of HIGR are:

- To provide a convenient online platform for participants (or caregivers) to self-report cases of HI in order to document the natural history and outcomes of individuals with HI.
- To improve knowledge of global prevalence of HI and any associated comorbidities.
- To better understand the role of timely diagnosis of HI on patient developmental outcomes.
- To better understand patient health outcomes of different HI treatment options, settings, and provider types.
- To identify both positive and negative effects related to different HI treatment options.
- To support the evolving standards of care for HI patients using natural history and outcome information from a global perspective.

The secondary objectives of HIGR are:

- To document the obstacles to accessing HI care, supplies, and medications.
- To measure the impact of HI and its management on patients' and caregivers' quality of life.
- To aid CHI and/or other country or region-specific HI patient organizations in identifying like genotypes or similar conditions to further connect HI patients/families within the larger HI community.
- To accelerate and facilitate HI clinical study development by identifying eligible research participants quickly and efficiently.
- To serve as an aggregated, de-identified resource to researchers seeking to study the pathophysiology of HI retrospectively in order to design prospective trials related to improving HI patient outcomes.
- To support the work of the CHI Collaborative Research Network by providing natural history data and providing a platform for future research studies.

Characteristics of HIGR Participants and Diagnosis

HI occurs worldwide, and the global prevalence (or frequency) of HI is poorly understood. HIGR has the potential to help calculate this vital figure one day. Figure 1a shows that HIGR already has participants from 46 countries and every inhabited continent. For this year's annual report, 335 individuals completed a total of 2,012 surveys. There is a wide range of ages among HIGR participants, from just a few weeks old to 60 years old (Figure 1b). Unless otherwise noted, the data presented in this report reflects the information available in HIGR as of September 1, 2021.

Figure 1a. HIGR Participants, by continent

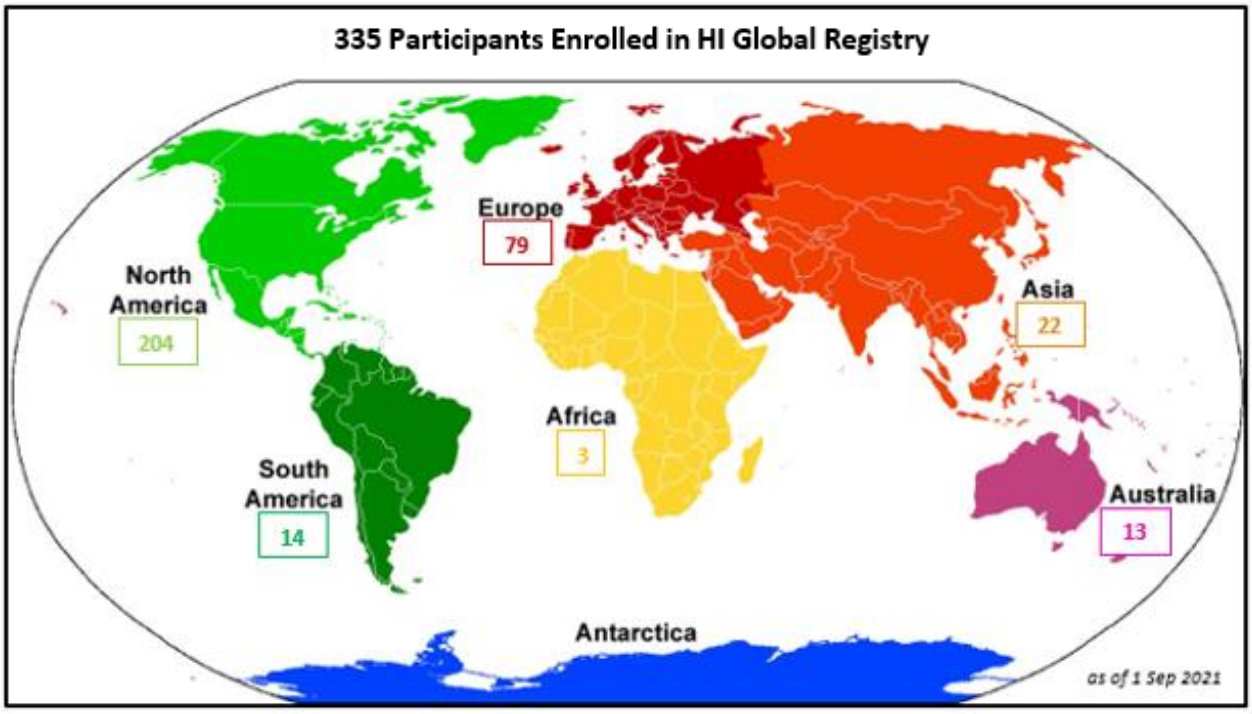


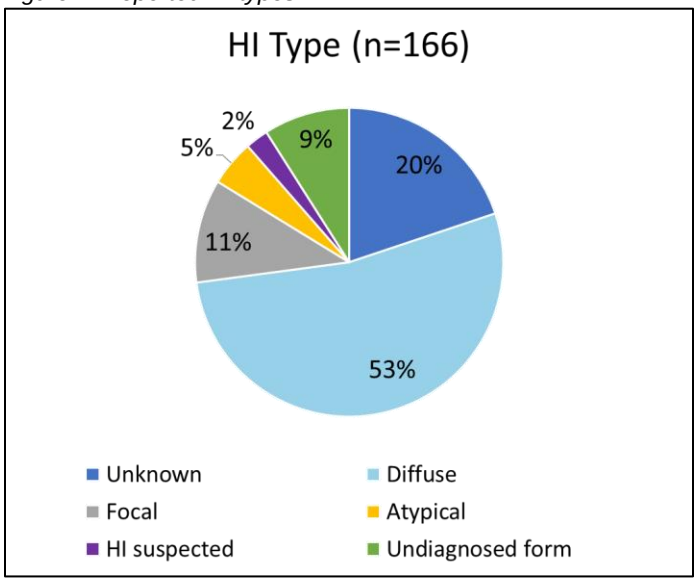
Figure 1b. HIGR Participants, by age

Age	Participants
0-2 years	71
3-5 years	102
6-9 years	73
10-12 years	17
13-17 years	23
18+ years	49
Youngest	4 weeks
Oldest	60 years

The data collected in the Diagnosis Survey provides high-level information on elements related to the prevalence of HI, such as type of diagnosis and genetic testing among HIGR participants.

HI Type

Figure 2. Reported HI types



Diffuse HI is a general term that includes several forms of HI that affect the entire pancreas, including KATP (potassium channel) defects, glucose dehydrogenase HI (GDH-HI, also known as hyperinsulinism hyperammonemia (HIHA)), glucokinase HI (GK-HI), those without a known genetic cause, and others. Figure 2 shows the proportion of reported HI types currently found in HIGR based on 166 participants. This year, 88 (53%) participants report diffuse disease; 18 (11%) report focal HI; 8 (5%) report receiving an atypical HI diagnosis. Another 52 (31%) report one of the unspecified responses available: 33 (20%) report an unknown type of HI; 15 (9%) report an undiagnosed status; and four (2%) report that HI is a suspected diagnosis. The HIGR investigators further analyzed the individuals who reported that HI was suspected, unknown, or undiagnosed and feel confident that these individuals received a medical diagnosis of HI, based on responses to other questions such as positive genetic results or reported methods of medical management.

Genetics

As seen in Figure 3a, 68% of the 144 participants reporting on genetic testing have positive results for a gene known to be associated with HI. Of the 144 participants that had at least one genetic test, 60% report positive genetics on the first test. Of the 40% who had unknown or negative results on the first genetic test, 32 had a second test, and 11 of those individuals had positive results.

There are many reasons, not explored in this report, why additional testing may have been performed. Examples include single-gene testing expanded to panel gene testing or initial testing that occurred before new genes related to HI were identified.

Figure 3a. Percent positive genetic testing

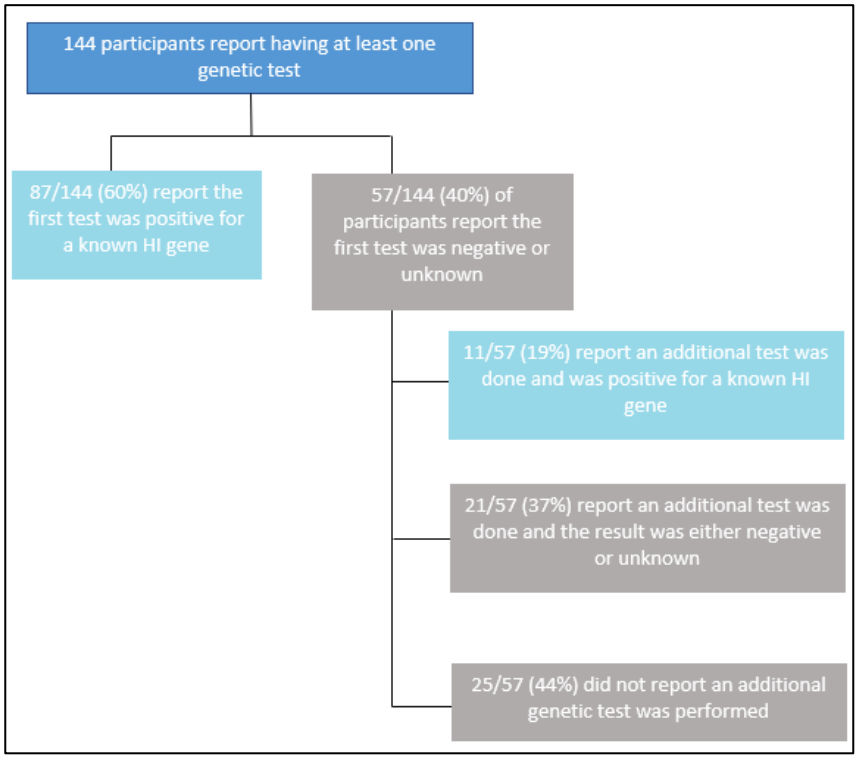


Figure 3b displays HI genetic testing results by HI type. Of the 139 individuals who provided both their HI type and their genetic testing results, 61% participants tested positive for a change/mutation in HI-related genes, 31% participants tested negative for change/mutation in HI-related genes, and 7% had unknown results. Of those who tested positive, 53 (62%) reported diffuse HI, 15 (17%) reported focal HI, and 18 (21%) reported their HI type was either unknown, atypical, suspected, or undiagnosed. The number of people reporting positive genetics but an unknown type underscores the need for more consistent nomenclature or names for the types of

HI and a greater understanding of how the community (patients and clinicians) describe an HI diagnosis.

Of those who tested negative, 16 (37%) reported diffuse HI, 2 (5%) reported focal HI, and 25 (58%) reported their HI type was either unknown, atypical, suspected, or undiagnosed. Greater HIGR participation over time will create a larger sample size and allow more specific reporting of genetic results and details without risking the release of potentially identifiable information.

