2020 Annual Report

Davelyn Eaves Hood[1], Tai Pasquini[2], Lauren Quinlan[3], Abigail Linsmeier[3], Sunny Chapel[3], Isabel Calderón[4], Julie Raskin[5]

[1]CHI Board President & HIGR Principal Investigator, [2]CHI Policy & Research Director, [3]A2PG, [4]CHI Board Emeritus and HIGR Investigator, [5]CHI Executive Director and HIGR Investigator

Address for correspondence

HI Global Registry Investigators
c/o Congenital Hyperinsulinism International
PO Box 135
Glen Ridge, NJ 07028, USA
info@higlobalregistry.org

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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. What follows is descriptive data that the investigators first introduced in the "An Early Glimpse at Data, Spring 2019" report, which now includes information provided by HIGR participants from launch through the end of January 2020.

The registry consists of a series 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). In order to allow collection of data over time for studying the natural history of HI, some surveys may be updated at the participant'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 set to be completed at specific time intervals. Only two surveys (Pregnancy and Birth) are final after the initial submission. The survey questions have been 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 which was developed and is hosted by the National Organization for Rare Disorders (NORD). The IAMRARE™ Platform was created with input from patient, caregiver, 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 a group of internationally recognized HI patient advocates and experts, known as the HI Global Registry Steering Committee.

A portion of the HIGR study protocol is shared below. This report also includes similar, high-level data elements from the previous report with analysis derived from the HIGR surveys on HI types, medication, feeding and surgical experiences, neurologic outcomes in relation to age when participants were diagnosed, and the quality of life of parents of HI children. The intended audience of this report is the HI community- made up of those who have HI, their families, and all those interested in HI and its related research.

The survey data shared in the following sections is based on data collected in the first fifteen months of HIGR enrollment. Each individual report presented in this document includes the number of participants who provided information related to each specific report. The variation in the number of individual responses is the result of three factors: 1) the majority of surveys and survey 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 and are able to save their responses in draft along the way. This may result in participants who are not included in certain sections of this report because they did not provide answers to all questions needed for full subgroup analysis. For each HIGR analysis reported below, the number of participants is listed as "N" and is followed by an equal (=) sign and the count of participants in that report. The discussion in each section also includes a reference to last year's "N" and how this year's data compares. This year's report remains observational with the intent to provide

a factual synopsis of key or commonly requested data elements as they have been reported by HIGR participants. Due to the expressed interest in certain data points, some smaller subgroup data has been included with a notice of caution stated for those topics.

The investigators carefully considered the issue of sample size for last year's publication with an acknowledgement given that less than 30 participants is a small sample size; the same parameters are set for this report. In small samples, the results may not be exactly 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. The investigators have also set a minimum threshold of responses of five participants that must be met before a topic can be shared in this type of publication. When comparing this year's results to those presented last year, not all comparisons (particularly those in smaller subgroups) are meaningful. Where possible, the investigators highlighted interesting similarities and differences.

Protocol Objectives

As introduced in last year's "An Early Glimpse at Data" report, HIGR is guided by a research protocol approved by an institutional review board (IRB), also known in some countries as an ethics committee. 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 experience 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 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 to design prospective trials related to improving HI patient outcomes.

Prevalence

HI occurs around the world and the global prevalence (or frequency) of HI is poorly understood. HIGR has the potential to help calculate this very important figure one day. Figure 1a shows that HIGR already has participants from 45 countries and every inhabited continent. For this year's annual report, there are an additional 114 individuals registered for HIGR and a total of 748 additional surveys completed by (or on behalf of) participants compared to last year's annual report. There is a wide range of ages among HIGR participants, from just a few weeks of age to 58 years old. Figure 1b lists the number of participants in each age group. Unless otherwise noted, the data presented in this report reflects the information available in HIGR as of February 1, 2020.

Figure 1a. HIGR Participants, by continent

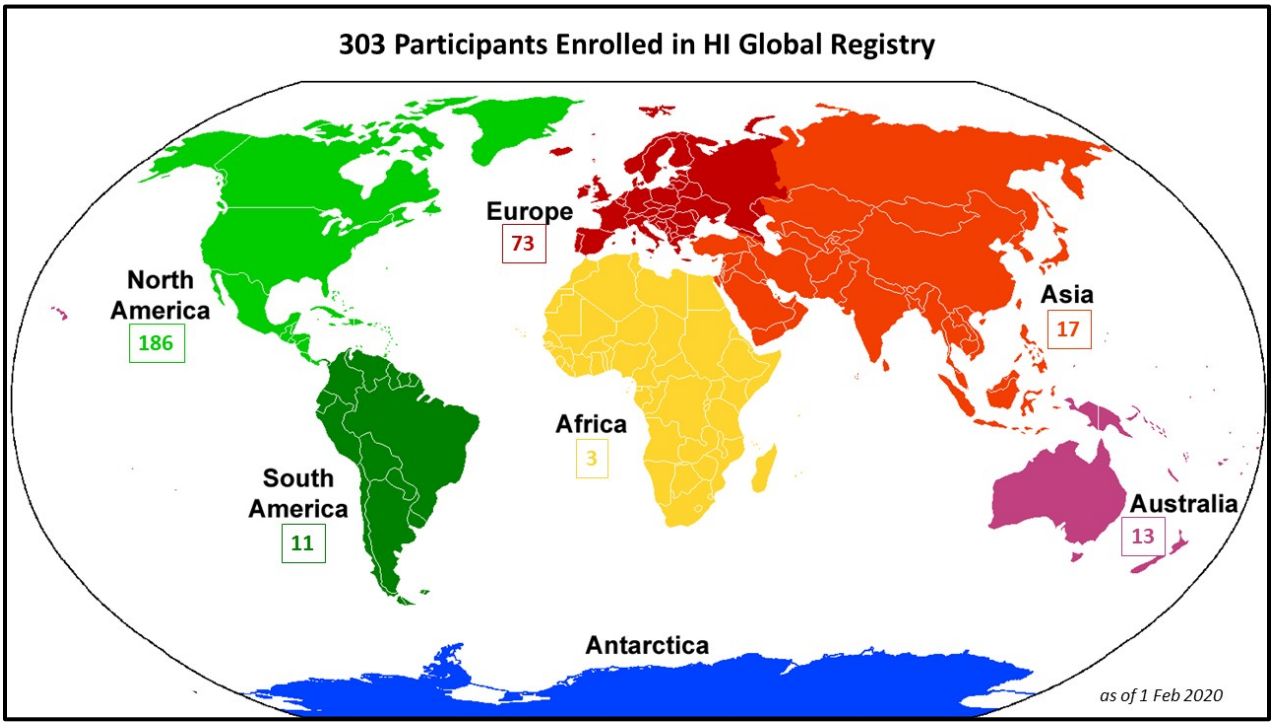


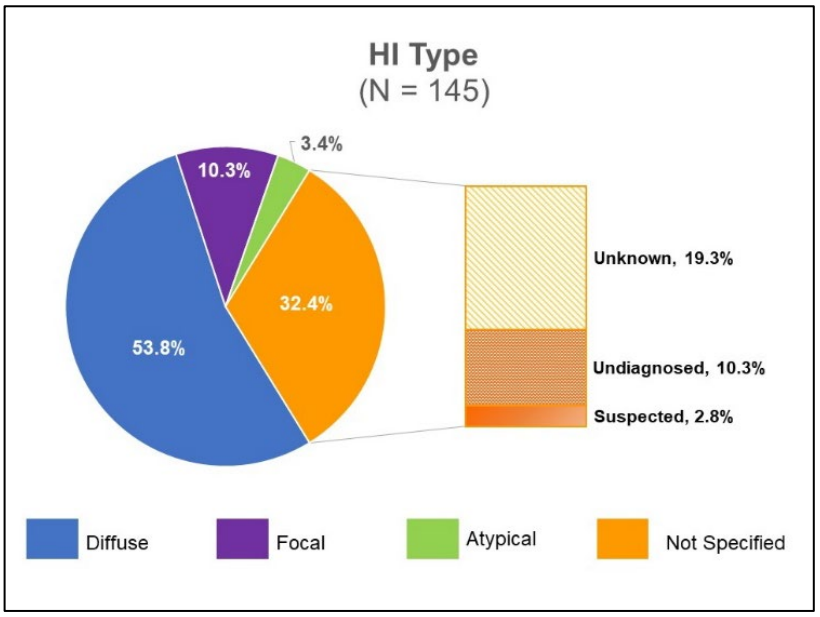
Figure 1b. HIGR Participants, by age

Age	Participants
0-2 years	92
3-5 years	95
6-9 years	39
10-12 years	16
13-17 years	18
18+ years	43
Youngest	5 weeks
Oldest	58 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

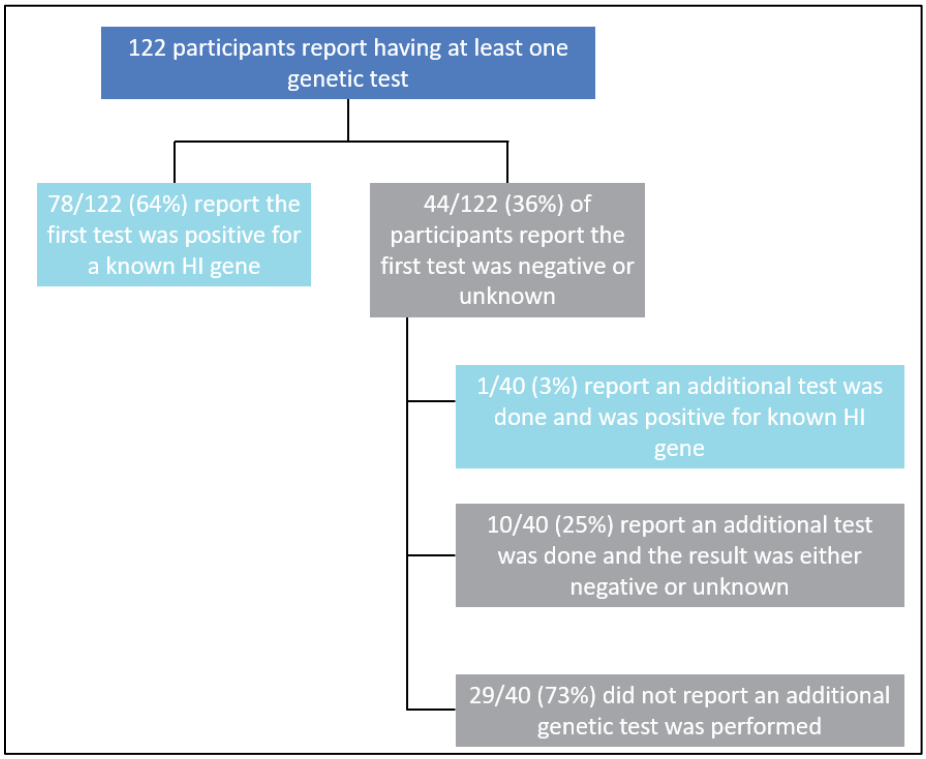
Figure 2. Reported HI types



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), and others. Figure 2 shows the proportion of reported HI types currently found in HIGR based on 145 participants (up 84% from last year's report of 79 participants). This year, 78 (53.8%) report diffuse disease; 15 (10.3%) report focal HI; 5 (3.4%) report receiving an atypical HI diagnosis. Another 47 (32.4%) report one of the unspecified responses available: 28 (19.3%) report an unknown type of HI; 15 (10.3%) report an undiagnosed status as of the time the data for this report was pulled; and four (2.8%) report that HI is a suspected diagnosis. Due to rounding, the totals do not add up to 100%. These figures are similar to last year, with a slight 7% shift down in the diffuse disease percentage now found in small (1-2%) shifts up in the other categories.

