



An Early Glimpse at Data Spring 2019

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Overview of This Report

The HI Global Registry (HIGR) is the first global patient-powered congenital hyperinsulinism (HI) patient registry. Many years in the making, HIGR launched on October 8, 2018. What follows is an initial report from the HIGR investigators including an introduction to the research project and an early glimpse of data from it. While the first annual report by investigators is not planned until early 2020, the intent of sharing these early findings is to further engage stakeholders in HIGR's work, better inform the preparation and data analysis of the HIGR annual reporting cycle, and encourage full and robust study participation from all potential study participants.

HIGR 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 new 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 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. The project 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.

To further acquaint the reader with HIGR, a portion of the HIGR study protocol is shared below. This report also includes information on the early recruitment and initial data 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 five months of HIGR enrollment. Each individual report presented in this document includes the number of participants who submitted 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 before submitting a survey as final when they are ready. For each report, the number of participants is listed as "N" and is followed by an equal (=) sign and the count of participants in that report.

The investigators carefully considered the issue of sample size for this publication and acknowledge that less than 30 participants is a small sample size. 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. The purpose of this report is to present factually what has been shared by HIGR participants at this early point in its operation as a point of discussion among key HI stakeholder. Due to the expressed interest in certain data points, some smaller subgroup data has been included with a notice of caution clearly stated for those topics. 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. With higher participation over time, HIGR and its published reports will become an increasingly reliable source for the research and clinical communities to better understand the natural history of HI.

Protocol Objectives

HIGR is guided by an institutional review board (IRB, also known in some countries as an ethics committee) research protocol. This protocol was drafted by the HIGR Steering Committee that is 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 in order to understand how HI develops, how it is treated, and the health and life impacts of HI. The objectives (or goals) of HIGR are defined below. The primary objectives are centered more around the condition, while the secondary objectives focus more 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 in order to document the natural history and outcomes of individuals with HI.
- To improve knowledge of global prevalence of HI and any associated co-morbidities.
- 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.

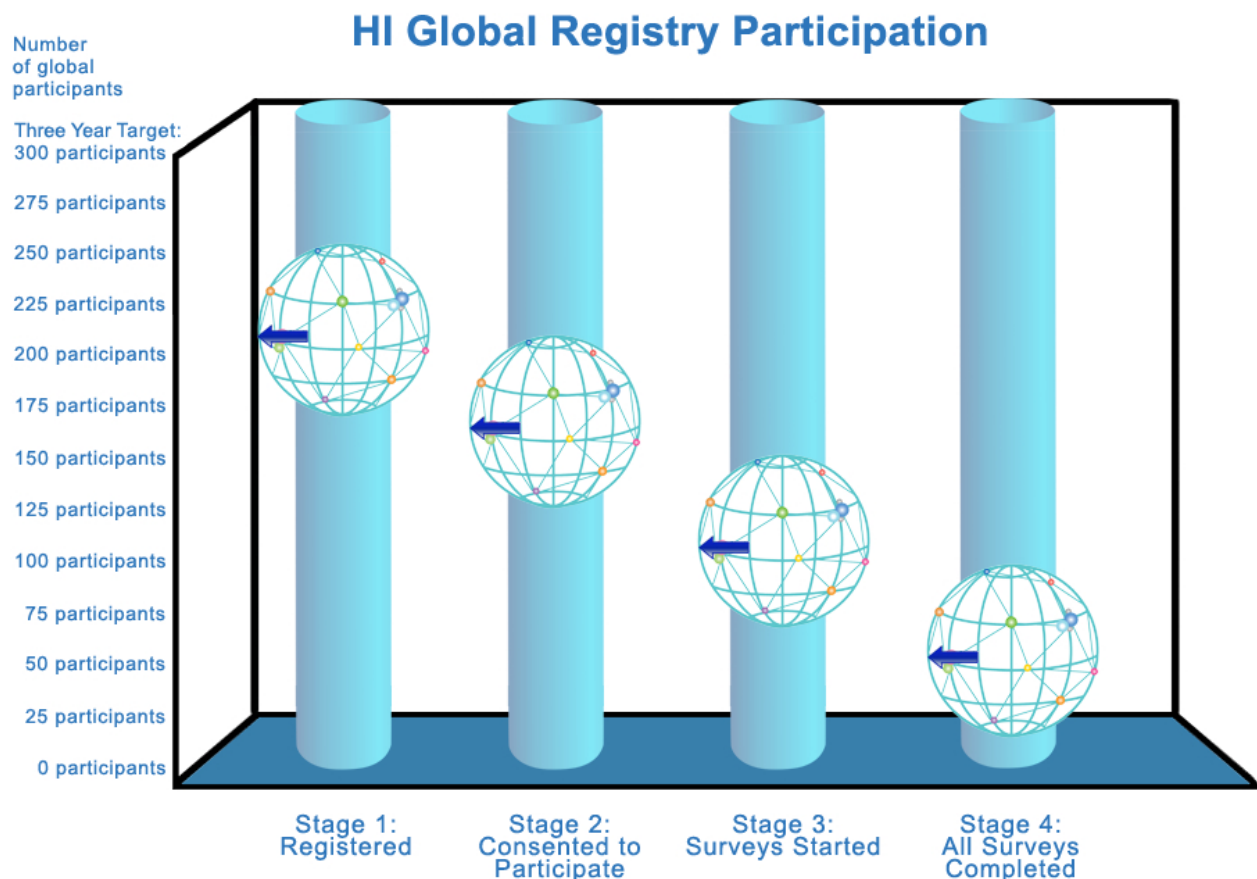
The secondary objectives of the Registry are:

- 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.

Registry 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 with respondent/participant completion of all relevant surveys. Figure 1 shows the participation at each stage as of February 16, 2019. The stages of participation are defined below.

Figure 1. HIGR participation, by stage



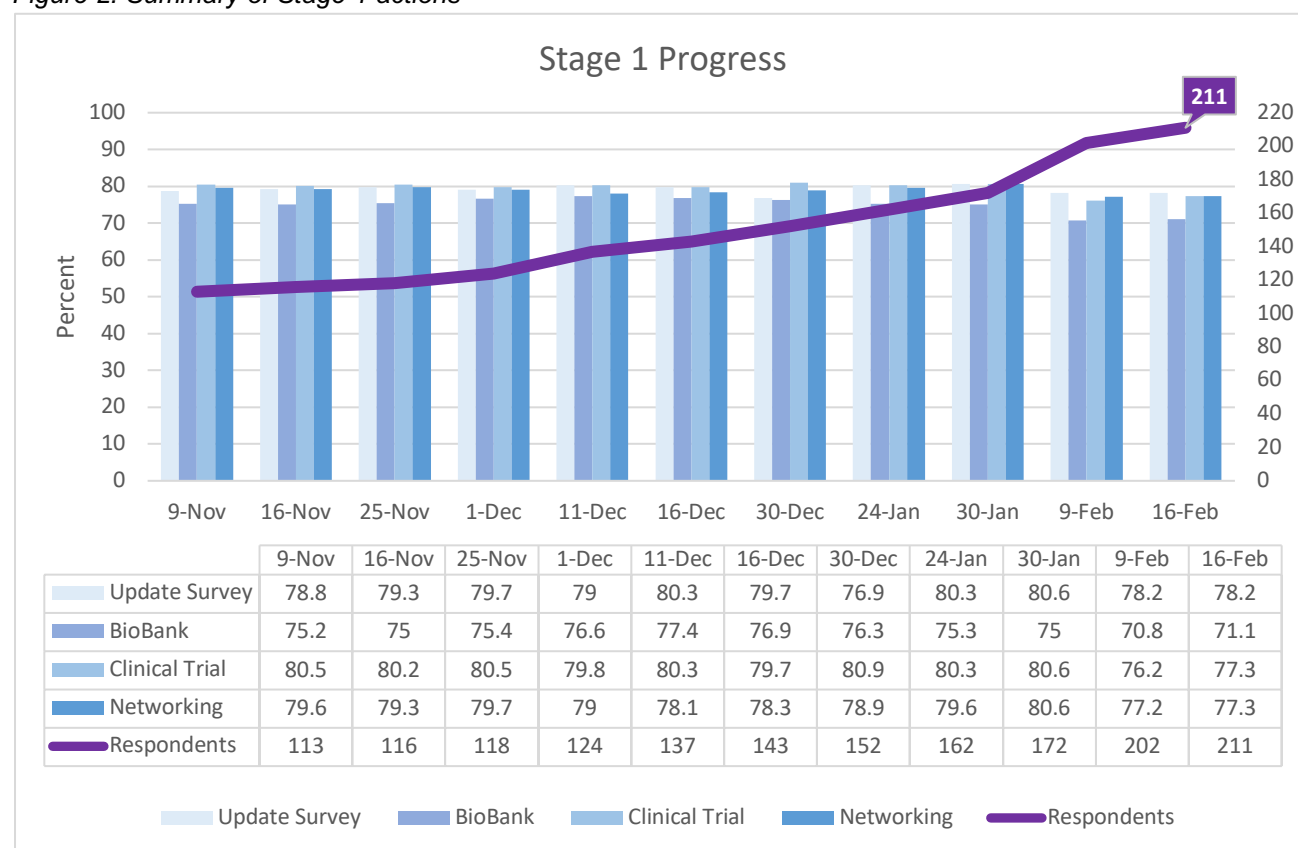
Stage 1 is defined as registration with the registry platform at www.higlobalregistry.org. The registration process includes basic identifying information provided by the respondent (HI patient or their legal authorized representation (parent/guardian) if the patient is a minor or unable to register due to cognitive difficulties).