Figure 3b: HI Genetic Testing Results by HI Type

	HI Genetic Testing Results		
HI Type	**Unknown**	**Positive for change/mutation in HI-related gene(s)**	**Negative for change/mutation in HI-related gene(s)**
Unknown	0	9	14
Diffuse	6	53	16
Focal	1	15	2
Atypical	1	5	1
HI suspected	1	1	1
Undiagnosed form	1	3	9
Total	**10**	**86**	**43**

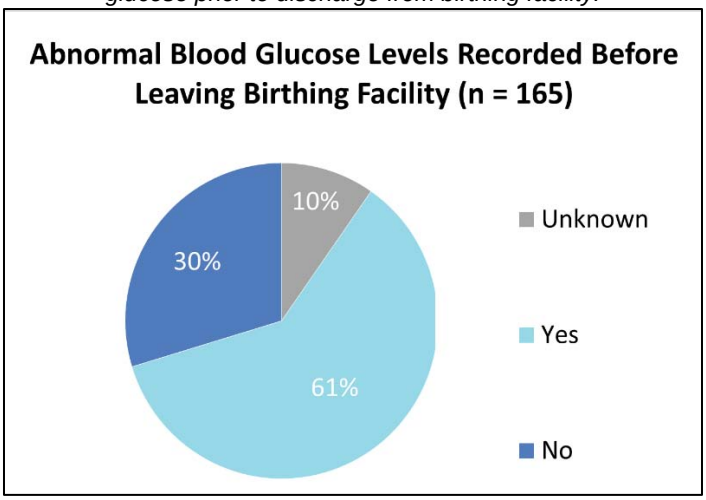
HI-related Syndromes

A syndrome is a condition that is categorized by a set of symptoms that commonly occur together. Eleven participants indicated the presence of a HI-related syndrome. The syndromes listed by HIGR participants include Beckwith-Weidemann (4), Kabuki, Turner, Sotos, Fanconi, Polycystic Kidney Disease, and Rubinstein-Taybi Type 2.

Abnormal Blood Sugar Before Leaving Birthing Facility

Figure 4 shows that of 165 participants, 100 (60%) report that an abnormal blood glucose level was recorded before the participant left the birthing facility. Of the 100 participants, 55% reported symptoms were present when the participants first abnormal blood sugar was tested, while 31% reported there were no symptoms present, and 14% did not know.

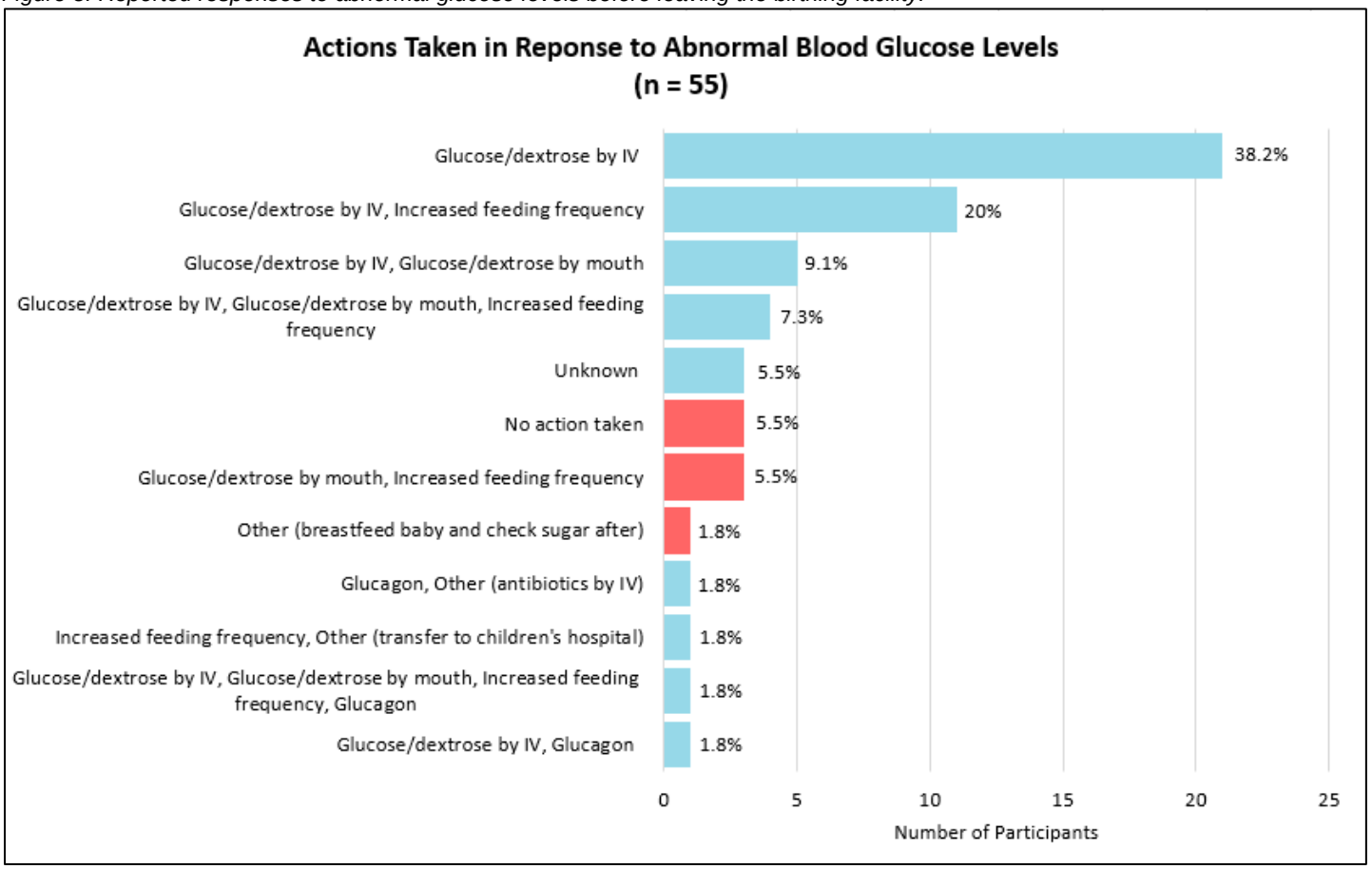
Figure 4. Percentage of participants reporting abnormal blood glucose prior to discharge from birthing facility.



Of 100 participants, 77% reported that an abnormal blood glucose was present at one day old, 13% reported two days old, 4% reported presence at three days old. Figure 5 lists the reported

action or combination of actions taken by healthcare professionals in response to the abnormal blood glucose readings of 55 participants. Actions reported included the use of glucagon (6%), intravenous (IV) glucose administration (78%), and increased feeding frequency (36%). Actions limited to oral strategies to address the abnormal blood glucose level are noted in red on the figure. Oral strategies alone are reported by 7% of participants, and another 6% reported no action was taken.

Figure 5. Reported responses to abnormal glucose levels before leaving the birthing facility.



Of 67 participants reporting an abnormal blood glucose level before leaving the birthing facility who also answered the relevant questions from the Diagnosis Survey, 75% also report receiving an HI diagnosis before leaving the birthing hospital. This indicates 25% of participants did not receive an HI diagnosis before leaving the hospital after birth despite reporting an abnormal blood glucose level. Of the 17 individuals who did not receive their diagnosis before leaving the birthing facility, nine report requiring one additional hospitalization before receiving an HI diagnosis; three report two hospitalizations; two report three to five hospitalizations; and three report more than six hospitalizations before an HI diagnosis was made.

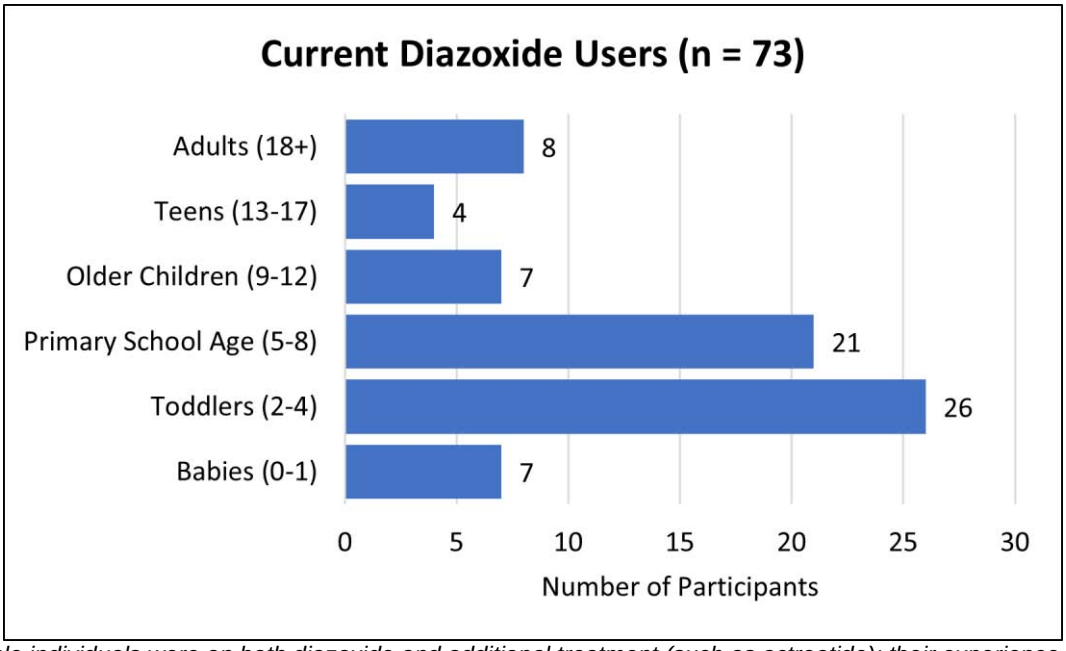
Medication Experience

The survey regarding the medical management of HI gathers data on medication the participant has taken to treat HI. A total of 133 people completed the medication experience survey. This section reports on past and current use of medication, combining information from other surveys, such as the age of the participants and reported blood sugars, to provide additional analysis on the medication experience of participants.

Diazoxide

Of the 112 participants who reported having taken diazoxide, 73 participants (65%) are currently taking diazoxide, and 39 (35%) have taken it in the past. The average age of those currently on diazoxide is eight years old, with a range of fifteen months to 46 years old. Figure 6 shows the breakdown by age group of those currently taking diazoxide. Thirty-three participants (45%) who report that they are currently taking diazoxide are under five years old.