Genetics

Figure 3. Percent positive genetic testing



As seen in Figure 3, 65% of the 122 participants reporting on genetic testing have positive results for a gene known to be associated with HI. Of the 122 participants reporting having at least one genetic test, 64% report positive genetics on the first test. Of the 36% who had unknown or negative results on the first genetics test, eleven had a second test and one of those individuals had positive results. This figure is similar to last year's with a notable correction in the second testing results found on deeper analysis.

Like last year, there are a variety of 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 occurred before new genes related to HI were identified. 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.

HI-related Syndromes

A syndrome is a condition that is categorized by a set of symptoms that commonly occur together. Seven participants indicated the presence of an HI-related syndrome. The syndromes listed by HIGR participants include Beckwith-Weidemann, Kabuki, Turner, Sotos, Fanconi, and Rubinstein-Taybi Type 2. This list includes two new syndromes not present in last year's report.

Abnormal Blood Sugar Before Leaving Birthing Facility

Figure 4 shows that of 136 participants, 85 (63%) report that an abnormal blood glucose level was recorded before participant left the birthing facility. While the number of participants responding to this question has increased by 72% since last year's report, the percentage of those reporting an abnormal glucose level before leaving the birthing facility is similar. Those reporting "Yes" has shifted down slightly from 67% to 63%; those reporting "No" has shifted up from 24% to 27%; and those reporting "Unknown" shifted up slightly from 9% to 10%.

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

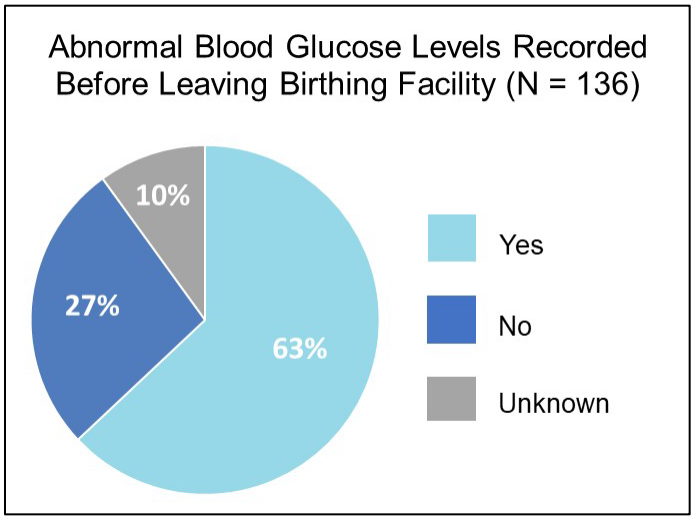
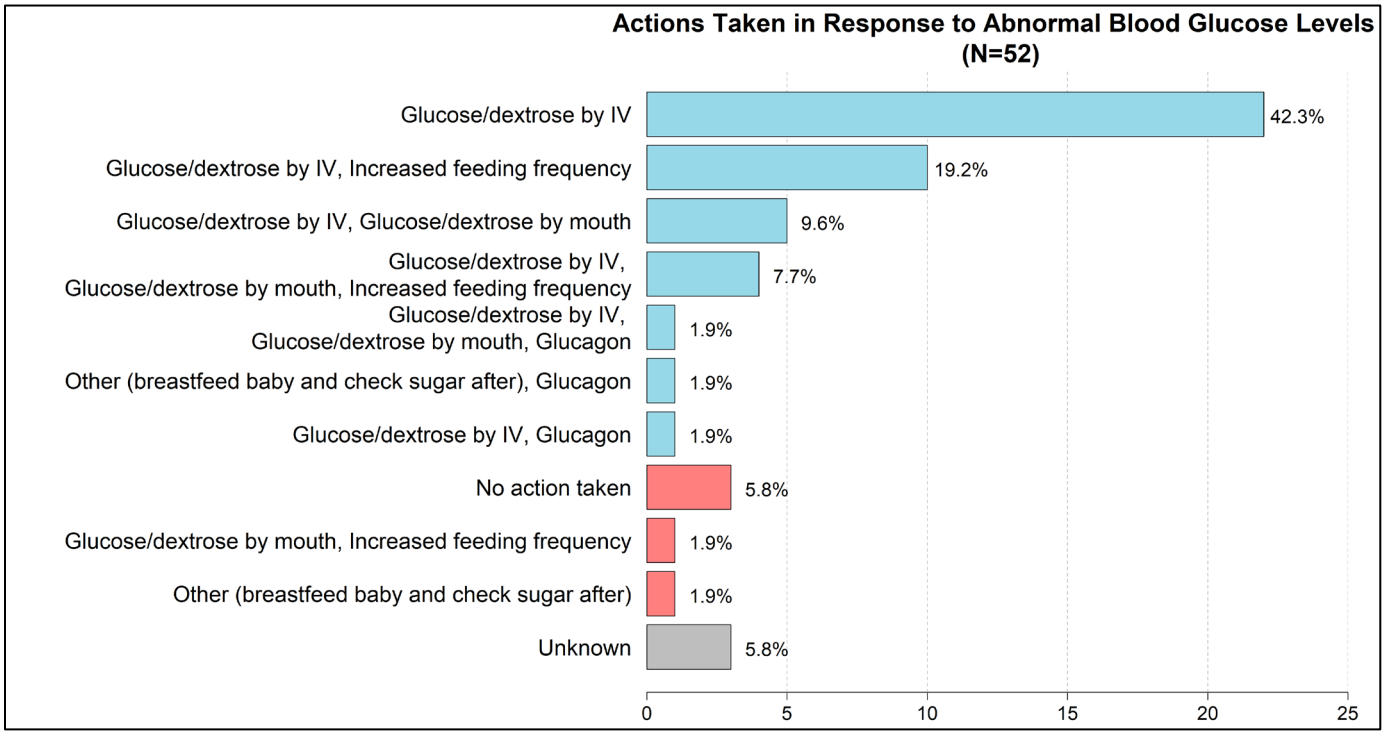


Figure 5 lists the reported action or combination of actions taken by healthcare professionals in response to the abnormal blood glucose readings of 52 participants (an increase of 63% over 32 reporting last year). Actions reported included the use of glucagon (6%); intravenous (IV) glucose administration (81%); and increased feeding frequency (29%). 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 3.8% of participants, and another 5.8% reported no action was taken, also noted in red. In comparison to the previous report, more participants are reporting that intravenous (IV) glucose was used to address abnormal glucose levels than before (up from 68% to 81%), and fewer are reporting no action or oral only strategies (down from 18% to 10%). Analysis to further explain these trend changes has not been done yet.

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



Of 85 participants reporting an abnormal blood glucose level before leaving the birthing facility who also answered the relevant questions from the Diagnosis Survey, 75% (the same percentage as previously reported) also report receiving an HI diagnosis before leaving the hospital. Stated another way, one in four participants report that they did not receive an HI diagnosis before leaving the hospital after birth despite reporting an abnormal blood glucose level. Of the 16 individuals who did not receive their diagnosis before leaving the birthing facility, eight report requiring one additional hospitalization before receiving an HI diagnosis; three report two hospitalizations; three report three to five hospitalizations; and two report more than six hospitalizations before an HI diagnosis was made.

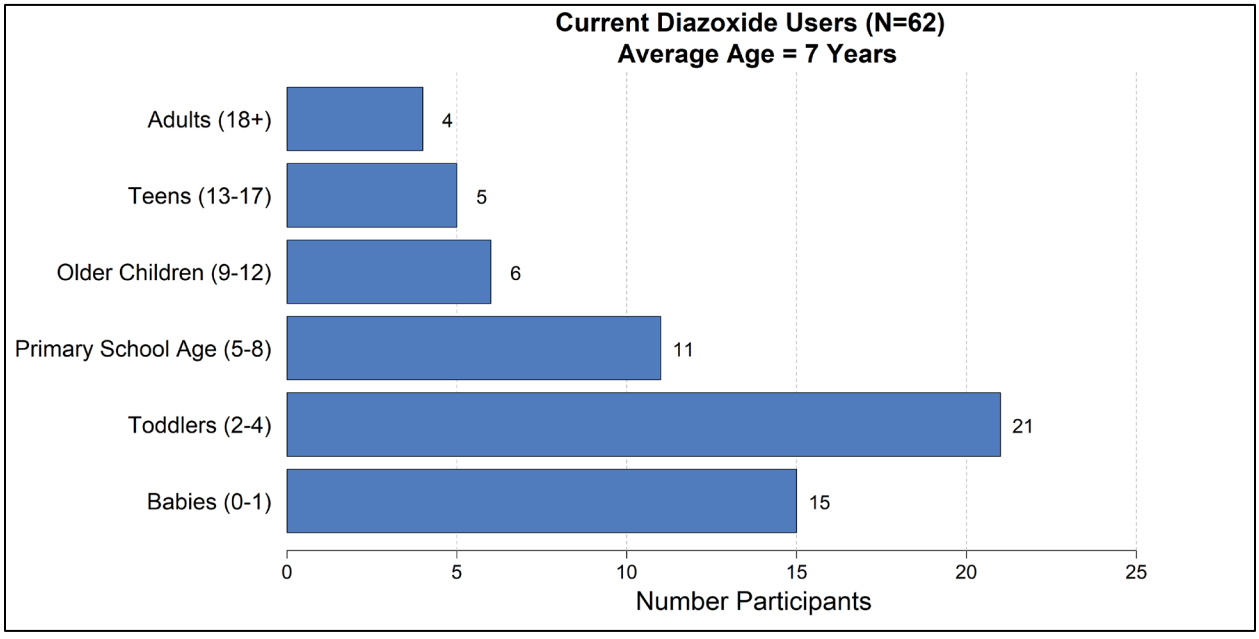
Medication Experience

The survey regarding the medical management of HI gathers data on medication the participant has taken to treat HI. Since last year's report, the number of participants completing the medication experience survey nearly doubled from 60 to 112 participants. 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. A few participants may have taken diazoxide and octreotide at the same time, which could have an impact on the figures below. Those individuals are included in the respective figures and not separately analyzed.