During registration, among other questions, the respondent is asked if they wish to be contacted by the HIGR staff in four possible scenarios: (1) to periodically update their survey information; (2) for a possible clinical trial the participant may qualify to take part; (3) for a tissue biobank project, if one is developed specific to HI; or (4) future

networking opportunities within the international HI community (such as by HI type or in a specific country or region).

Figure 2 shows the trend of registration from HIGR's official launch date on October 9, 2018 to February 16, 2019. As of February 16, 2019, 211 respondents have enrolled on the registry platform and 71-78% of respondents have given permission to be contacted regarding each of the key additional opportunities available to HIGR respondents/participants.

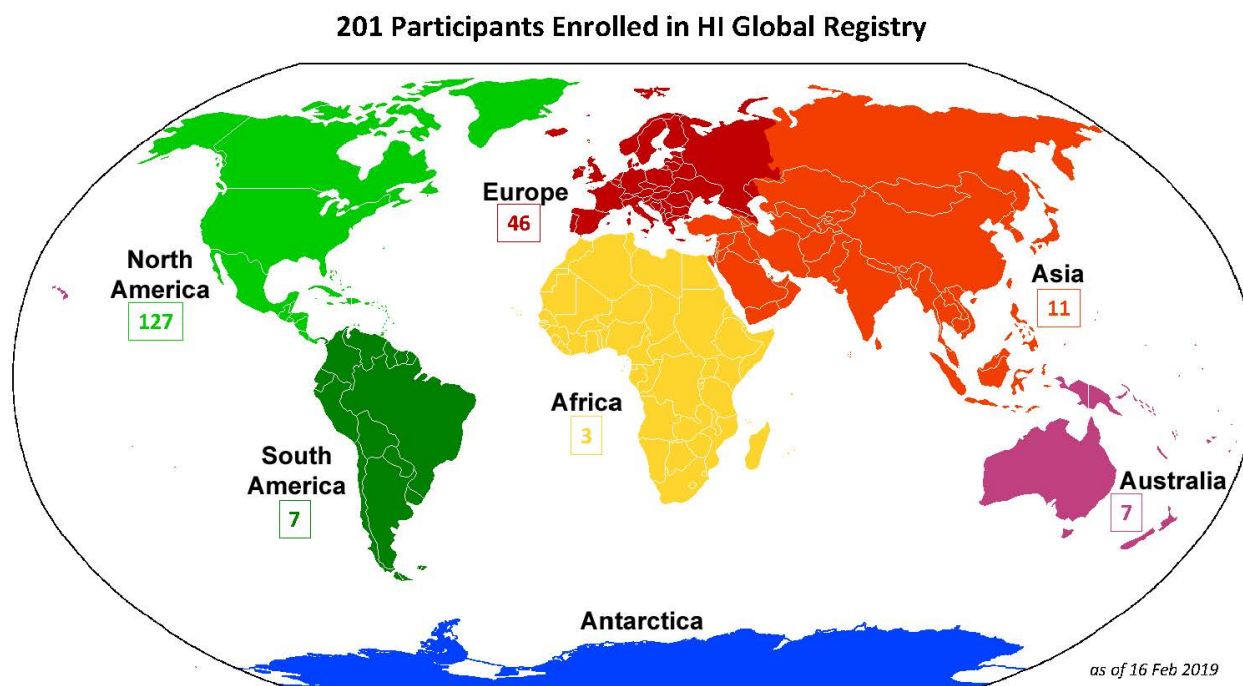
Figure 2. Summary of Stage 1 actions



Stage 2 is defined as the step when respondents (whether 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 fully describes the benefits and potential risks of participation in the HIGR study, participants may provide their agreement to all of the terms and conditions outlined in the consent form by clicking on the consent button. Currently the 211 registered respondents have generated 201 participants (26 adults, 175 minors) but only 172 participants (94% of the 201

participants) have completed the consent process, thus allowing access the survey questions. Figure 3 shows where each of the 201 participants reported living.

Figure 3. HIGR Participants, by continent