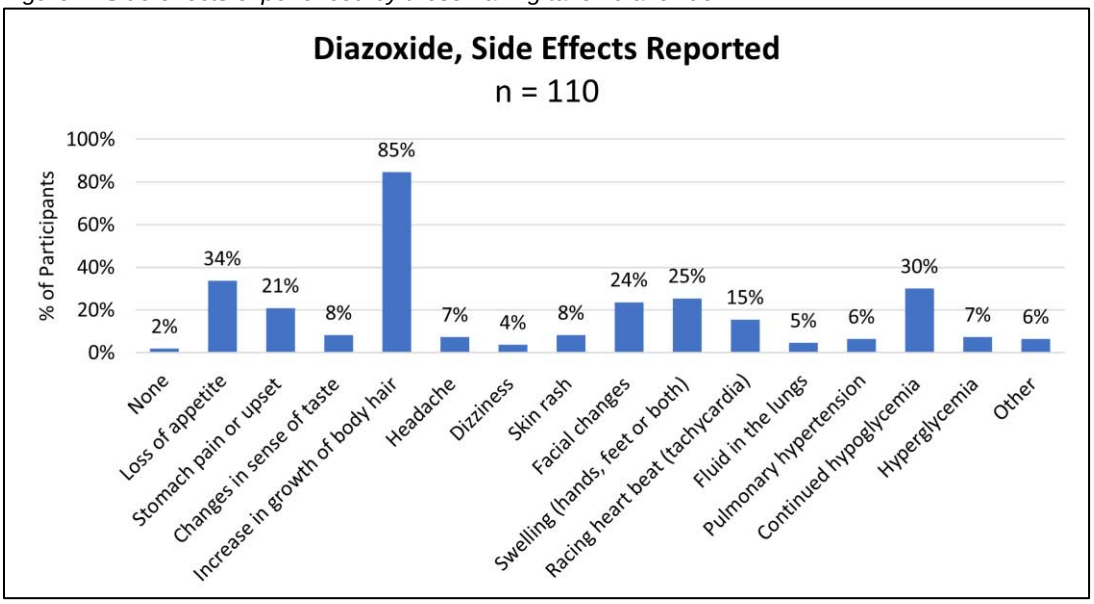
Figure 6. Age of those currently taking diazoxide



**Note: It is possible individuals were on both diazoxide and additional treatment (such as octreotide); their experience is captured in this chart and not analyzed separately.*

As illustrated in Figure 7, all but two (98%) of the participants who reported having taken diazoxide (both past and current) experienced some adverse effect(s). The most common side effects reported include increased body hair (85%), loss of appetite (34%), continued hypoglycemia (30%), swelling (25%), facial changes (24%), and stomach pain or upset stomach (21%). Other than the listed response choices, participants reporting side effects noted hypertension, severe nausea, vomiting, fluid retention, scrotal swelling, thrombocytopenia (low platelet count), and congestive heart failure.

Figure 7. Side effects experienced by those having taken diazoxide



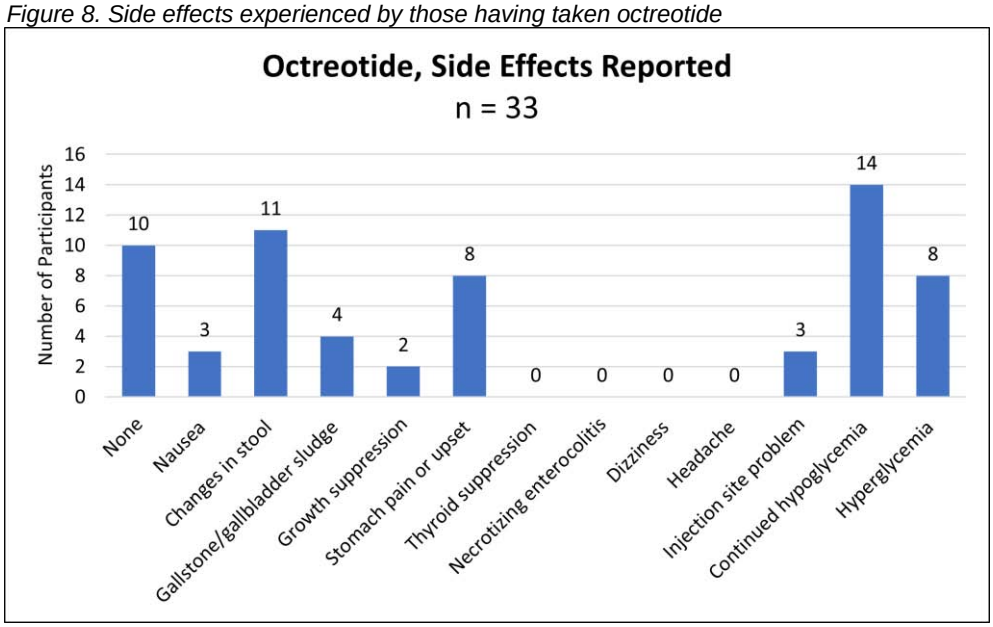
Sixty-five (89%) participants currently taking diazoxide also reported low blood sugar frequency. Twenty-six (40%) of those participants (all ages included) experienced at least one hypoglycemic event per week; 17 (26%) experienced at least one hypoglycemic event per day.

Octreotide

Thirty-four participants reported having taken octreotide; of those, seven are currently taking octreotide. The average age of those currently taking octreotide is four years old with an age range of two to seven years.

Twenty-three (70%) of the 33 who reported having taken octreotide (both past and current) report experiencing some adverse effect, and 19 participants responded to the specific side effects experienced (see Figure 8). The most common side effects include continued hypoglycemia (14 participants), changes in stool (11 participants), hyperglycemia (eight participants), stomach pain or upset (eight participants), and gallstones/gallbladder sludge (four participants). Some participants reported experiencing more than one side effect. Although no participants reported thyroid suppression, necrotizing enterocolitis, dizziness, or headache, we have included them in this report as they are either listed on the octreotide label as possible adverse effects or are symptoms of interest to clinicians and researchers.

Figure 8. Side effects experienced by those having taken octreotide



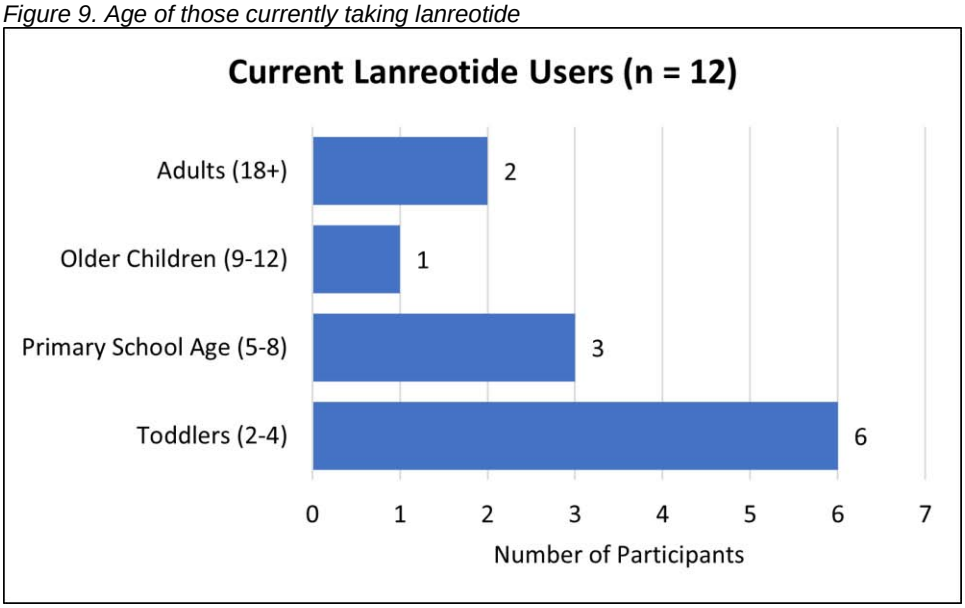
The following is a report that includes a small sample size. Six participants currently taking octreotide reported on low blood sugar frequency. All of those participants experienced several hypoglycemic events per week, and four experienced at least one hypoglycemic event per day.

Octreotide LAR

Four participants reported taking long-acting injections (octreotide LAR). The threshold for reporting further analysis on the experience of these participants with this medication was not met at the time of this report.

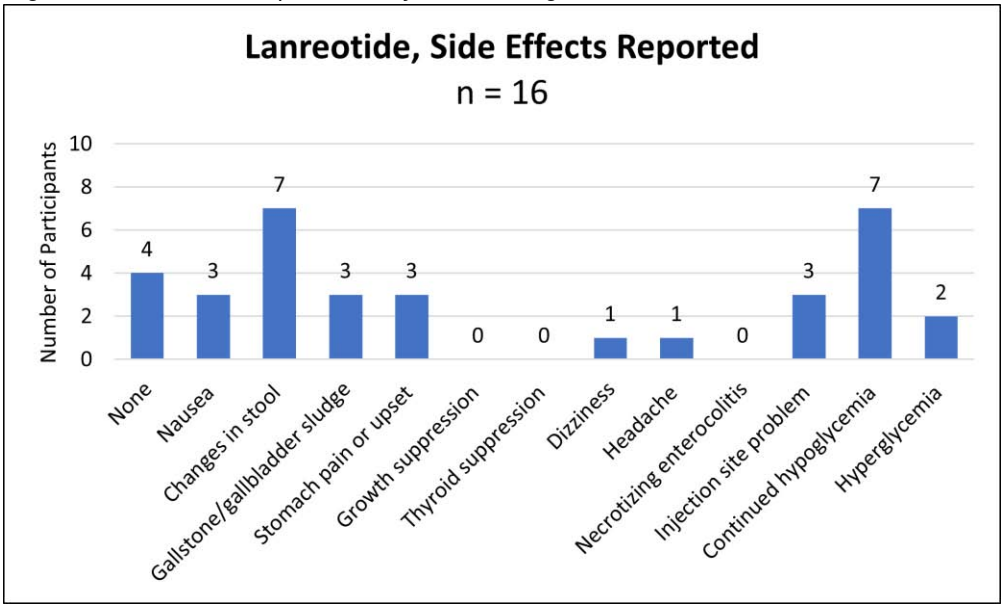
Lanreotide

Figure 9. Age of those currently taking lanreotide



The following is a report that includes a small sample size. Of the 16 participants who reported having taken lanreotide, 12 are currently taking it, and four have taken it in the past. Figure 9 shows the breakdown by age group of those currently taking lanreotide. The average age of those taking lanreotide is currently eight years old, ranging from 2 to 24 years old.

Figure 10. Side effects experienced by those having taken lanreotide



Twelve of the 16 participants who have taken lanreotide injections (past and current) experienced some adverse effects (see Figure 10). The most common side effects include continued hypoglycemia (seven participants), changes in stool (seven participants), injection site problems (three participants), gallstones/ gallbladder sludge (three participants), stomach pain, or upset (three participants), and nausea (three participants). Some participants noted more than one side effect. While no participants reported growth suppression, thyroid suppression, or necrotizing enterocolitis, we have included them in this report as they are either listed on the lanreotide label as possible adverse effects or are symptoms of interest to clinicians and researchers.

Twelve participants currently taking lanreotide also reported low blood sugar frequency. Five of those participants (all ages included) experience more than one hypoglycemic event per day.

<u>Sirolimus</u>

Two participants reported taking sirolimus. Sirolimus duration of use ranged from two to five months for one participant and one to two years for the other. The threshold for reporting further analysis on the medication experience of these participants was not met at the time of this report.