Diazoxide

Of those who reported having taken diazoxide (96 participants, up 81% from 53 last year), 62 participants (65%) are currently taking diazoxide, and 34 (35%) have taken it in the past. The average age of those currently on diazoxide is seven years old, with a range of six months to 45 years old. Figure 6 shows the breakdown by age group of those currently taking diazoxide. Thirty-six participants (58%) who report that they are currently taking diazoxide are under the age of five years old. Compared to last year's report, this year's report includes a much broader age range of current users as evidenced by a slightly older average age (up from five years to seven years) and a greater percentage of members aged 5 or above (from 17% to 42%). The category with the most growth was the primary school age (five to eight years of age) group with now 11 participants in contrast to just one last year.

Figure 6. Age of those currently taking diazoxide



As illustrated in Figure 7, all but one (99%) of the participants who reported having taken diazoxide (both past and current) experienced some adverse effect. The most common side effects reported include: increased body hair (82%), loss of appetite (32%), continued hypoglycemia (30%), swelling (26%), facial changes (25%), and stomach pain or upset stomach (22%). Those participants reporting side effects other than the listed response choices noted hypertension, nausea, vomiting, fluid

retention, scrotal swelling, and thrombocytopenia (low platelet count). The top five reported side effects (increased body hair, loss of appetite, continued hypoglycemia, swelling, and facial changes) are the same in a year-to-year comparison with slight shifts in reported frequencies. Figure 8 illustrates the comparison.

Figure 7. Side effects experienced by those having taken diazoxide

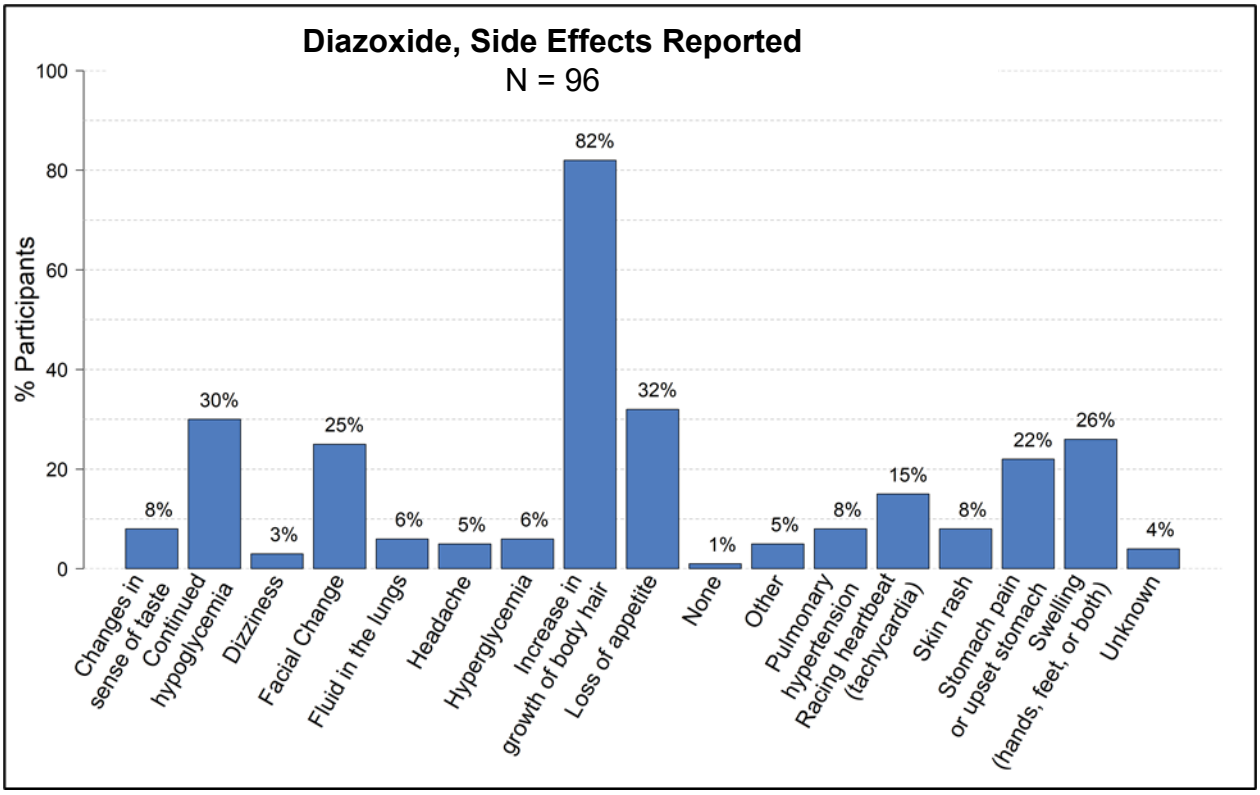


Figure 8. Side-by-side frequency comparison of the top five reported side effects of Diazoxide (2019-2020)

Reported Side Effect	**2019**	**2020**
Increased body hair	83%	82%
Loss of appetite	30%	32%
Continued hypoglycemia	32%	30%
Swelling	34%	26%
Facial Change	32%	25%

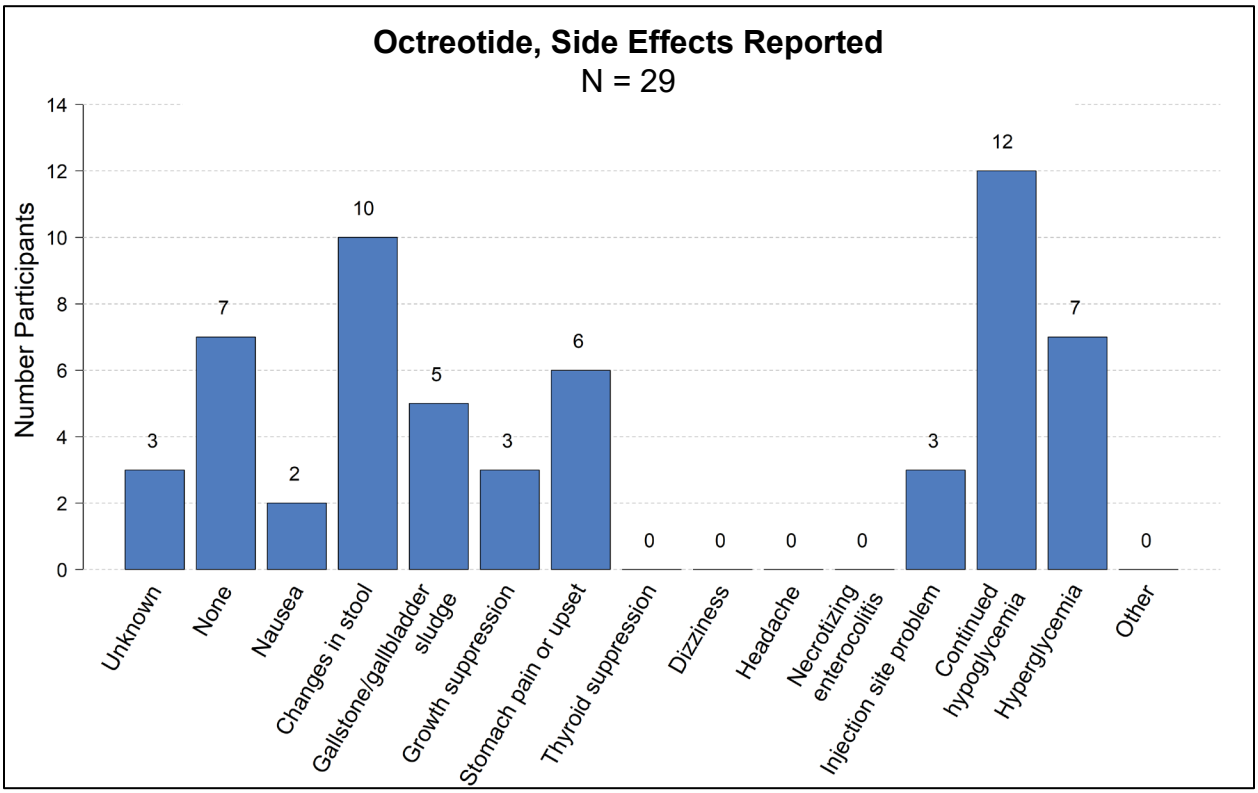
Forty-seven (76%) participants currently taking diazoxide (up from 32 participants last year) also reported on low blood sugar frequency. Seventeen (36%) of those participants (all ages included) experience at least one hypoglycemic event per week; eight (17%) experience at least one hypoglycemic event per day. Despite the larger number of participants in this year's report, the percentage of persistent hypoglycemia in both listed subsets remains relatively stable.

Octreotide

Of those who reported having taken octreotide (up 116% this year from 19 to 41 respondents), nine are currently taking octreotide and 32 have taken octreotide in the past. The average age of those currently taking octreotide is two years old (similar to last year's average age of 2.6 years), with an age range of six months to five years (also similar to last year's age range of eight months to four years).

Twenty-two (76%) of the 32 who reported having taken octreotide (both past and current) report experiencing some adverse effect, and 29 participants provided a response to the specific side effects experienced (see Figure 9). The most common side effects include: continued hypoglycemia (12 participants), changes in stool (ten participants), hyperglycemia (seven participants), stomach pain or upset (six participants), and gallstones/gallbladder sludge (five participants). Some participants reported experiencing more than one side effect.

Figure 9. Side effects experienced by those having taken octreotide



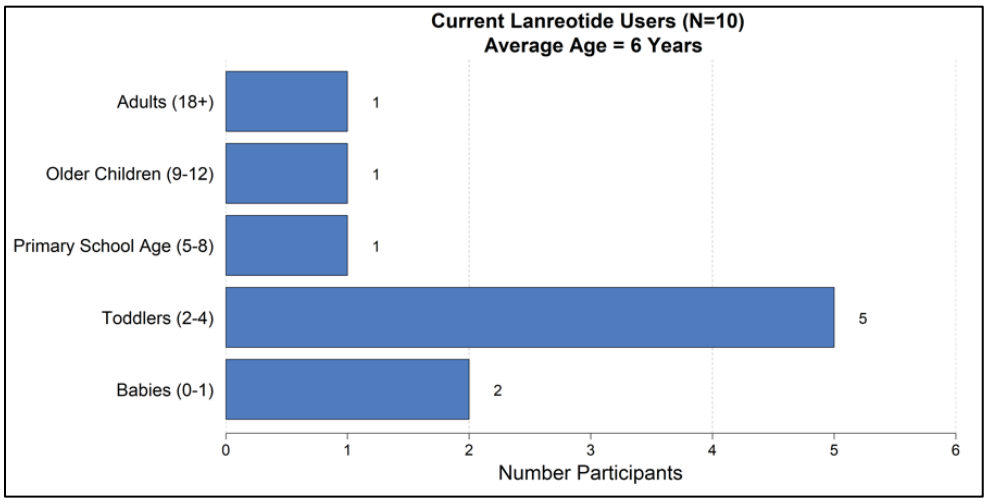
The following is a report that includes a small sample size. Eight participants currently taking octreotide reported on low blood sugar frequency. Seven of those participants experienced at least one hypoglycemic event per week and six experienced at least one hypoglycemic event per day.