Stage 3 is defined as the step when a participant (or LAR on behalf of a participant) submits at least one survey. The investigators track both surveys in draft (survey begun but not deemed complete and ready for submission by the participant or LAR) and those that have been officially submitted to the registry's database. Currently 120 participants have at least one survey in draft, and 111 participants (55.2% of all potential registered participants) have submitted at least one survey.

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, 55 participants (27.4% of all potential registered participants) have completed all relevant surveys. For each available survey, the completion rate based on all potential registered HIGR participants is noted in Figure 4.

Figure 4. Survey completion rates

Survey	% Completed
Contact	51.7%
Demographics	46.3%
Pregnancy	46.3%
Birth	39.3%
Diagnosis	40.3%
- <i>genetics uploaded</i> -	6.0%
Diet and Feeding	31.3%
Medication	30.8%
Surgery	31.8%
Other Dx	31.3%
Glucose Monitoring	31.8%
Development	30.3%
QOL Parent	36.6%
QOL Participant	13.6%

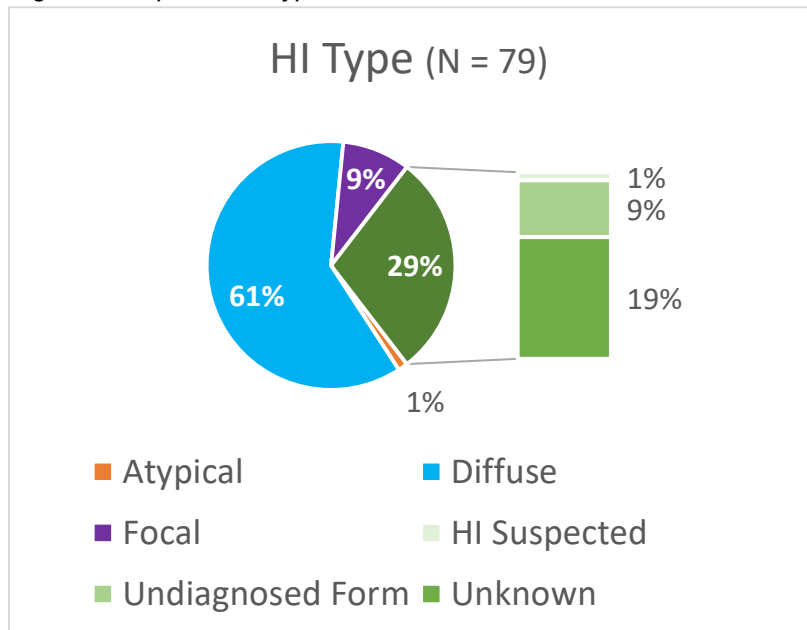
Prevalence

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. This information gives context to the sections that follow in this report.

HI Type:

Diffuse HI is a general term that includes several forms of HI that affect the entire pancreas, including K-ATP (potassium channel) defects, glucose dehydrogenase HI (GDH-HI, also known as hyperinsulinism hyperammonemia (HIHA)), glucokinase HI (GK-HI) and others. Figure 5 shows the proportion of reported HI types currently found in HIGR based on 79 participants. 61% report diffuse disease, 9% report focal and 1% report atypical. Of the remaining 29%, the responses include that HI is suspected but no formal diagnosis has been given (1%), the participant has an undiagnosed form of HI (9%), or the specific type of HI is unknown to the participant (19%).