Feeding Experience

The Diet and Feeding Management Survey collects data about past and current feeding and eating methods, schedules, and potential issues. This section looks at reported feeding issues, the number of daily feeds, and the use of tube feeds to manage HI.

Feeding Issues

Figure 11 presents reported feeding issues for the 132 participants who have completed the Diet and Feeding Management Survey. Of those, 111 also provided information on their HI type and surgery experience, the subgroup analysis in Figure 11. The "Other" type of HI grouping (n=34) includes the undiagnosed form of HI, unknown HI type, and atypical HI.

Of the 132 participants (all HI types and treatments included), 91 (69%) reported having one or more feeding issues. The most-reported feeding issues were poor appetite (40%) and refusing to eat (39%). Over a quarter of the participants answering this question reported reflux, problems with texture, gagging, vomiting, uncoordinated oral skills, and slow eating.

Sixty-six participants reported diffuse HI, 29% of those individuals had a pancreatectomy, and 84% of those individuals with diffuse HI and a pancreatectomy reported feeding issues. Among the individuals who had diffuse and did not have surgery, 68% of participants reported feeding issues. Feeding issues were also reported in 73% of participants with focal disease and 62% of those reporting other types of HI.

Figure 11. Reported feeding issues

Has the participant experienced any feeding issues regularly (check all that apply)?	All Participants	Diffuse			Focal			Other HI Type
	W/WO Surgery	No Surgery	Pancreatectomy	Total	No Surgery	Pancreatectomy	Total	No Surgery
	N (%)	N	N	N (%)	N	N	N	N (%)
No feeding issues	41 (31%)	15	3	18 (27%)	0	3	3	13 (38%)
Feeding Issues(s)	91 (69%)	32	16	48 (73%)	1	7	8	21 (62%)
Poor appetite	53 (40%)	20	10	30 (45%)	1	1	2	12 (35%)
Refusing to eat	52 (39%)	18	8	26 (39%)	1	4	5	13 (38%)
Reflux	38 (36%)	16	7	23 (35%)	0	4	4	6 (18%)
Problems with texture	38 (29%)	14	9	23 (35%)	1	3	4	8 (24%)
Gagging	35 (27%)	14	7	21 (32%)	0	1	1	6 (18%)
Vomiting	34 (26%)	12	6	18 (27%)	1	4	5	6 (18%)
Uncoordinated oral skills	27 (20%)	10	7	17 (26%)	1	1	2	6 (18%)
Slow eating	34 (26%)	16	8	24 (36%)	0	1	1	6 (18%)
Coughing	19 (14%)	8	6	14 (21%)	0	0	0	3 (9%)
Overeating	11 (8%)	7	2	9 (14%)	0	0	0	1 (3%)
Total	**132**	**47**	**19**	**66**	**1**	**10**	**11**	**34**

Of the 88 individuals who reported whether the participant's feeding issues were resolved, 38% shared that the reported feeding issue had been fully resolved. Parents said that the participant's feeding issues resolved within the first year of life (29%), 1-3 years of age (26%), 4-6 years of age (26%), and over the age of 7 years of age (17%).

Feeding methods and frequency

Figure 12 presents reported feeding methods for the 139 participants who completed the Diet and Feeding Management Survey, and 113 provided the information needed for the further subgroup analysis shown on the chart. The tube feeding group combines tube feeds of all types: nasogastric (NG), orogastric (OG), gastronomy button (G), and jejunostomy tube (J).

Figure 12. Use of tube feeds in HI patients

What routes have been used to feed the participant since HI was suspected (check all that apply)?	**All Participants**	**Diffuse**			**Focal**			**Other HI Type**
	W/WO Surgery	No Surgery	Pancreatectomy	Total	No Surgery	Pancreatectomy	Total	No Reported Surgery
	N (%)	N	N	N (%)	N	N	N	N (%)
Both Tube & Oral Feeding	59 (44%)	19	19	38 (55%)	0	7	7	9 (27%)
Tube Feeding (NG/OG/J/G) Only	20 (14%)	4	2	6 (9%)	0	2	2	4 (12%)
No Tube Feeding	56 (42%)	24	1	25 (36%)	1	1	2	20 (61%)
Total	**139**	**47**	**22**	**69**	**1**	**10**	**11**	**33**

Of all respondents, 79 (58%) report that tube feeding was used to provide nutrition and/or background sugar to the participant since HI was suspected. Of the individuals who reported tube feeding, 52% of individuals used continuous tube feeding at some point to manage the participant's blood sugar, and 9% of individuals are currently using continuous tube feeds. Of the 40 individuals who reported when they stopped using continuous tube feeds, 55% reported that it was discontinued within the first year of life. An additional 13% said that the participant no longer received tube feeding when they were three years old. Six participants said they are currently using continuous tube feeding; of those individuals, four reported diffuse disease, one reported focal, and one reported an undiagnosed form of HI. A total of 141 people reported the average number of meals/snacks the participant received by mouth or tube feeding in 24 hours. The majority (70%) of participants eat 4-7 times a day, 18% of people reported eating 8-11 times a day, and 5% reported feeding more than 12 times a day or continuously.

Surgery Experience

This section focuses on data collected from the Surgical Management and Other Diagnoses surveys. The Surgical Management survey gathers information about pancreatic surgery to treat HI and its outcomes. The survey is intended for all participants, whether or not they require a pancreatectomy. The Other Diagnoses survey reports on conditions that may be associated with HI. In this section, we focus specifically on diabetes and pancreatic insufficiency.

Fifty-five participants (39%), out of the 142 completing the Surgical Management survey, reported that a pancreatectomy was considered for the treatment of their HI. Forty-one of those 55 participants (75%) report undergoing at least one pancreatectomy. Of the 41 that had a pancreatectomy, 22 reported diffuse HI, 12 reported focal HI, three reported atypical HI, and four did not provide a HI type.

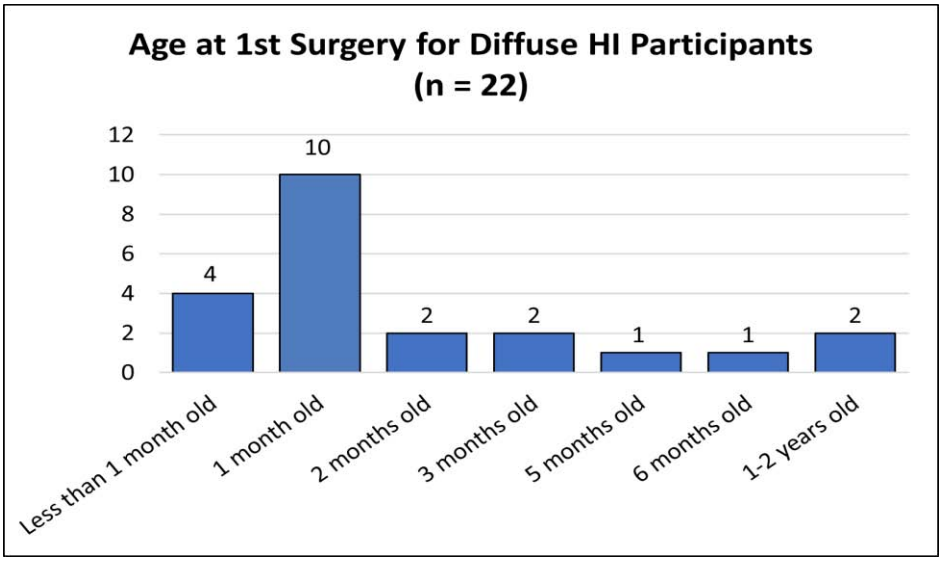
Focal

Twelve participants in HIGR reported having focal HI and underwent at least one pancreatectomy. Three participants with focal disease required a second pancreatectomy. When the first pancreatectomy was performed, the reported participant age was less than one month old for three participants, one month old for three participants, two to three months old for two participants, and five to nine months old for four participants.

The total amount of pancreas removed in focal participants, whether in a single surgery or combined for the participant requiring a second pancreatectomy, was less than 25% for five participants, 25-49% for two participants, 50-74% for four participants, and 75-94% for one participant.

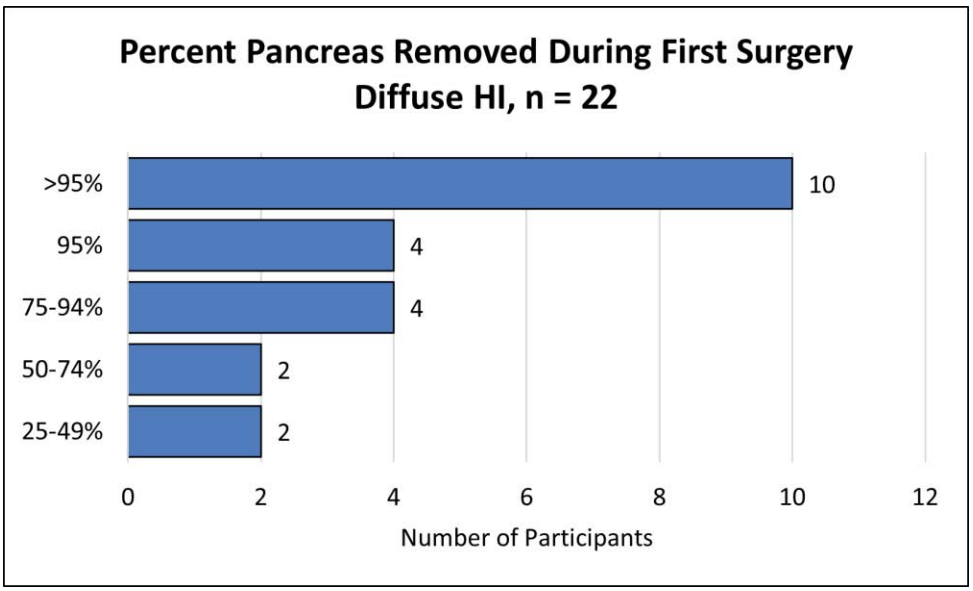
Diffuse

Figure 13. Age of the first pancreatectomy in diffuse HI



Twenty-two participants with diffuse HI report having at least one pancreatectomy. Figure 13 shows that 46% of the 22 participants reporting diffuse HI, who had a pancreatectomy, had their first surgery within the first month of life.

Figure 14. Percent of pancreas removed at first surgery in diffuse HI participants



As seen in Figure 14, of the 22 diffuse HI participants who underwent pancreatectomy, 14 reported at least a 95% pancreatectomy, while eight had less than 95% of their pancreas removed during their first surgery. Six participants required at least a second or subsequent pancreatectomy; two participants reported needing a third pancreatectomy. This report's high-level look at pancreatectomy in diffuse disease may include confounding factors that are not fully explained without further subgroup analysis.