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

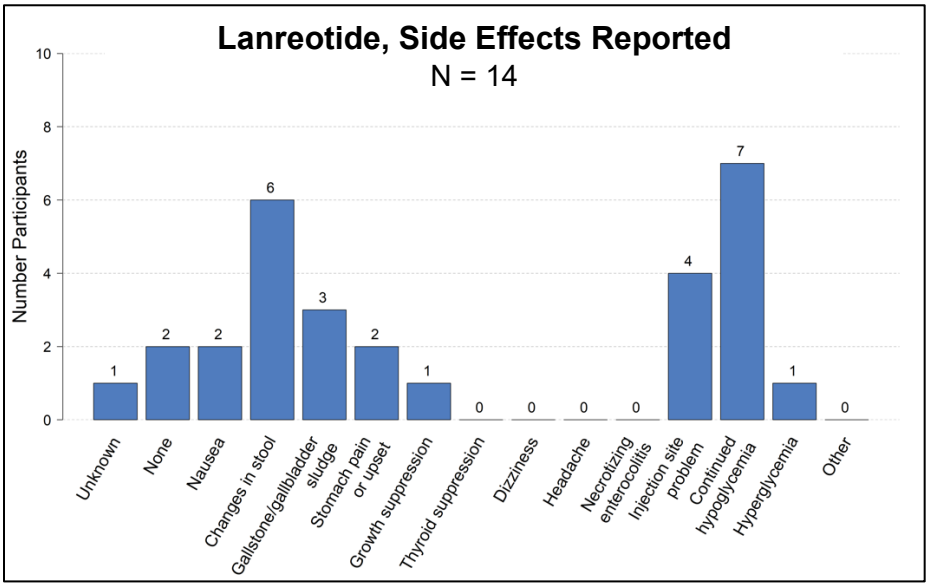
Figure 10. Age of those currently taking lanreotide



The following is a report that includes a small sample size. Of the 14 participants who reported having taken lanreotide, ten are currently taking it and four have taken it in the past. Figure 10 shows the breakdown by age group of those currently taking lanreotide. This year's report includes four additional participants currently taking lanreotide with an increase in average age from three years to now six years old. The age range is broader this year (18 months to 21 years old) compared to last year (eight months to ten years old).

Twelve of the 14 participants who have taken lanreotide injections (past and current) experienced some adverse effect (see Figure 11). The most common side effects include: continued hypoglycemia (seven participants), changes in stool (six participants), injection site problems (four participants), and gallstones/gallbladder sludge (three participants). Some participants noted more than one side effect. Last year, nine participants reported taking or having taken lanreotide with a similar reported side effect profile.

Figure 11. Side effects experienced by those having taken lanreotide



Nine participants currently taking lanreotide also reported on low blood sugar frequency. Four of those participants (all ages included) experience at least one hypoglycemic event per day. The small number reporting on lanreotide use does not make for an effective year-to-year comparison.

Sirolimus

Two participants (same as last year) reported taking sirolimus. Sirolimus duration of use ranged from two to five months for one participant and 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 routes, schedules, and potential issues. This section looks at reported feeding issues as well as the use of tube feeds to manage HI.

Feeding Issues

Figure 12 presents reported feeding issues for the 98 participants who have completed the Diet and Feeding Management Survey and also provided the information needed for the further subgroup analysis shown on the chart. The "Other" type of HI grouping includes those reporting HI is suspected but not diagnosed, unknown HI type, and atypical HI.

Of the 98 participants (all HI types and treatments included), 67 participants (68%) report having one or more feeding issue. Among the most commonly reported feeding issues, 42% report poor appetite or refusing to eat. Reflux, gagging, problems with texture, vomiting, and slow eating were each reported in over a quarter of the participants completing the surveys included in this analysis.

Figure 12. Reported feeding issues

Has the participant experienced any feeding issues on a regular basis (check all that apply)?	**All Participants**	**Diffuse**			**Focal**			**Other HI Type**
	W/WO Surgery	No Surgery	Pancrea-tectomy	Total	No Surgery	Pancrea-tectomy	Total	No Reported Surgery
	N (%)	N	N	N (%)	N	N	N	N (%)
No feeding issues	31 (32%)	15	2	17 (29%)	0	2	2	12 (40%)
Feeding Issues(s)	67 (68%)	29	14	43 (72%)	1	5	6	18 (60%)
Poor appetite	41 (42%)	17	9	26 (44%)	1	2	3	12 (40%)
Refusing to eat	41 (42%)	17	6	23 (39%)	1	4	5	13 (43%)
Reflux	33 (34%)	18	7	25 (42%)	0	2	2	6 (20%)
Problems with texture	28 (29%)	12	8	20 (34%)	1	2	3	5 (17%)
Gagging	28 (29%)	15	6	21 (36%)	0	1	1	6 (20%)
Vomiting	27 (28%)	13	5	18 (31%)	1	2	3	6 (20%)
Uncoordinated oral skills	22 (22%)	8	7	15 (25%)	1	1	2	5 (17%)
Slow eating	27 (28%)	14	7	21 (36%)	0	0	0	6 (20%)
Coughing	15 (15%)	7	6	13 (22%)	0	0	0	2 (7%)
Overeating	11 (11%)	7	2	9 (15%)	0	1	1	1 (3%)
Other	3 (3%)	0	0	0	0	0	0	3 (10%)
Total	**98**	**44**	**16**	**60**	**1**	**7**	**8**	**30**

This year's data shows there has been 38 more (63% increase) participants who completed the Diet and Feeding management since last year's report. The proportion of those reporting feeding issues remains exactly the same (68%) year-to-year. Poor appetite and refusing to eat are also reported at

the same frequency (42%) as last year. These two feeding issues continue to be the most commonly reported. All other reported feeding issues are similarly ranked.

Feeding methods

Figure 13 presents reported feeding methods for the 102 participants who completed the Diet and Feeding Management Survey and 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 13. 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	Pancrea-tectomy	Total	No Surgery	Pancrea-tectomy	Total	No Reported Surgery
	N (%)	N	N	N (%)	N	N	N	N (%)
Both Tube & Oral Feeding	50 (49%)	21	17	38 (61%)	0	4	4	8 (26%)
Tube Feeding (NG/OG/J/G) Only	9 (9%)	2	1	3 (5%)	0	2	2	4 (13%)
No Tube Feeding	43 (42%)	22	0	21 (34%)	1	1	3	19 (61%)
Total	**102**	**45**	**18**	**63**	**1**	**7**	**8**	**31**

As a whole (all HI types and surgical states), 59 (58%) report that tube feeding has been used to provide nutrition and/or background sugar to the participant since HI was suspected. As a comparison, there has been an additional 42 participants (a 70% increase) answering the relevant questions regarding feeding methods since last year's report with essentially the same percentage reporting the need for supplemental or nutritional support using tube feeds.

Surgery Experience

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

Forty-three HIGR participants, out of the 116 completing the Surgical Management survey (along with other relevant survey questions to make subgroup analysis possible), reported that a pancreatectomy was considered for the treatment of their HI; and 31 of those 43 participants (72%) report undergoing at least one pancreatectomy. Of the 31 that had a pancreatectomy, 19 reported diffuse HI, nine reported focal HI, one reported atypical HI and two did not provide a response about HI type. This year's report includes 13 additional participants who have undergone at least one pancreatectomy, with a similar breakdown of HI types compared to last year.

Focal

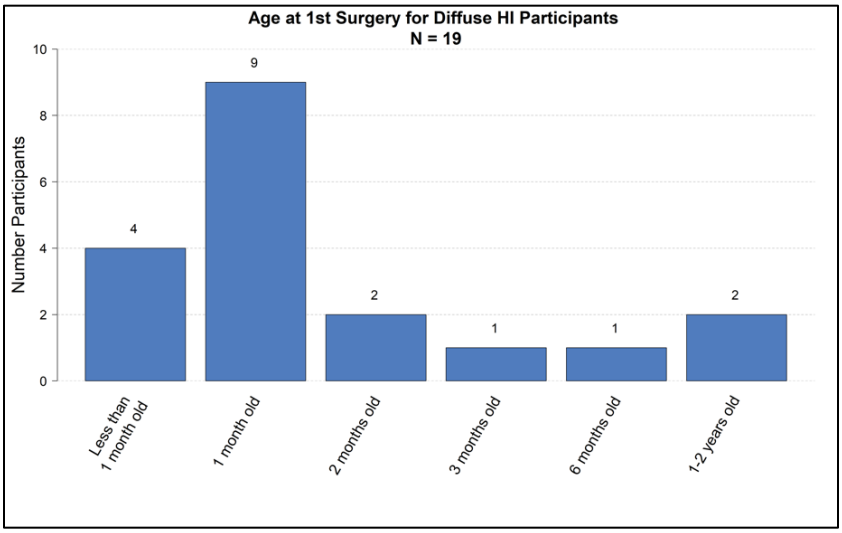
Ten participants in HIGR who report having focal HI also shared their surgical experience. Nine of those participants underwent at least one pancreatectomy, with two participants with focal disease requiring a second pancreatectomy. The reported participant age when the pancreatectomy was performed was less than one month old for three participants, one month old for three participants, five to eight months old for two participants, and between one-two years old for one participant.

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 three participants, 25-49% for two participants, 50-74% for three participants, and 75-94% for one participant. Due to the small sample size and young age of these participants, long-term outcomes are not included in this report.