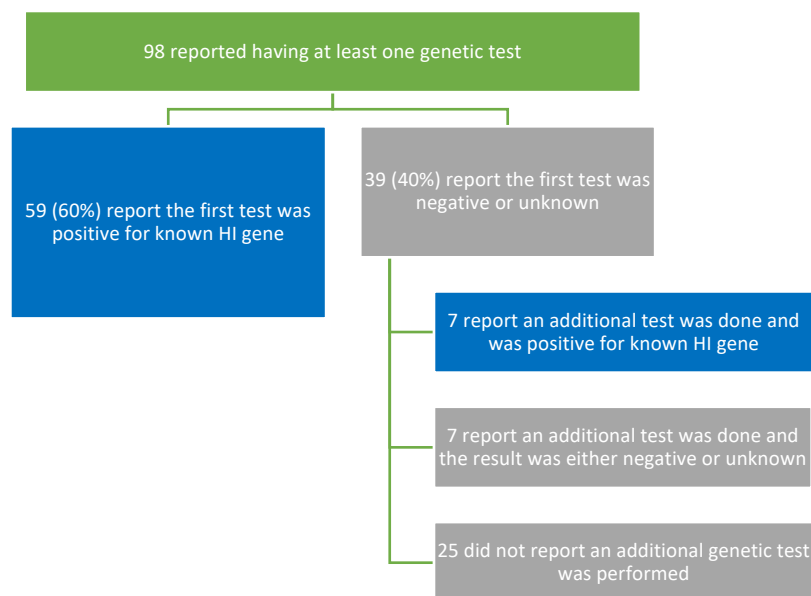
Figure 5. Reported HI types



Genetics:

As seen in Figure 6, 67% of the 98 participants reporting on genetic testing have positive results for a gene known to be associated with congenital hyperinsulinism. Of the 98 participants reporting having 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 genetics test, fourteen had a second test and half of those had positive results.

Figure 6. Percent positive genetic testing



There are a variety of reasons not explored for this report why additional testing may have been necessary. 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:

Of the 80 participants completing this question, four participants have an HI-related syndrome. A syndrome is a condition that is categorized by a set of symptoms that commonly occur together. The syndromes listed by HIGR participants include Kabuki, Turner, Fanconi and Rubinstein-Taybi, Type 2.

Abnormal Blood Sugar Before Leaving Birthing Facility

Figure 7. Percentage of participants reporting abnormal blood glucose prior to discharge from birthing facility.

Figure 7 shows that of 78 participants, 67% report that an abnormal blood glucose level was recorded before participant left the birthing facility.