Six of the 22 participants with diffuse HI who had a pancreatectomy report having diabetes. Four of the 6 with diabetes report being at least ten years old when diabetes was diagnosed. The other two participants report diabetes developed in infancy, shortly after undergoing a subtotal pancreatectomy. Of the remaining 16 participants with diffuse HI who had a pancreatectomy and did not report having diabetes, 12 are under nine years old, and three are between 9 and 12 years old. The lower percentage of diabetes currently reported in this group is not unexpected because of their young age. It is established in the existing medical literature that nearly all patients who undergo a subtotal pancreatectomy ultimately develop insulin-dependent diabetes by adolescence (Bertrand, J Diabetes Care, 2011).

Four individuals with diffuse HI who had a pancreatectomy report also having pancreatic insufficiency (PI). Two of those who report being diagnosed with PI began taking pancreatic enzymes during infancy within months of their last pancreatectomy, and two participants began taking pancreatic enzymes between 15-19 years old, many years after the pancreatectomy.

Medical Management Elected

Of the 55 participants reporting that the medical team and family considered a pancreatectomy for the treatment of HI (all ages and all HI types, known and unknown, included in this count), 14 report opting for medical management rather than a pancreatectomy. Ten listed medical management preferred, three listed health concerns (ex. diabetes, surgery, complications, psychological stress etc.) as the reason for selecting medical management, and one did not provide information about why they decided not to have the pancreatectomy. Of those medically managed, five are under the age of 8, three are between 9 and 17 years old, and six are 18 years old or older.

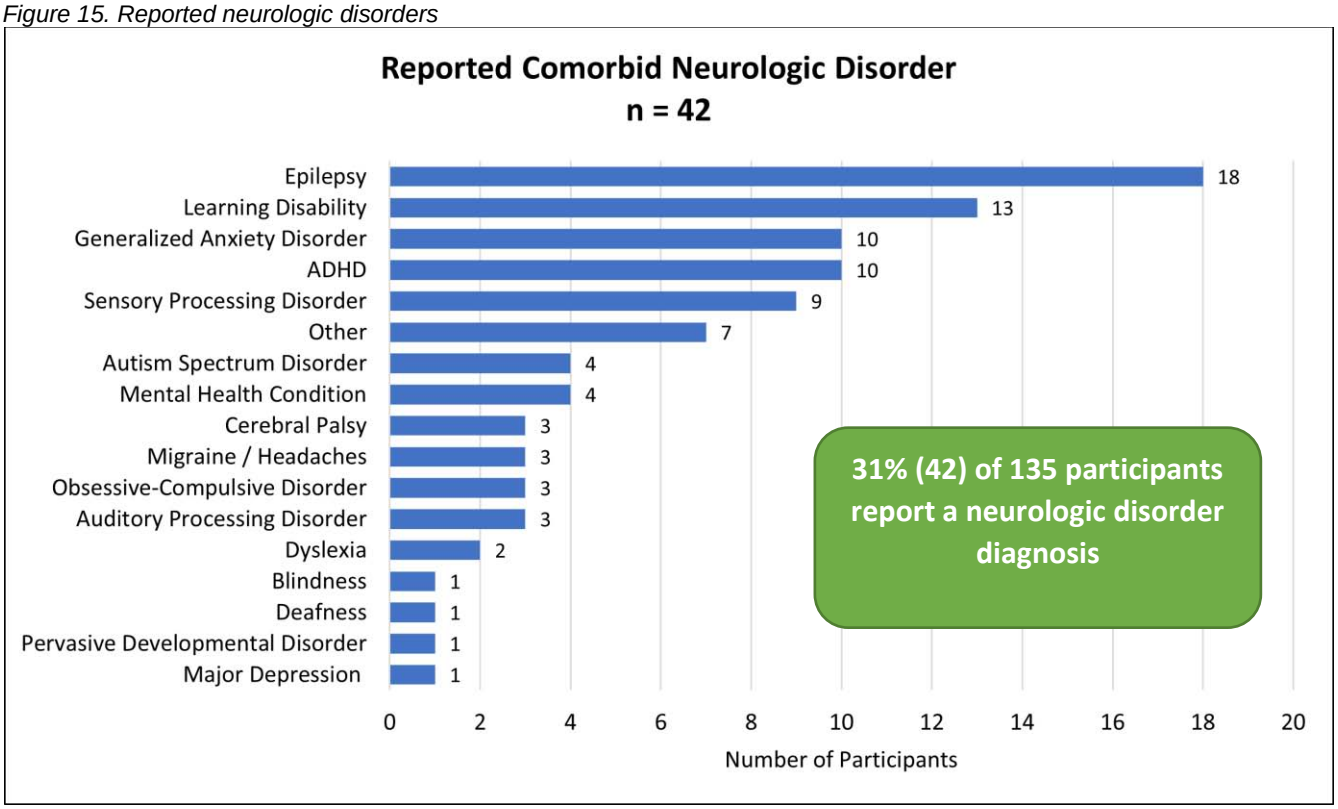
Nine individuals reported that they were positive for change/mutation in one or more HI-related gene(s). Tube feeds and/or background glucose supplementation are reported by seven participants in this subgroup. Five of twelve of the individuals who opted for medical management are currently taking diazoxide. Three of these individuals are still experiencing hypoglycemia more than once a day.

Neurologic Outcomes

Neurologic Disorder

Forty-two (31%) of the 135 participants who completed the Other Diagnoses survey report having been diagnosed with one or more neurologic disorders. Epilepsy remains the most commonly reported neurologic disorder, accounting for 13% of participants who completed the other diagnoses survey. Figure 15 shows the other neurologic diagnoses reported ranked from most common to least common. The most frequently reported neurologic diagnoses included learning disability (9%. Learning disabilities are also reported on in the Developmental Survey), generalized anxiety disorder (7%), ADHD (7%), and sensory processing disorder (6%). The "other" category includes participants with suspected, but not yet confirmed, diagnoses similar to those listed above and visual, motor, and/or neurocognitive issues of a more general nature.

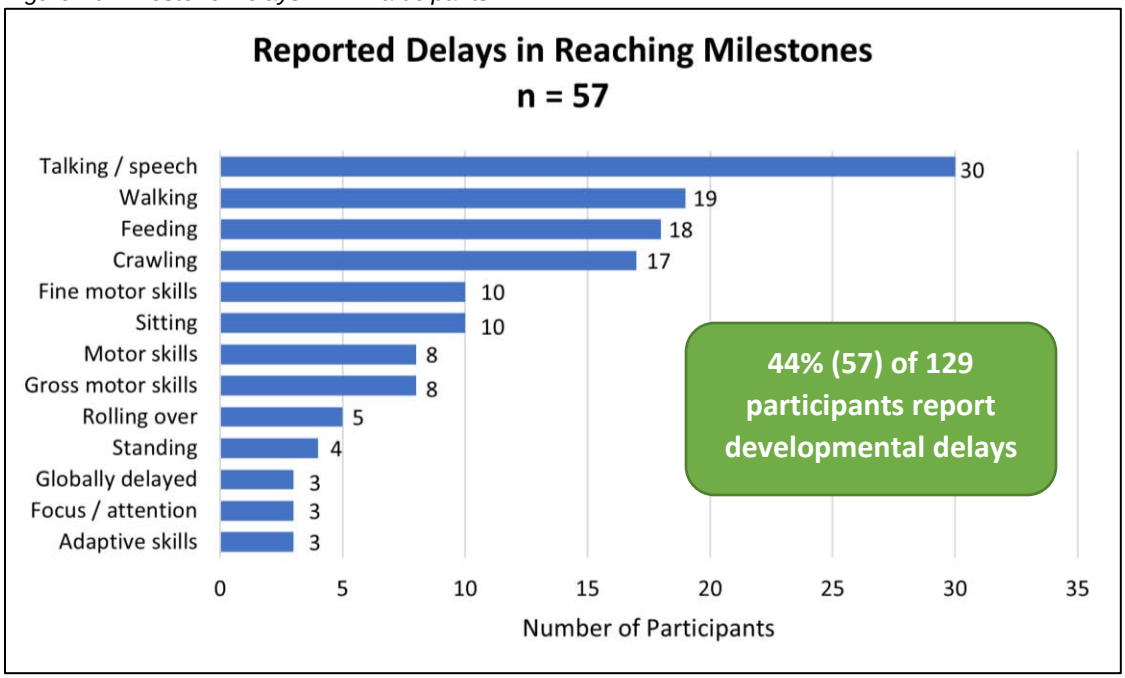
Figure 15. Reported neurologic disorders



Developmental Delay

Of 129 participants who completed the Developmental Survey, 57 (44%) participants report delays in reaching developmental milestones. Delays reported include: 30 (23%) participants report delay in talking; 19 (14%) in walking; 18 (14%) in feeding; 17 (13%) in crawling; 10 (7%) in sitting; and 10 (7%) in fine motor skills. Some participants reported delays in more than one milestone. The data is reported as a percent of those reporting a delay.

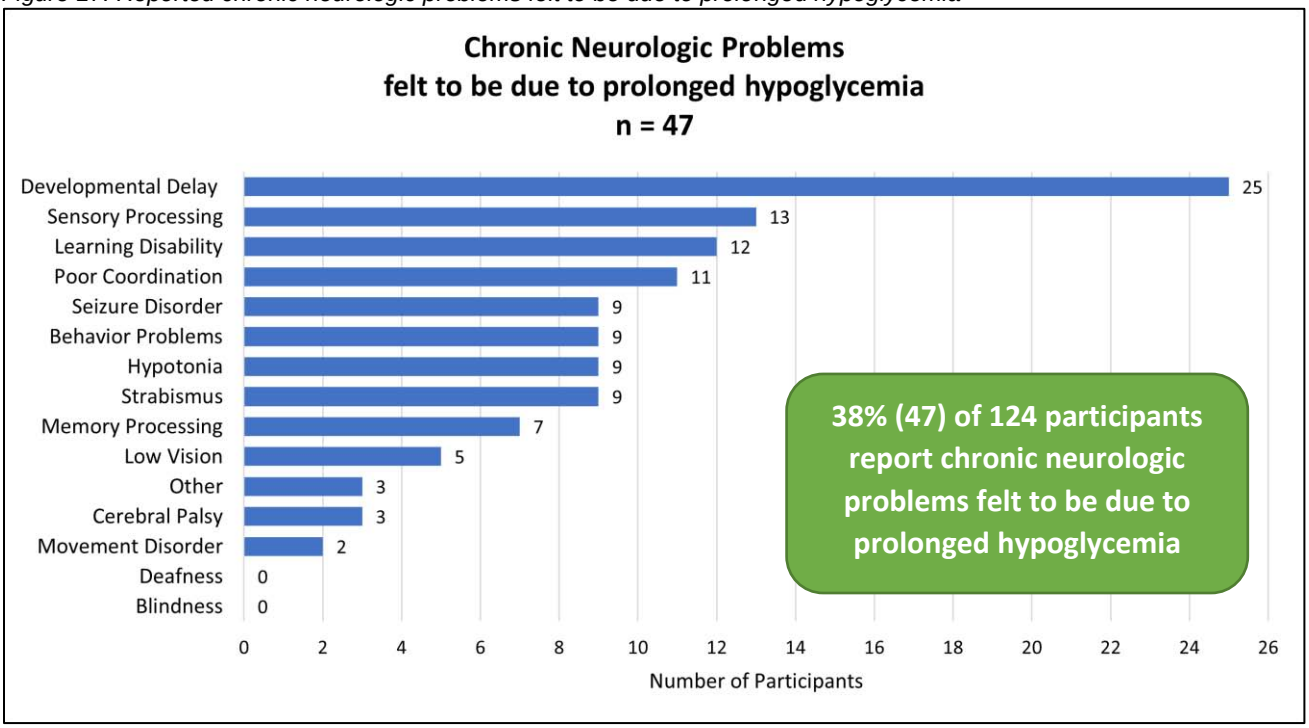
Figure 16. Milestone Delays in HI Participants



Reported Neurologic Problem Felt to be Due to Prolonged Hypoglycemia

Forty-seven (38%) of 124 participants report having a chronic neurologic problem that they feel is due to prolonged hypoglycemia. Figure 17 shows the list of neurologic problems reported by participants in this Developmental Survey question. Some participants noted more than one neurologic problem. Developmental delay (25 participants, 53%), sensory processing (13 participants, 28%), and learning disability (12 participants, 26%) were the most commonly reported chronic neurologic problems felt to be due to prolonged hypoglycemia.