Diffuse

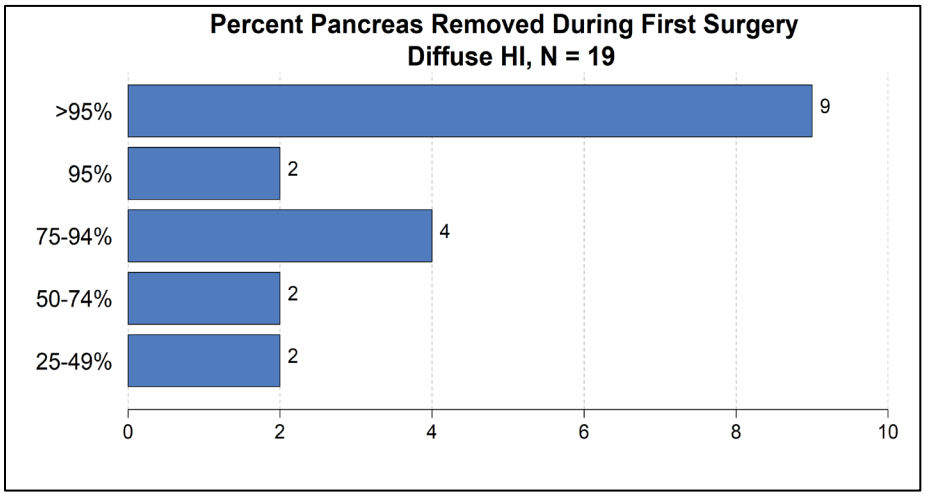
Nineteen participants (up 58% from 12 last year) that report having at least one pancreatectomy have diffuse disease. The current age range of this group is six months to 26 years old, with 14 participants under 13 years old and five participants now being 13 years or older. Figure 14 shows that of the 19 participants reporting diffuse HI and having undergone a pancreatectomy, most had their first

Figure 14. Age of first pancreatectomy in diffuse HI



surgery within the first few months of life. This is consistent with the reporting on this subject last year.

Figure 15. Percent of pancreas removed at first surgery in diffuse HI participants



As seen in Figure 15, of the19 diffuse HI participants who underwent a pancreatectomy, 11 reported at least a 95% pancreatectomy while eight had less than 95% of their pancreas removed during their first surgery. Five participants required at least a second or subsequent pancreatectomy; two participants reported requiring a third pancreatectomy. The high-level look at pancreatectomy in diffuse disease for this report may include confounding factors that are not fully explained without further subgroup analysis.

Five of the 19 participants with diffuse HI, who had a pancreatectomy, report having diabetes. Four of the 5 with diabetes report being at least ten years old when diabetes was diagnosed, and one participant reports diabetes developed in infancy, shortly after undergoing a subtotal pancreatectomy. Of the remaining 14 participants with diffuse HI who had a pancreatectomy and who do not report having diabetes, 11 have not reached adolescence (age 10 years or older). The lower percentage of diabetes currently reported in this group is not unexpected because it is established in the existing medical literature that nearly all patients that undergo a subtotal pancreatectomy ultimately go on to develop insulin-dependent diabetes by adolescence (Bertrand, J Diabetes Care, 2011). Due to the small number that still exists in this subgroup, year-to-year comparison is not meaningful.

Four of those 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 2 participants began taking pancreatic enzymes between 15-19 years old, many years after the pancreatectomy.

Medical Management Elected

Of the 43 participants reporting that a pancreatectomy was considered by the medical team and family for the treatment of HI (all ages and all HI types, known and unknown, included in this count), along with the other relevant survey questions for subgroup analysis, eight report opting for medical management rather than a pancreatectomy and have completed other survey questions that allow for subgroup analysis in this report. Six listed medical management preferred, and two listed health concerns (ex. diabetes, surgery, complications, psychological stress etc.) as the reason for selecting medical management. The genetics of the participants in this subgroup include ABCC8 mutation(s) in five participants, glucokinase mutation in two participants, and one participant had no genetic mutation identified upon testing. Half of these participants report currently taking diazoxide, although frequency of hypoglycemia in those on diazoxide suggests these individuals may only be partially diazoxide responsive. Tube feeds and/or background glucose supplementation are reported by five

participants in this subgroup. The average age of those medically managed in this subgroup is currently 10 years old, with ages ranging from three to 24 years old. Due to the small number that still exists in this subgroup, year-to-year comparison is not meaningful.

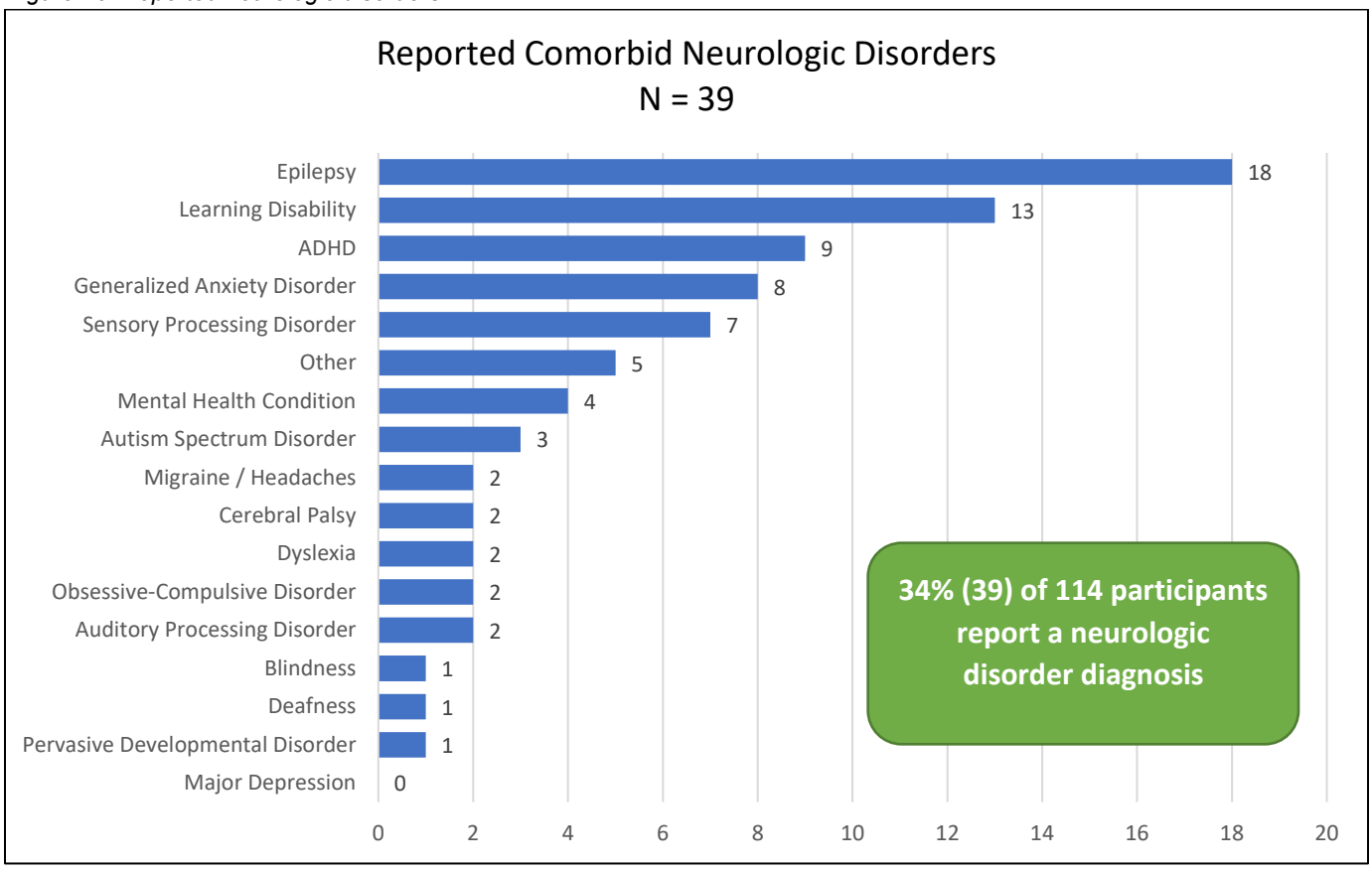
Neurologic Outcomes

Two surveys of HIGR address neurologic outcomes: Other Diagnoses Survey and the Development Survey. This section presents data extracted from both surveys.

Neurologic Disorder

Thirty-nine (34%) of the 114 participants who completed the Other Diagnoses survey report having been diagnosed with a neurologic disorder which is a similar percentage to last year (32%). Some participants noted more than one disorder. Epilepsy remains the most commonly reported neurologic disorder, now accounting for 18 (46%) of those who report having a neurologic disorder. Similarly, 44% of last year's participants reported a diagnosis of epilepsy. Figure 16 shows the other neurologic diagnoses reported ranked from most common to least. The most common neurologic diagnoses, such as learning disability, ADHD, generalized anxiety, and sensory processing disorder, remain similar when compared to last year's report. The "other" category includes participants with suspected, but not yet confirmed, diagnoses similar to those listed above as well as visual, motor, and/or neurocognitive issues of a more general nature.

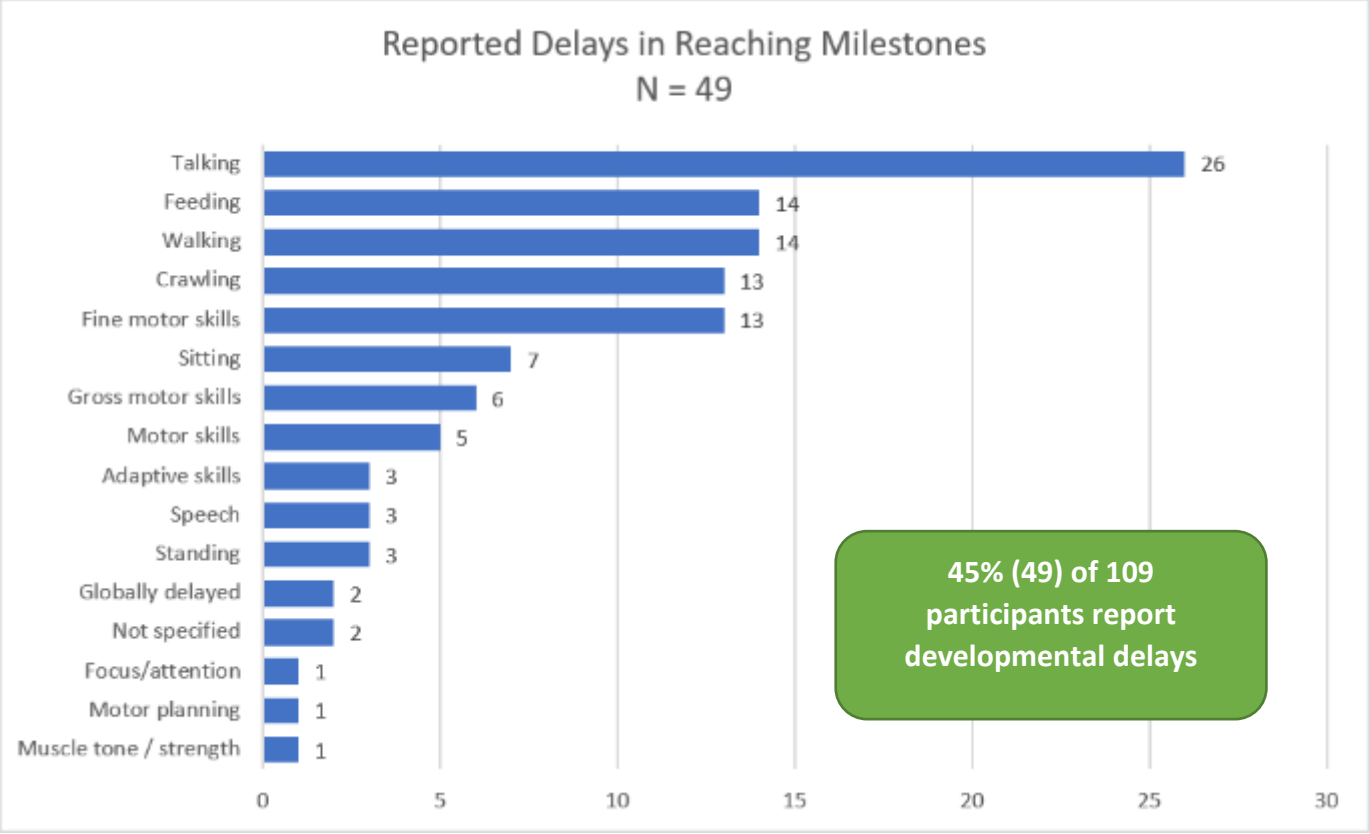
Figure 16. Reported neurologic disorders