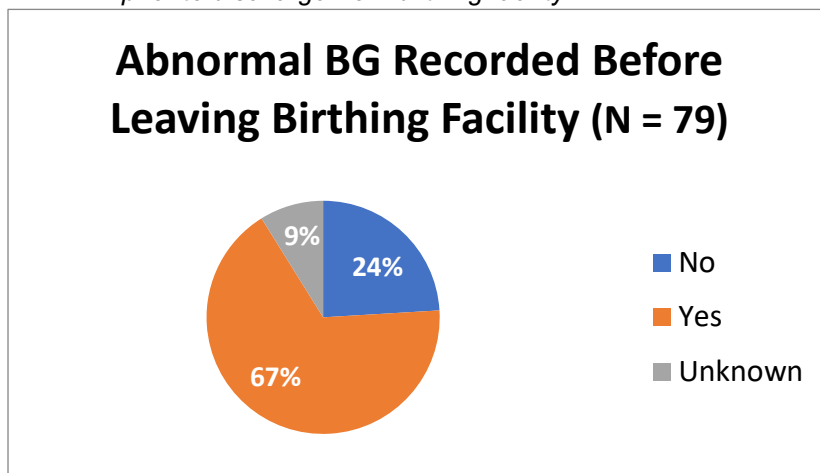
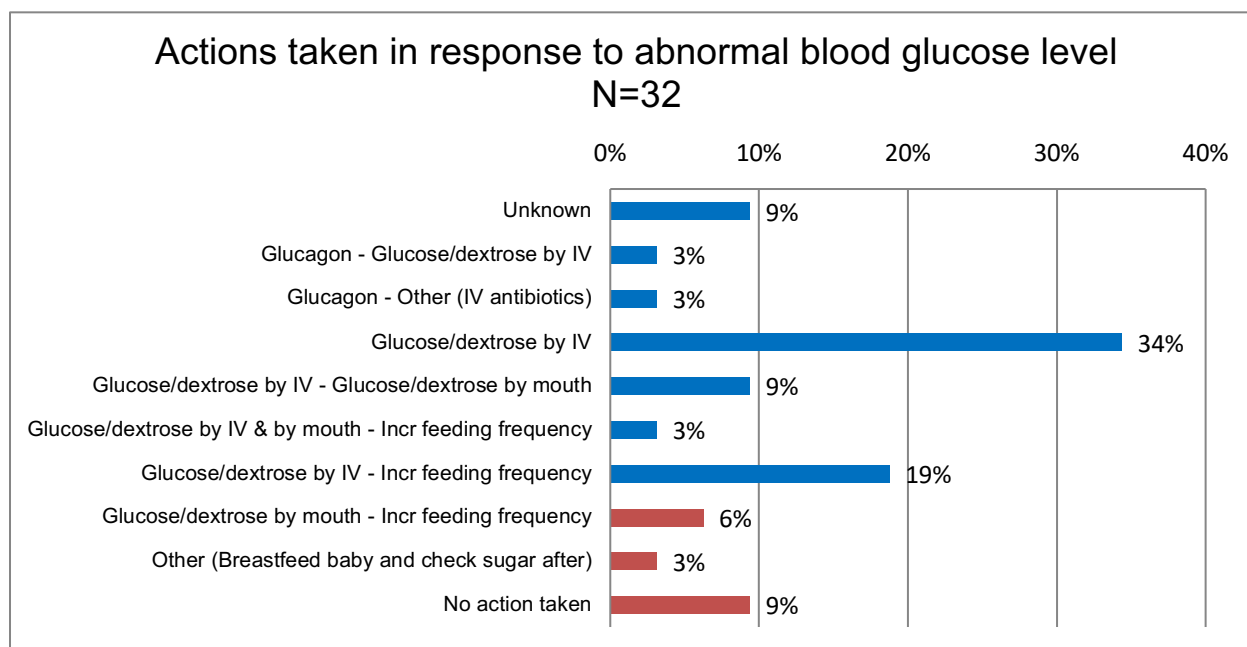


Figure 8 lists the reported action or combination of actions taken by healthcare professionals in response to the abnormal blood glucose readings of 32 participants. Actions including the use of glucagon were reported by 6% of the 32 participants; intravenous (IV) glucose administration was reported by 46%; and increased feeding frequency was reported by 21%. Actions limited to oral strategies to address the abnormal blood glucose level are noted in red on the figure. These were reported by 9% of participants, and another 9% reported no action was taken.

Figure 8. Reported responses to abnormal glucose levels reported before leaving the birthing facility.



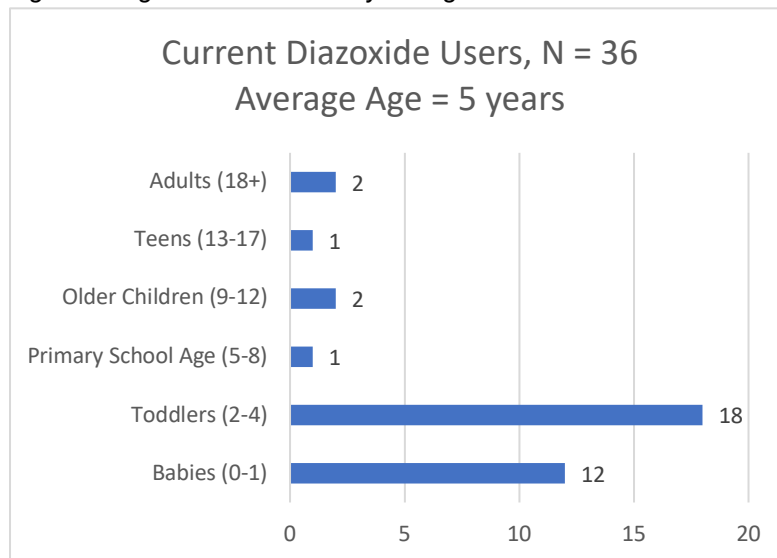
Of 39 participants reporting an abnormal blood glucose level before leaving the birthing facility, 74% also report receiving an HI diagnosis before leaving the hospital. Stated another way, one in four participants report that they did not receive an HI diagnosis before leaving the hospital after birth despite reporting an abnormal blood glucose level. Of those not receiving an HI diagnosis, seven report requiring one additional hospitalization before receiving an HI diagnosis; one reported two hospitalizations; one reported three to five hospitalizations; and one reported more than ten 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. For each type of medication, participants can report on past and current use and on side effects (among other questions). The HIGR also allows us to combine medication data with responses from other surveys such as the age of the participants and reported blood sugars. This section includes such cross-survey data reported by sixty (60) participants. A few (up to six participants) may have taken diazoxide and octreotide at the same time which could have an impact on the reports below. Those individuals are still included in the respective reports below and not separately analyzed.