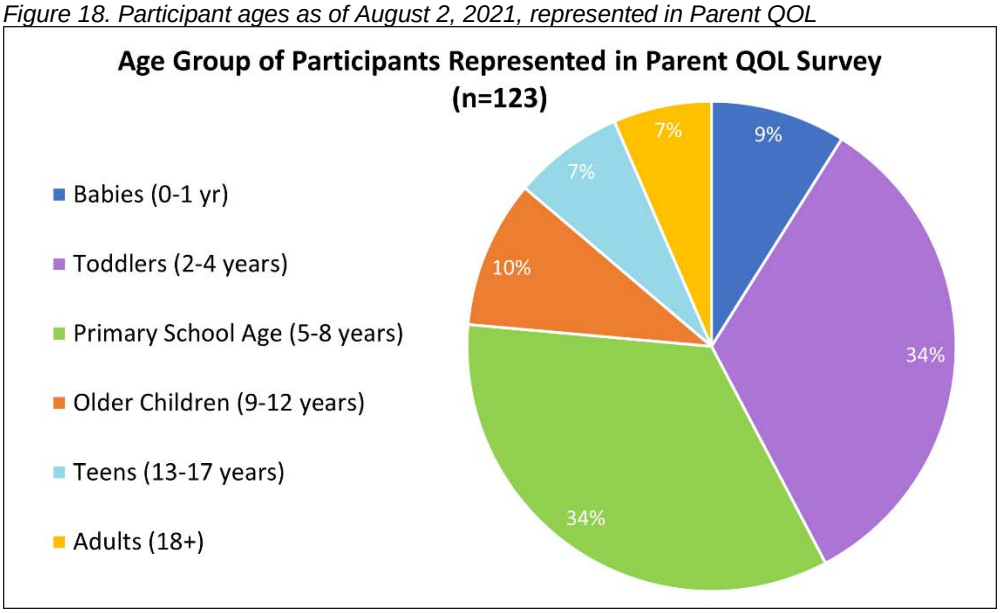
Figure 17. Reported chronic neurologic problems felt to be due to prolonged hypoglycemia



Parent Quality of Life

The Parent Quality of Life (QOL) survey covers a range of topics such as health, social support, school/work, and medical care. It is completed by one parent of the participant, regardless of the child's age. In this section, we focus on parent health, family planning, relationships, household income, the management of HI, and the parent's general quality of life.

Figure 18. Participant ages as of August 2, 2021, represented in Parent QOL



Parents of 123 participants (only one parent for each participant) completed the Parent Quality of Life (QOL) survey. Figure 18 shows the age groups of the participants reflected in this report. As of August 2, 2021, the youngest child reflected in this QOL report is six weeks old, and the oldest is 60 years old. Unless otherwise specified the data reported in this section includes the answers from parents of participants from all age groups. If a participant was 18 years or older, their parent or previous guardian could complete the survey by sitting with the individual or record their responses and have the participant fill in the survey on their behalf.

It is important to note that this discussion section includes all HI types, including focal HI that was cured and transient HI that may have resolved by the time those parents completed the QOL Parent survey.

Parent Health

Parents of 48% of the 123 participants responding report that their physical health has suffered from having a child with a HI-related condition. Parents of 67% of the 123 participants responding report that their mental health has suffered from having a child with a HI-related condition. Individuals were included if they answered that their health suffered "somewhat," "quite a lot," or "very much."

Family Planning, Relationships, and Household Income

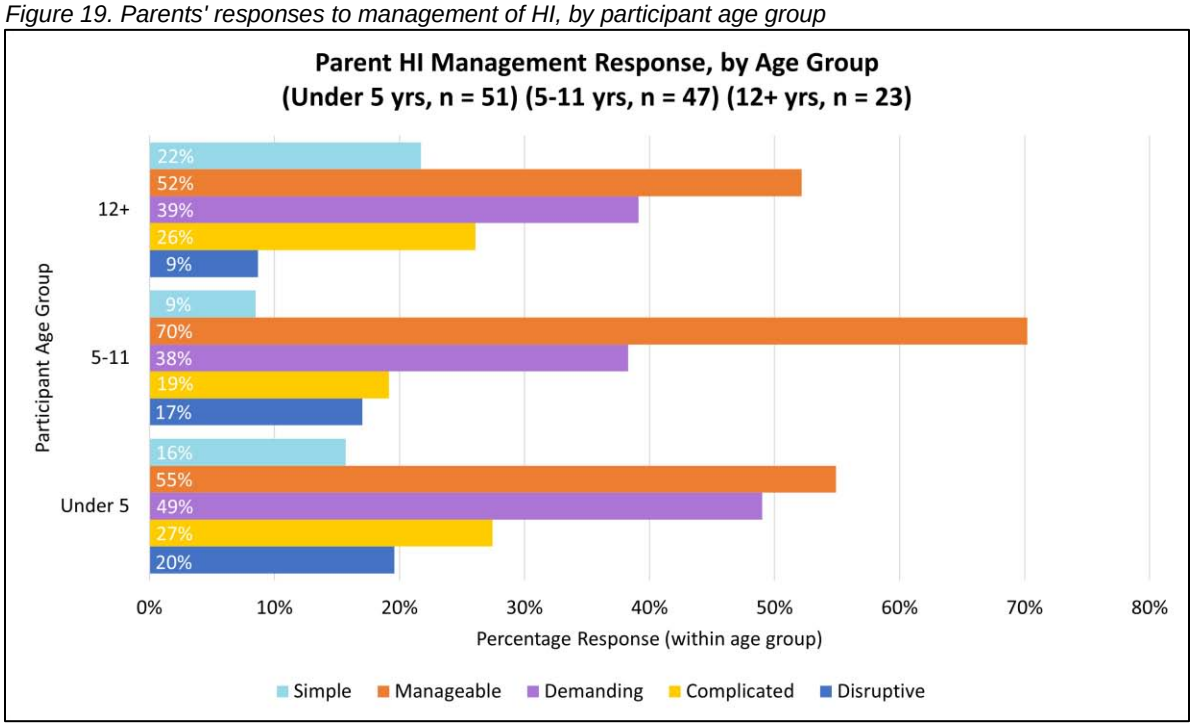
Of 123 HI parents of participants responding, 36% report choosing not to have additional children, and another 19% report delaying having additional children. Of 112 surveyed parents who are in relationships, 58% reported that having a child with HI strengthened their relationship with their partner; however, 17% reported a negative impact, including an additional 5% who said their relationship ended. Of 122 parents, 32% report that having a child with HI has negatively impacted their household income quite a lot or very much. Additionally, of 121 parents 43% said their work/career plans changed "quite a lot" or "very much" due to their child's HI condition. Of the 52 individuals who responded that their work/career plans changed, 48% had children under five years old, 42% had children 5-11 years old, and only 10% had children 12 years and over.

Management of HI

Figure 19 shows the various responses 121 parents gave to describe the management of HI. Parents could select more than one response to this question. In each age group, the most common responses amongst the parents were "manageable" and "demanding". A higher percentage of parents of the youngest children with HI reported the management of HI can be "demanding" with 49% of parents of children under five, 38% of parents with children 5-11 years old, and 39% of parents with children twelve or older selecting this response.

Parents of children in all age groups reported that the management of HI could be "disruptive," but a larger percentage of parents with children under five described their experience this way. Only 8% of parents with children ages 5-11 reported that their experience managing their child's HI was "simple," compared to 15% of parents of children under five and 21% of parents of children twelve and older.

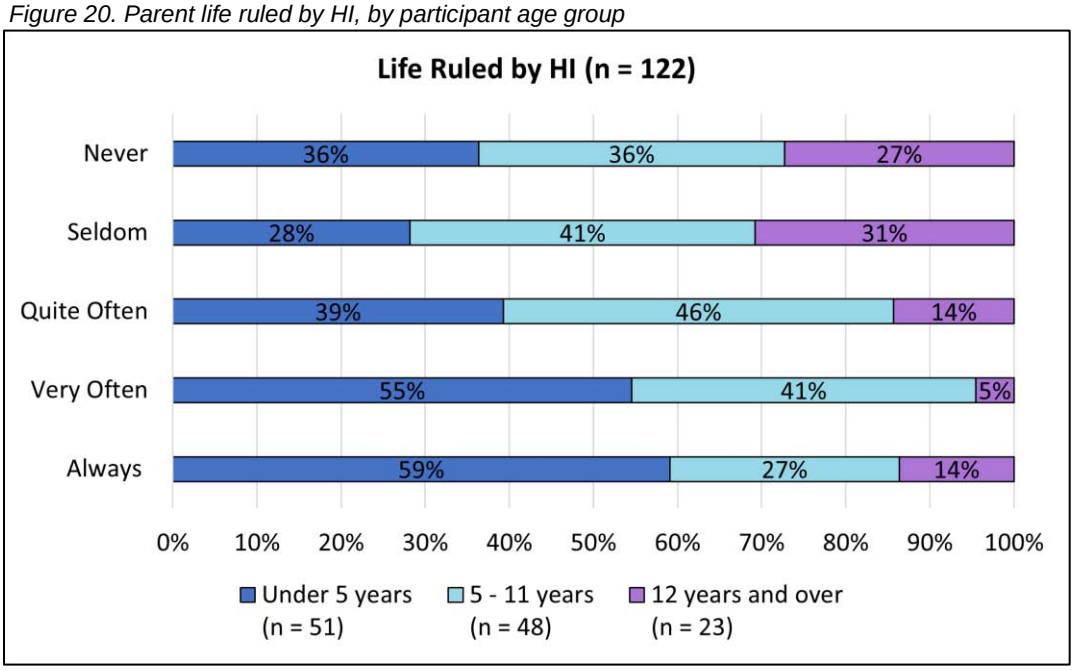
Figure 19. Parents' responses to management of HI, by participant age group