Developmental Delay

Of 109 participants who completed the Developmental Survey, 49 (45%) participants report delays in reaching developmental milestones. Compared to last year's report, this year there are 23 more participants (an increase of 89%) answering this question with a similar percentage (46% last year) reporting a delay. Delays reported include: 26 (53%) participants report delay in talking; 14 (29%) in feeding; 14 (29%) in walking; 13 (37%) in crawling; and 13 (37%) in fine motor skills. Some participants reported delays in more than one milestone. Last year, these delays were reported as a percent of all participants completing the relevant survey questions. This year, the data is reported as a percent of those reporting a delay which is aligned with the format of the comorbid neurologic diagnoses data above. While comparison of the percentages year-to-year is not meaningful, it can be noted that the specific delays reported remain similarly ranked.

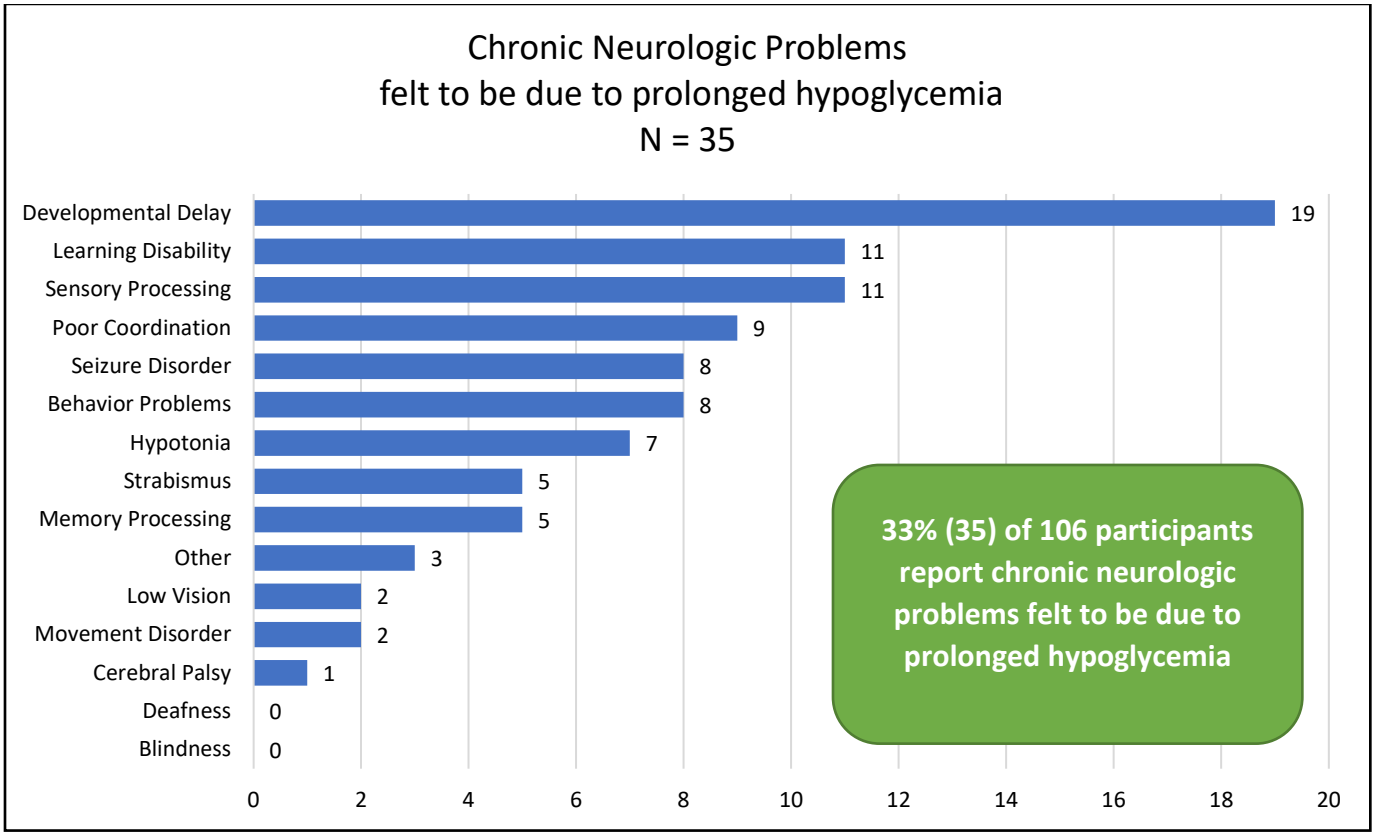
Figure 17. Milestone Delays in HI Participants



Reported Neurologic Problem Felt to be Due to Prolonged Hypoglycemia

Thirty-five (33%) of 106 participants report having a chronic neurologic problem which they feel is due to prolonged hypoglycemia. This is an increase of 18 participants (more than double last year's total) reporting a problem in this survey question, and the overall percentage of participants (up slightly from 30% last year) reporting a problem has remained similar. Figure 18 shows the list of neurologic problems reported by participants in this Developmental Survey question. Some participants noted more than one neurologic problem. Developmental delay (19 participants, 54%), sensory processing (11 participants, 31%), and learning disability (11 participants, 31%) were the most commonly reported chronic neurologic problems felt to be due to prolonged hypoglycemia again this year.

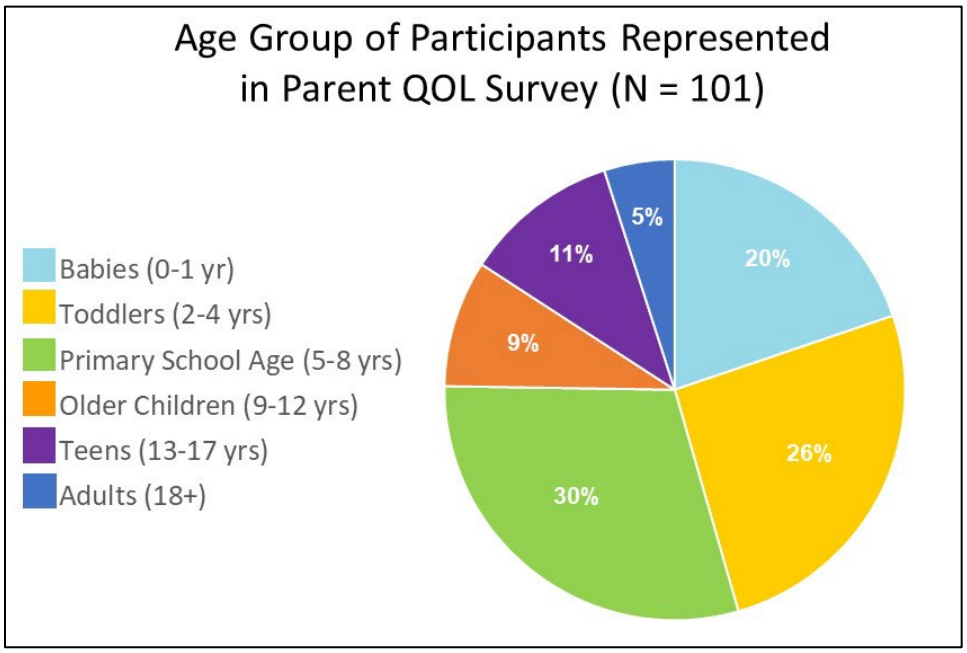
Figure 18. Reported chronic neurologic problems felt to be due to prolonged hypoglycemia



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 meant to be completed by one parent of the participant, regardless of his 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 19. Participant ages as of February 1, 2020 represented in Parent QOL



Parents of 101 participants (only one parent for each participant) completed the Parent Quality of Life (QOL) survey. This is up from just 61 participants (increase of 66%) in last year's report. Figure 19 shows the age groups of the participants reflected in the QOL surveys in this report. The largest subgroup change from last year occurred in the Primary School Age group, which increased from 7% to 30% of the parents reporting on QOL. The Adults subgroup remained the same at 5%, while the Toddlers subgroup saw a decrease from 47% to 26% of the total group of parents reporting. As of February 1, 2020, the youngest child reflected in this QOL report is seven months old and the oldest is 30 years old.

Parent Health

Parents of 67% (63) of the 94 participants responding (all age groups included) report that their physical health has suffered from having a child with an HI-related condition. Parents of 87% (82) of the 94 participants responding (all age groups included) report that their mental health has suffered from having a child with an HI-related condition.

Family Planning, Relationships, and Household Income

Of 94 HI parents of participants responding (all age groups), 39% report choosing not to have additional children, and another 19% report delaying having additional children. Of 85 surveyed parents of participants (all age groups) responding who were in relationships, 60% (51) report that having a child with HI strengthened their relationship with their partner; however, 26% (21) reported a negative impact, including 5% (4) who reported their relationship ended. Of 93 parents of participants (all age groups), 35% (33) report that having a child with HI has negatively impacted their household income quite a lot or very much.