Diazoxide:

Figure 9. Age of those currently taking diazoxide

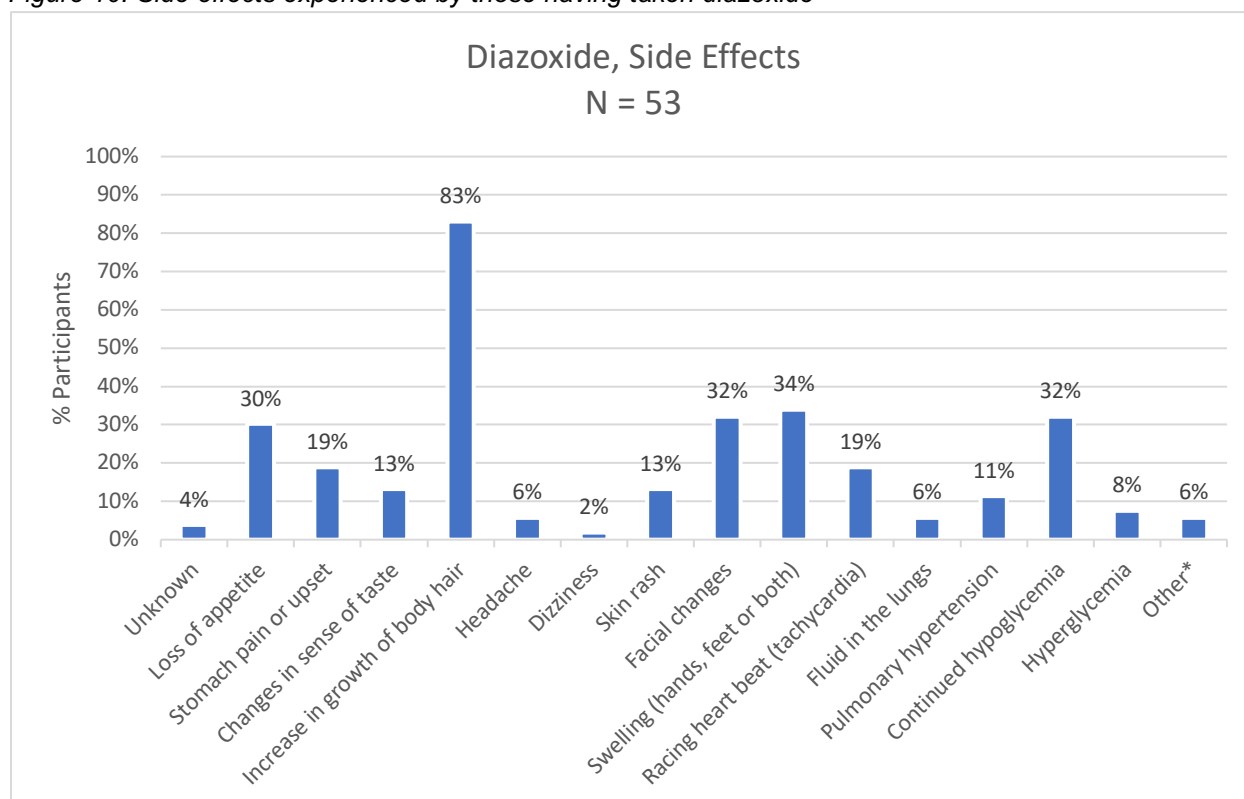


Of those who reported having taken diazoxide, 36 are currently taking diazoxide and seventeen have taken it in the past. The average age of those currently on diazoxide is five years old, with an age range of four months to 44 years.