General Quality of Life

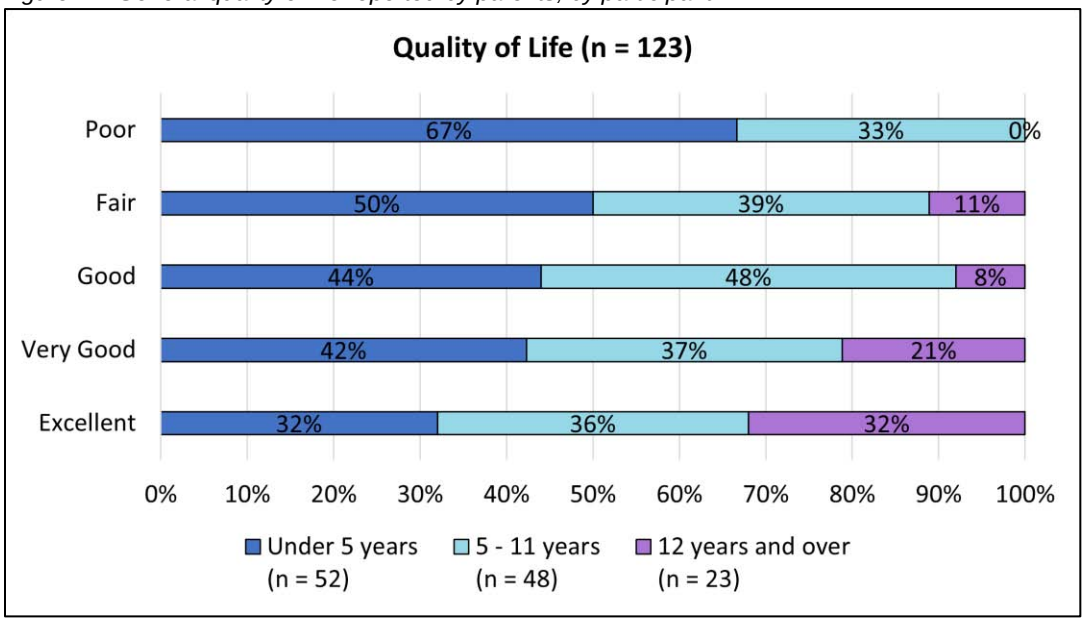
Fewer parents of older children report feeling their lives are ruled by HI. Of 51 HI parents of children under five years old, 70% parents report they "quite often," "very often," or "always" feel HI rules their lives; this number decreases to 58% of the HI parents of children aged 5-11 years and to 34% for the HI parents of children aged twelve years and older. Figure 20 shows the various responses of parents to this question by participant age group.

Figure 20. Parent life ruled by HI, by participant age group



Regardless of age group, 82% of the 122 reporting parents, worry about their children. Fewer parents of older children (39%) report worrying about their child "quite often," "very often," or "always" compared to 82% of parents of children under five years old and 83% of parents of children 5-11 years of age.

Figure 21. General quality of life reported by parents, by participant



Self-reported general quality of life for an HI parent appears to improve as children get older. Of the 123 parents who answered this question (Figure 21), 78% of the 52 parents of children with HI under five rate their QOL as "good," "very good," or "excellent"; the number increases to 83% for the 48 with children 5-11 years old and to 91% of the 23 guardians with children twelve years old and older.

Patient Quality of Life

The Patient Quality of Life (QOL) survey covers a range of topics such as health, social support, the impact of HI at school/work, and medical care. This is the first year we are including a report from this survey and focus on overall physical and mental health, the management of HI, and the participant's general quality of life.

Twenty-two participants completed the Patient Quality of Life (QOL) survey. As of September 2021, the average age of individuals who took the survey was 29 years old, the youngest was 17 years old, and the oldest was 59 years old. As the following report shares information from all 22 participants, it is important to understand the characteristics of this group. Of the 14 participants who responded with their HI type, ten reported a diffuse form of HI, two reported an unknown type of HI, one reported atypical HI, and one reported an undiagnosed form of HI.

Of the 11 participants who shared their surgical history, seven (64%) reported that a pancreatectomy was performed to treat their HI. Six of the seven individuals who had a pancreatectomy report that they now have diabetes.

Six of the sixteen individuals who completed the relevant survey reported that their HI has resolved. These patients said that their HI had resolved as they had now transitioned to diabetes (three), no longer required medication or attention to diet (two), or through prolonged inpatient fasting test (one).

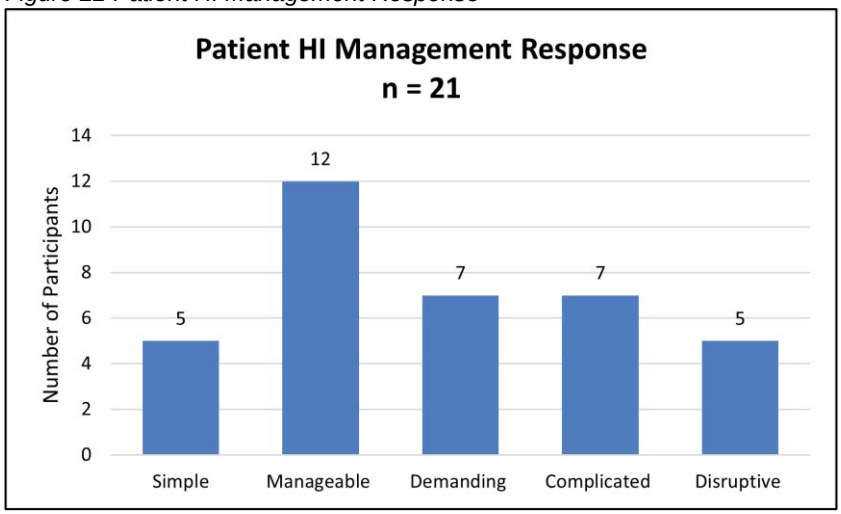
Patient Health

When asked about their physical health, 14 (67%) participants report their physical health is "excellent" or "very good," and 8 (38%) participants report their physical health is "good" or "fair." When asked about their mental health, which includes mood and ability to think, 15 (71%) participants report their mental health is "excellent," "very good," or "good," while 6 (29%) participants report their mental health is "fair" or "poor." Of 21 participants responding, 12 (57%) report they "very often" or "quite often" feel HI rules their lives, while 9 (43%) report they "seldom" or "never" feel HI rules their lives.

Management of HI

Figure 22 shows the various responses 21 participants gave to describe their experience with the daily management of HI. Participants could select more than one response to this question. "Manageable" was the most common response (57%), with another 24% describing the management of their HI as "simple." Another 67% of participants report the management of HI as "demanding" or "complicated," while 24% participants felt the management of HI can be "disruptive."

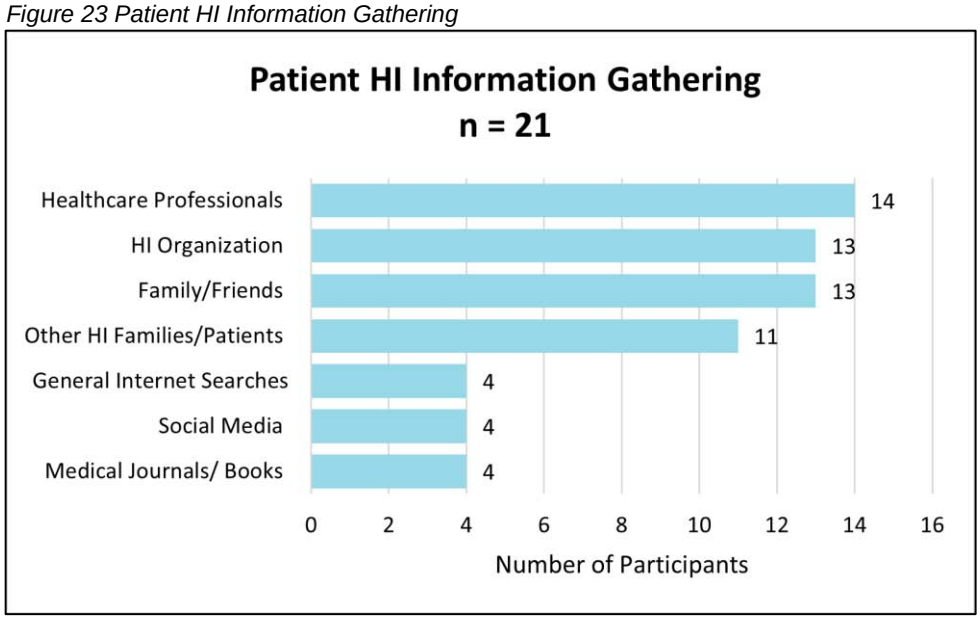
Figure 22 Patient HI Management Response



Seventeen participants report they rarely or never have to miss school/work due to their HI condition. Two participants report having to miss school/work "very frequently" or "quite a lot," while another two report having to miss school/work "sometimes." One individual responded that the question did not apply.

Figure 23 displays the various responses 21 patients gave regarding where they get HI-related information. Patients could select more than one response to this question. The majority of patients report getting their information from healthcare professionals (67%), HI organizations (62%), family/friends (62%), or other HI families/patients (52%).

Figure 23 Patient HI Information Gathering



General Quality of Life

When asked how participants would rate their general quality of life, five (23%) responded with "excellent," 13 (59%) responded with "very good," and four (18%) responded with "good."

Registry Recruitment and Engagement

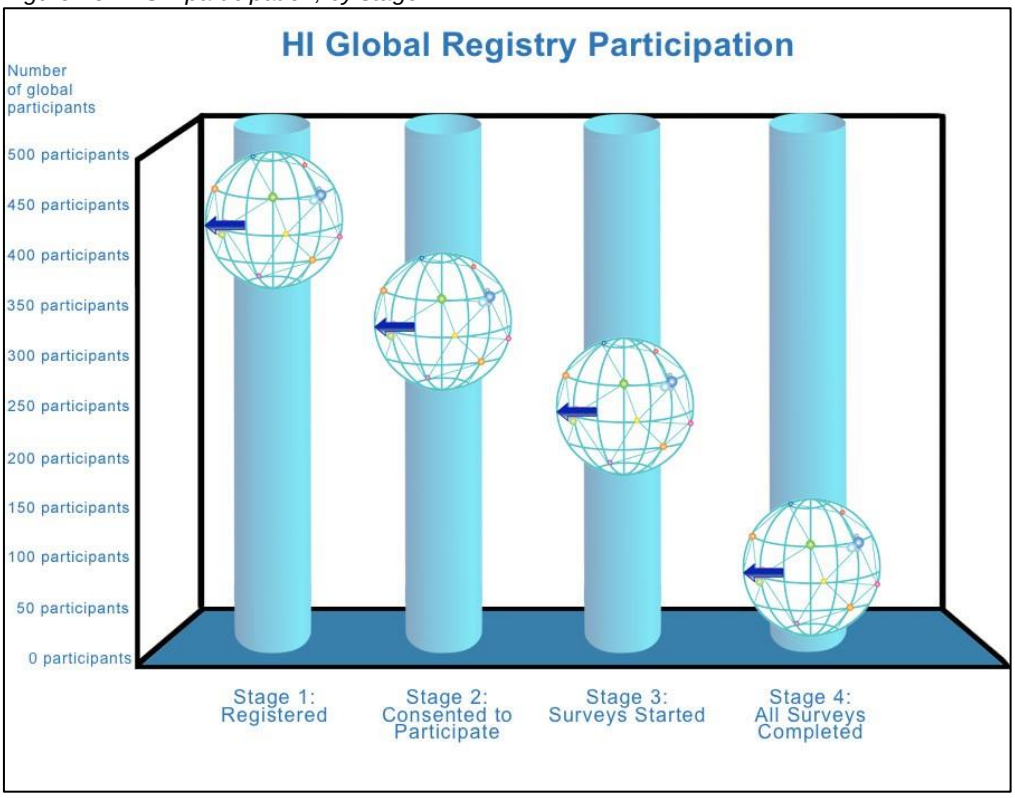
The success of the registry is dependent on the engagement and broad participation of the HI community. This section provides information on the registry recruitment steps and engagement efforts to date, including clear calls to action for individuals at every stage of registry participation.