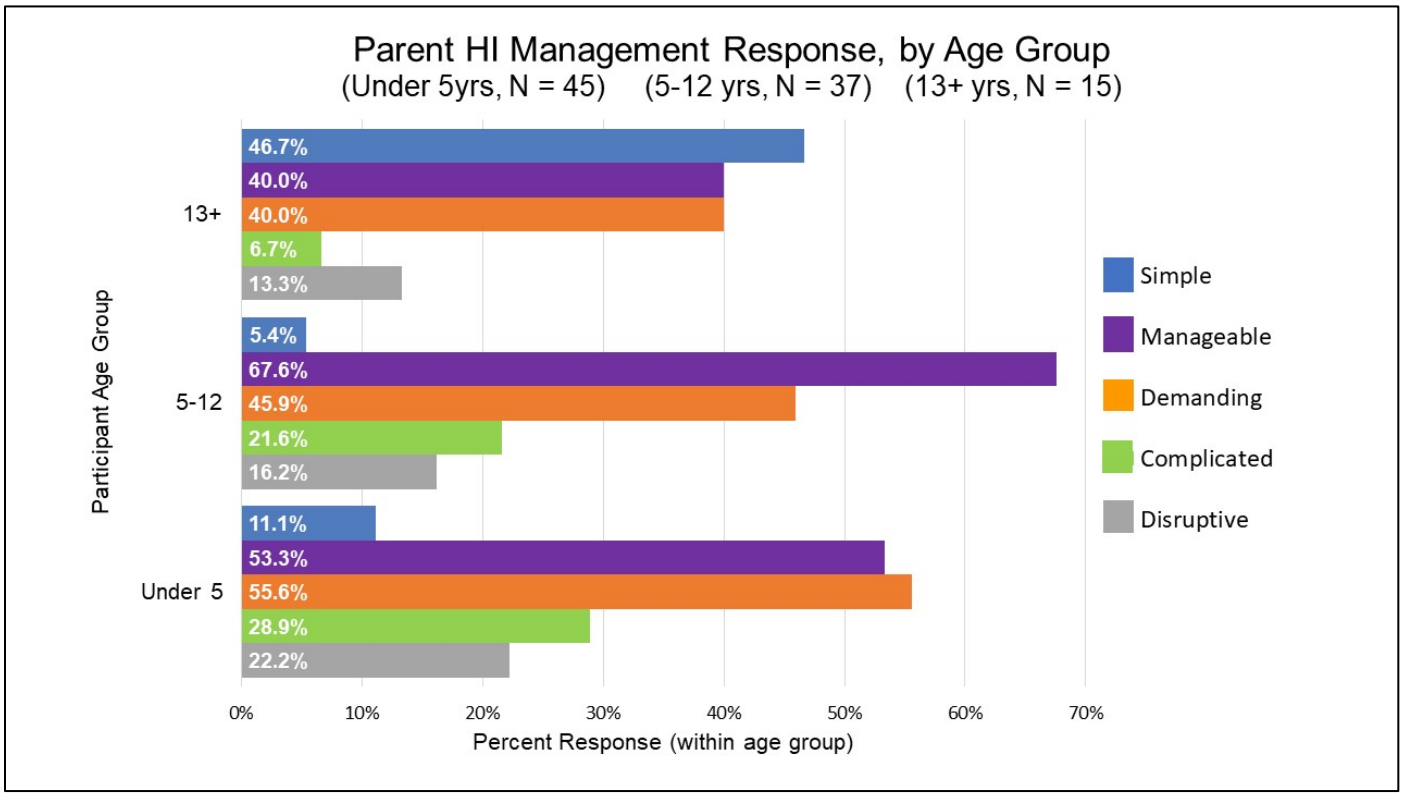
Management of HI

Figure 20 shows the various responses parents gave to describe the management of HI. Parents could select more than one response to this question. This report includes 38 additional unique parent responses (up 64% from last year). Parents of children with HI in each age group, including the oldest age group, still report the management of HI can be “demanding” with 56% (25) of parents of children under five (N=45), 46% (17) of parents with children 5-12 years old (N = 37), and 40% (6) of parents with children thirteen or over (N=15) selecting “demanding” to describe the daily management of HI. The most notable difference in the demanding response from last year’s report is in the 5-12 year old age group (up from 11%). This age group has also seen the most increase (up from just 9 previously) in parents representing this group.

Last year, only parents in the under five years of age group described the management of HI as disruptive. This year, the disruptive response was selected by some in each reported age group: 22% (10) in those with children under five years, 16% (6) with children five to 12 years of age, and 13% (2) with children 13 years old and older.

More parents of older participants select “simple” to describe the management of HI than parents of younger children. While only 11% (5) of parents of children under five and 5% (2) of parents of children 5-12 selected “simple”, 47% (7) of parents of children thirteen and older selected it. A similar trend was seen in last year’s report.

Figure 20. Parents’ responses to management of HI, by participant age group

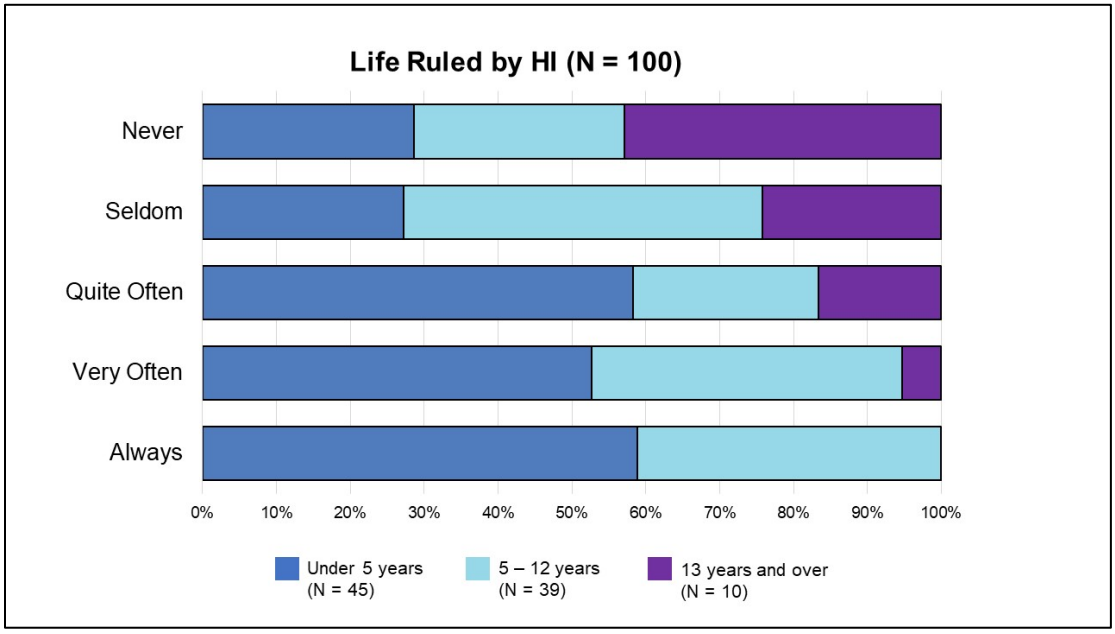


General Quality of Life

Fewer parents of older children report feeling their lives are ruled by HI. Of 45 HI parents of children under five years old, 76% (34) parents report they quite often, very often, or always feel their lives are ruled by HI; this number decreases to 54% (21) of the 39 HI parents of children aged 5-12 years and

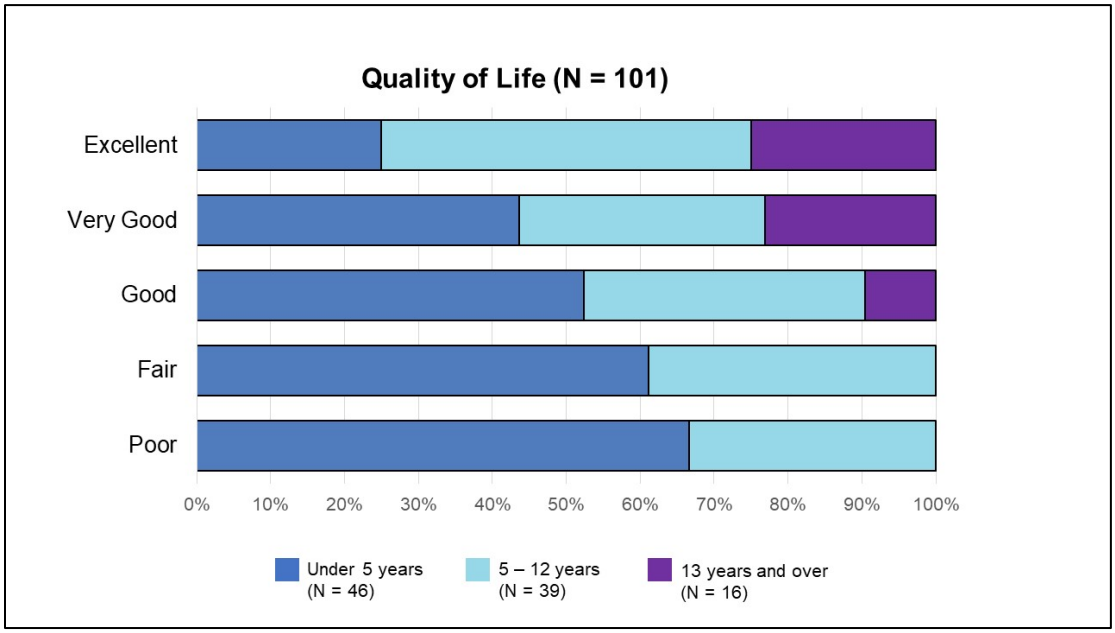
to 31% (5) for the 16 HI parents of children aged thirteen years and older. This year's reporting exhibits a similar trend to the 2019 data. Figure 21 shows the various responses of parents to this question by participant age group. It is important to note that this discussion section includes all HI types, including focal HI that has been cured and transient HI that may have resolved by the time those parents completed the QOL Parent survey.

Figure 21. Parent life ruled by HI, by participant age group



Regardless of age group, most parents (99 of the 100 reporting) worry about their children. Fewer parents of older children report worrying about their child quite often, very often, or always. This year's data shows a consistent trend to last year's report with 91% (41) of the 45 parents of children under five years old, 87% (34) of the 39 parents of children 5-12 years of age, and 81% (13) of the 16 parents of children thirteen years and older reporting worrying at least quite often.

Figure 22. General quality of life reported by parents, by participant



Similar to last year's report, the self-reported general quality of life of an HI parent this year again appears to improve as children get older. Of the 101 parents who answered this question (see figure 22), 72% (33) of the 46 parents of children with HI under five rate their QOL as good, very good, or excellent; the number increases to 80% (31) for the 39 with children 5-12 years old and to 100% of those with children thirteen years old and older.

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, engagement efforts that have been conducted to date, and clear calls to action for individuals at every stage of registry participation.