The work of HIGR is continuous. In research, data becomes more meaningful as the sample size (the number of participants) increases. With more participants answering more surveys over time, we will report on additional aspects of the HI experience and make more meaningful comparisons across groups, such as the type of HI.

Stages of Recruitment

HIGR recruitment has been defined in four stages to help track respondent and participant utilization of the system and identify strategies to assist individuals in completing all relevant surveys. Figure 23 reflects the number of participants at each stage as of September 2021 and the four participation steps. The Calls to Action outlined below are for those with HI and their families.

Figure 23. HIGR participation, by stage



Stage 1 is registration on the registry platform at www.higlobalregistry.org. The registration process includes basic identifying information provided by the respondent (HI patient or their legal, authorized representation (parent/guardian) if the patient is a minor or unable to register due to cognitive difficulties). As of September 2021, 438 respondents have enrolled on the registry platform. During registration, respondents are asked a few questions, including if they wish to be contacted by the HIGR staff in four possible scenarios:

(1) **To periodically update their survey information** – Updated information over time improves researchers' ability to truly understand the natural history of how HI affects individuals throughout

their lives. By agreeing to be contacted occasionally with a reminder means you agree to be an active research participant.

(2) **For a possible clinical trial, the participant may qualify to take part** – Your information will not be given to the clinical trial sponsor if you select yes to this preference. However, you will be notified by the CHI staff of clinical trial opportunities and receive information about the opportunity to participate. Choosing to be contacted does not commit you to participate in the trial.

(3) **For a tissue biobank project, if one is developed specific to HI** – Although a biobank doesn't currently exist, an HI specific study on genetics or other identified biomarkers could help detect and/or diagnose HI and HI subtypes. Agreeing to be notified of tissue biobank projects does not commit you to participate or provide samples to the proposed biobank. This is simply a notification about the opportunity should you be interested.

(4) **Future networking opportunities within the international HI community** – HIGR is here to support those with HI worldwide. By agreeing to be contacted about networking opportunities, you will receive a notice of any effort to connect with other participants with HI in your country, region, or with certain matching characteristics of HI should there be a desire by others in the HI community to connect at that level.

The contact permissions set at registration can be updated at any time.

Stage 1: Call to Action

- *Parents or caregivers of a child living with HI: register with HIGR.*
- *Individual over 18 who has been diagnosed with H: register for HIGR.*
- *If you are registered: revisit and update your contact preferences, don't miss opportunities to connect and learn about exciting opportunities in the community!*

Stage 2 is defined as the step when respondents, HI patient or legally authorized representative (LAR), consents to participate in the HIGR study. This is a two-part process. The respondent must first add the participant (self or respondent's child/ward) then provide the appropriate consent of that participant to take part in the study. After reading the online consent form that describes the benefits and potential risks of participation in the HIGR study, participants may provide their agreement to the terms and conditions outlined in the consent form by clicking on the consent button. Currently, 438 registered respondents have added 400 participants (45 adults, 355 minors); 337 participants (77%) have completed the consent process, allowing access to the survey questions.

Stage 2: Call to Action

For those that have signed up, but have not yet consented:

- *revisit the site,*
- *read the consent document, and*
- *follow the instructions there to provide your consent.*

Stage 3 is when a respondent submits at least one survey. Currently, 243 participants have completed at least one survey (72% of all enrolled participants). Each survey asks questions related to different aspects of HI. They utilize a branching logic, so you will not be asked additional questions related to that experience if something is not relevant. Even if a survey does not seem relevant to you on face value, sometimes knowing what you haven't experienced is equally as important as knowing what you have experienced. For example, even if you have not had a pancreatectomy to treat your HI, it is important to complete the surgery survey to let us know that it was not recommended or was not performed and why. When pulling reports, researchers cannot make assumptions about survey questions left blank. Researchers rely on you to tell your whole HI story.

Stage 3: Call to Action

Please complete all surveys available to you. If at any point you have any questions related to what the surveys are referring to, the HIGR team is always here to assist!

Stage 4 is when a respondent completes all relevant surveys. Depending on the participant's age, there are 12-13 surveys to be completed and submitted to achieve full participation in HIGR. Currently, 78 have completed all relevant surveys. A complete set of surveys is the best way to evaluate HI and make the desired cross-comparisons for more thorough reporting. For example, in the section on Feeding Issues, the chart included the survey questions from three different surveys. When participants do not complete all the included surveys, they are likely to be excluded from deeper analysis on that topic.

Stage 4: Call to Action

For those that have completed surveys, please consider revisiting the registry site periodically, particularly if something about your HI experience has changed significantly, or whenever you receive a reminder about one of the longitudinal surveys.

Engagement

From 2020 to 2021, CHI has employed a variety of engagement strategies to help grow the HIGR. HIGR data was displayed at two virtual scientific meetings, the Pediatric Endocrine Society and the Global Genes conference. The HIGR team presented data at the CHI Virtual Patient and Family Conference and the CHI Virtual Research Conference.

Social media continues to be an important place to connect with patients and share information about the registry. One of this year's campaigns played off Facebook's wallpaper design by utilizing patient frequently asked questions (Figure 24). The accompanying text included information related to the insights provided through the registry and how to join to see how the individual's experience compared to others in the community.

Figure 24. Examples of HIGR engagement campaigns.

Every member of the HI community can help play a part in growing HIGR and providing better evidence for diagnosis, treatment, and eventually cures. We encourage parents and patients to join the registry and answer surveys. Everyone can help by sharing social media posts and information about HIGR that encourages others to visit the registry and participate.

Discussion

The activity in HIGR has built a strong foundation for an HI natural history study reported by those who live with the disease. As the sample size grows, we can become more confident in some of the reported trends. However, the reader should remain judicious when making conclusions about treatment, care, or the condition's natural history based on what is reported here. HI is a heterogeneous disease, and meaningful long-term analysis will require more comprehensive investigation into the experience related to HI subgroups. The purpose of this high-level report is to introduce readers to the type of information that can be retrieved from the registry while addressing some of the frequent topics discussed by the HI community.

Just over 50% of participants in HIGR are five years old or younger. As HI is a pediatric-onset condition, this is not surprising; however, understanding the experience of older children and adults is equally important to understand the long-term disease progression and outcomes. Our wish is that those who joined while infants and toddlers continue to share their experience and update information, especially related to diet and feeding, medication, developmental outcomes, and glucose monitoring, so that we can tell a complete story of living with HI.

Diffuse disease is the most represented HI type, which we would expect based on other studies and data from academic studies. Within HIGR, 40% of individuals received a negative result for a HI-identified gene; this is consistent with findings from the University of Exeter, which reports a disease-causing mutation in 40-50% of all cases[1]. Consistent disease sub-type names for treatment plans, research, and patient information are critical and a priority of the CRN project.

Despite diazoxide's widespread use, almost all patients report side effects, including 30% who report continued hypoglycemia. A better understanding of what it means to be "diazoxide responsive" would benefit the community, as would new treatments for patients.

Feeding issues are experienced by 69% of individuals in HIGR, with 73% of diffuse participants reporting feeding issues. Tube feeding, either by itself or combined with oral feeding, is also reported by 64% of diffuse patients and 57% of all patients. The feeding experience further underscores the importance of understanding the patient experience by HI subtype to fully understand the family burden of disease and the impact of managing HI on the overall quality of life.

Of individuals who reported focal HI, 100% who considered a pancreatectomy had the surgery. For individuals with diffuse HI, 67% of individuals who considered a pancreatectomy had the surgery. Understanding surgical trends, including the timing, is essential in developing new treatments and expanding options to those considering medical management.

31% of participants had one or more neurological problems, including 13% who reported epilepsy. 44% of participants reported developmental delays. As individuals report on progress over time, we will share more data on how neurological conditions and developmental delays progress over time.

As previously discussed, each of these components of care needs impacts the individual with HI and their entire family. Understanding quality of life is critical in demonstrating the unmet needs and finding ways to support patients and families in our community. This is another area where the individual experience can be highly variable, and subgroup analysis will provide a more robust picture of the community. As investigators, our goal is to show the big picture for all HI patients while highlighting meaningful differences in experiences.

HIGR is currently available only in English. The investigators recognize an accurate global representation of the natural history of HI will be possible when HIGR is available in other languages. With time, additional languages, better mobile integration, and more participants fully completing all available surveys, HIGR will genuinely reflect the global HI experience. The HIGR team is actively pursuing the addition of other languages and encourages all those comfortable in English to enroll and complete the relevant surveys.

Acknowledgments

The Congenital Hyperinsulinism International Registry team would like to take the opportunity to thank everyone who has made it possible to conduct this critical registry research and present its findings. It has been a pleasure to work with all our sponsors and community stakeholders, and we are excited to share our present findings and plans with the growing HI community.

First and foremost, thank you to HIGR participants who have dedicated their time to contribute their data, without which this research would not be possible. Next, a warm thank you to the HI community for its continual support of HIGR. Thank you to the CHI Board of Directors for continuing to provide support to HIGR. The investigators wish to express our appreciation to the HIGR Steering Committee, who volunteer their expert advice and guidance to ensure the success of the HIGR research program.

HIGR Steering Committee Members:

Sarah Dearman – United Kingdom
María Paz Oviedo - Paraguay
Ulrike Seyfarth – Germany
Rianna Sommers - United States of America
Michelle Walkley – United Kingdom
Dr. Jean-Baptiste Arnoux – France
Dr. Indi Banerjee – United Kingdom
Dr. Henrik Christesen - Denmark
Dr. Diva D. De León-Crutchlow – United States of America
Dr. Sarah Flanagan – United Kingdom
Dr. Klaus Mohnike – Germany
Dr. Pratik Shah – United Kingdom
Dr. Charles Stanley – United States of America
Dr. Paul Thornton – United States of America

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