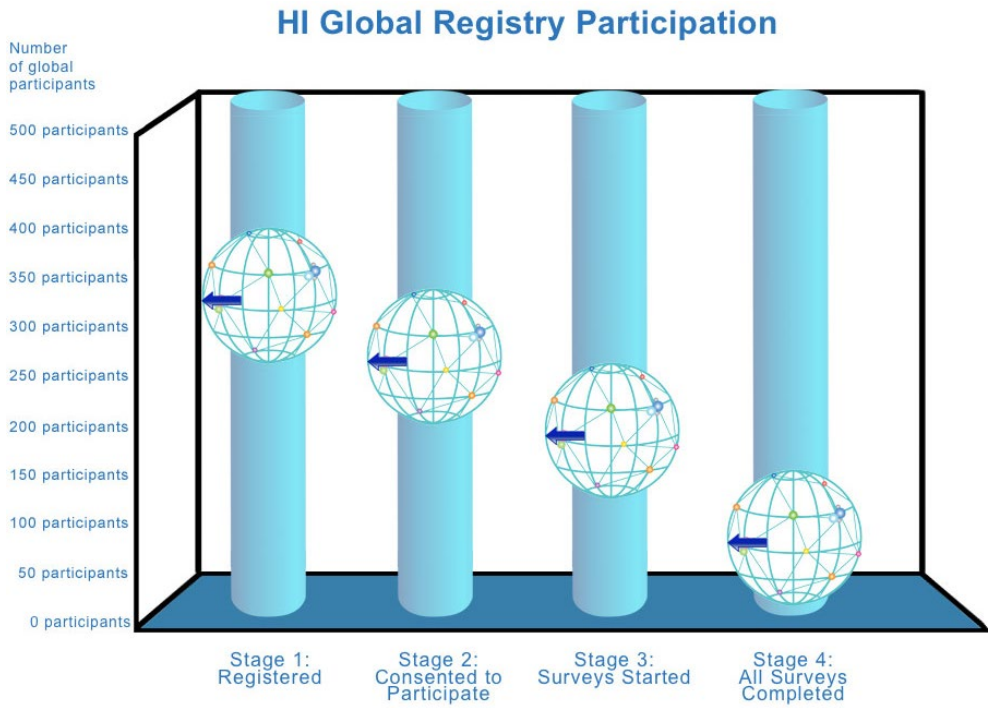
HIGR launched October 10, 2018, and the initial three-year recruitment goal was to have 300 participants register for the study. Last year saw great interest in HIGR from the HI community, and on the day before HIGR's first anniversary, the 300th individual signed up to participate.

The work of HIGR, in many ways, has just begun. In research, data becomes more meaningful as the sample size (number of participants) increases. With more participants answering more surveys over time, we will be able to 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 investigators track respondent and participant utilization of the system and identify strategies to assist individuals in the completion of all relevant surveys. Figure 23 reflects the number of participants at each stage as of early February 2020. The four stages of participation are outlined below. The Calls to Action outlined below are for those with HI and their families.

Figure 23. HIGR participation, by stage



Stage 1 is defined as 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). 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** – Agreeing to be notified of clinical trials that might include participants like you does not commit you to participate in the trial. Your information will not be given to the clinical trial sponsor if you select yes to this preference. It does mean that if the HIGR staff identifies a clinical trial that includes characteristics of the participant entered in the registry, that participant will receive a notice describing the clinical trial opportunity and information about how to contact the clinical trial sponsor.

(3) **For a tissue biobank project, if one is developed specific to HI** – This might include future genetic studies or other identified biomarkers that help detect and/or diagnose HI and HI subtypes. Like for clinical trials above, 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 around the world. By agreeing to be contacted about networking opportunities, you will receive a notice of any organized 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.

As of the beginning of February this year, 325 respondents have enrolled on the registry platform and 68-76% of respondents have given permission to be contacted regarding each of the key opportunities available to HIGR respondents/participants. The contact permissions set at registration can be updated at any time.

Stage 1: Call to Action

If you are the parent or caregiver of a child living with HI or an individual over 18 who has been diagnosed with HI, we invite you to register with HIGR. It is incredibly important to understand everyone's unique HI experience, regardless of your current HI status or management. If you have already registered on the platform, we encourage you to revisit the site and confirm each of your contact permissions is set to your desired preference.

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 325 registered respondents have added 303 participants (44 adults, 259 minors); 263 participants (86.8% of the 303 participants) have completed the consent process which then allows access the survey questions.

Stage 2: Call to Action

For those that have signed up, but have not yet consented, we kindly request that you revisit the site, read the consent document, and follow the instructions there to provide your consent. The HIGR team is here for you should you have any questions about this step or any stage of registry participation.

Stage 3 is defined as the step when a participant (or LAR on behalf of a participant) submits at least one survey. Currently 184 participants have completed at least one survey (60.7% of all enrolled participants). Each survey asks questions related to different aspects of HI. They utilize a branching logic, so if something is not relevant, you will not be asked additional questions related to that experience. Individuals should complete all relevant surveys. 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 set aside time, whether a little each day or one or two longer stretches, and 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 defined as a participant (or LAR on behalf of a participant) having completed all relevant surveys. Depending on the age of the participant, there are 12-13 surveys to be completed and submitted in order to achieve full participation in HIGR. Currently, 85 participants (28.1% of all potential registered participants) have completed all relevant surveys. For each available survey, the completion rate based on all potential registered HIGR participants for 2019 and 2020 is noted in Figure 24. 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 of the included surveys, they are likely to be excluded from deeper analysis on that topic. The resulting smaller number may not be as reliable to achieve the objectives of that given report.

Stage 4: Call to Action

Congratulations! You have completed all the initial surveys! You are a patient-powered researcher! 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

CHI has employed a variety of engagement strategies to help grow HIGR since its launch, including partnerships with HI centers globally, ongoing social media campaigns such as #recognizeHI, CHI Team Scrabble, and the "I'm a Researcher Too!" badges (see Figure 25). There was also active HIGR staff and volunteer support at the 2019 family conferences to help participants enroll in the registry and get started on surveys.

The "I'm a Researcher Too" campaign is designed to engage participants by highlighting the important value of each participant in the research process. By completing surveys, participants are providing the data needed to understand the natural history of the disorder. A deep and robust HIGR is only possible when participants update and complete surveys on a regular basis. With the "I'm a Researcher Too" campaign, participants can also share the vital role they play in research on their social media channels. By sharing that they participate and their experience in the process, they also engage others in the community, which helps to increase participation in HIGR.

The #recognizeHI campaign was born of the fact that Microsoft does not recognize hyperinsulinism as a word, so that each time it is spelled in a document, it is labeled as a misspelled word. This lack of recognition from Microsoft spellcheck is a real-world example of just how unknown the condition is to the general public. The investigators also realized that word play and gamification are important ways to engage the community, and to interest them in joining HIGR and completing survey. The #recognizeHI Scrabble campaign is a way to educate the community on the condition in an entertaining way, while reminding them to engage with HIGR.

It goes without saying that the COVID-19 pandemic has had a major impact on all in the HI community with most people with the condition confined to their homes, except for those who have been hospitalized or are essential workers. With most of life as we know it shut down, the activity of completing HIGR surveys has been alive and well, with no interruption. To highlight that HIGR is an activity open and available during the pandemic, the investigators created a series of social media posts to encourage active participation in HIGR at a time when many research activities have been postponed.

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.

Figure 25. Examples of HIGR engagement campaigns.

Discussion

The first full year of HIGR has seen a great deal of activity that has laid a strong foundation for an HI natural history study reported by those who live with the disease. In this still early period, the reader should remain judicious when making any conclusions about treatment, care, or the natural history of the condition based on what is reported here. For the most part, the combination of data in the various topics is not meant to provide cause and effect. Instead, the investigators have provided this report as a robust introduction into the type of information that can be retrieved from the registry while addressing some of the topics frequently discussed by key HI community stakeholders. Year-to-year comparison is presented here as observation without deeper statistical analysis.

Since its launch, the registry has been actively providing deidentified data to both the community of participants and to clinical researchers. The HIGR platform allows participants to see charts related to individual survey questions once they have submitted a survey. The charts are much like those in this report that show the percentage of participants providing each response to a specific question. In the past year, HIGR opened the door to CHI providing data to help get diazoxide added to the World Health Organization's Essential Medication List. Presentations informed by deidentified HIGR data were given to numerous HI community stakeholders including HI families at family conferences, physicians at medical conferences, and a mixed rare disease constituency conference. Deidentified HIGR data has also been used to help researchers understand details about HI in relation to drug development study design.

This year's report reflected the growth in many areas. Some consistencies seen from last year's report to this year's include: (1) the diffuse subtype remains the most prominent form on HI among registry participants; (2) one in four participants that has an abnormal glucose detected at the birthing facility and later diagnosed with HI requires additional hospitalization before receiving that HI diagnosis; (3) nearly all who are taking or have taken diazoxide report side effects from it, and the most common adverse effects remained similarly ranked; (4) over two-thirds of participants (all HI types included) report feeding issues; (5) neurologic outcomes, whether reported as a diagnosed disorder (34%), developmental delay (45%), or chronic neurologic problem (33%), affect a similar proportion of participants with twice as many participants responding to these questions; and (5) the trends in the Parent Quality of Life section remain consistent to previous reporting.

The process to register, consent, complete surveys, and keep responses up to date is outlined in this report. The investigators acknowledge that completing surveys can be time-consuming and require much effort from participants to gather the necessary information to answer many questions. Yet, the investigators strongly encourage each participant to complete all relevant survey questions. A robust and diverse collection of HI stories, as collected by the HIGR surveys, strengthens the value and potential of the registry. HIGR has already begun demonstrating its potential to give back to the HI community, and exciting opportunities are on the horizon where HIGR will play an integral role in developing and supporting a patient-powered research agenda. The HIGR team will continue to focus on engagement with the hope that participants all over the world will enroll in the registry, complete the full set of surveys, update them when appropriate, and take the longitudinal surveys (such as the

Diet and Feeding Management and Quality of Life Surveys) that are meant to be retaken on a scheduled basis.

As mentioned last year, HIGR is currently available only in English. The investigators recognize a true 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 truly reflect the global HI experience. The HIGR team is actively pursuing the addition of other languages and once again encourages all those who are comfortable in English to enroll and complete the relevant surveys.

This annual report is meant to continue fostering 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.

This research is being overseen by New England Institutional Review Board (IRB), Protocol #120190390. An IRB is a group of people who perform independent review 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 (800) 562-4789 or info@neirb.com.

Acknowledgements

The investigators would like to take the opportunity to thank everyone who has made it possible to conduct this important 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 continue to share our present findings and future 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. The investigators are also extremely grateful to and would like to thank Dr. Sunny Chapel and the A2PG staff for their data analytics work in preparing for this report, and Dr. Tai Pasquini, CHI's new Research and Policy Director, for her early insights and assistance with moving this vital research program forward. Thank you to the CHI Board of Directors for continuing provide support to HIGR. The investigators wish to express our deepest appreciation to the HIGR Steering Committee who volunteer their invaluable expert advice and guidance to ensure the success of the HIGR research program.

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Dr. Diva D. De León-Crutchlow – USA
Dr. Sarah Flanagan – UK
Dr. Klaus Mohnike – Germany
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