Figure 9 shows the breakdown by age group of those currently taking diazoxide. Thirty participants (88%) of those reporting currently taking diazoxide are under the age of five years old.

As illustrated in Figure 10, 96% of those who reported having taken diazoxide (both past and current) experienced some adverse effect. The most common side effects include: increased body hair (44 participants, 83%), swelling (18 participants, 34%), facial changes (17 participants, 32%), continued hypoglycemia (17 participants, 32%) and loss of appetite (16 participants, 30%). Those participants reporting side effects other than the listed response choices noted hypertension, scrotal swelling and thrombocytopenia (low platelet count).

Figure 10. Side effects experienced by those having taken diazoxide



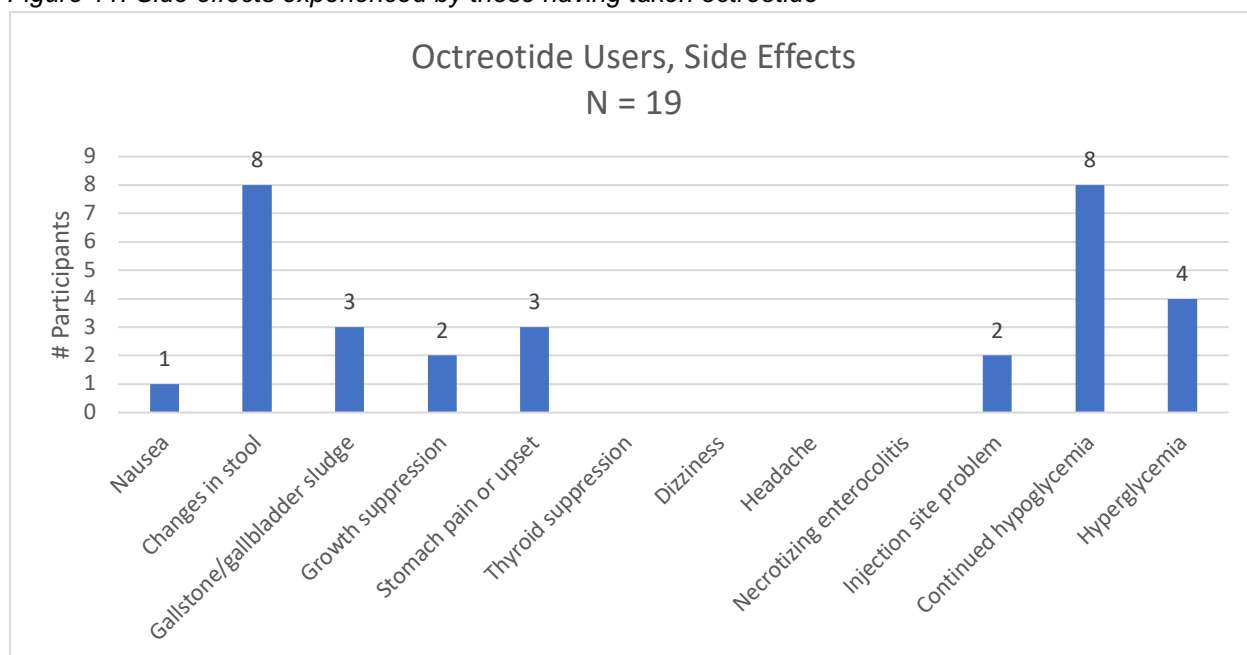
Thirty-two participants currently taking diazoxide reported on low blood sugar frequency. Eight (38%) of those participants (all ages included) experience at least one hypoglycemic event per week; four (13%) experience at least one hypoglycemic event per day.

Octreotide:

The following is a report that includes a small sample size. Of those who reported having taken octreotide, five are currently taking octreotide and fourteen have taken octreotide in the past. The average age of those currently taking octreotide is 2.6 years old, with an age range of eight months to four years.

Fifteen of those who reported having taken octreotide (both past and current) experienced some adverse effect (see Figure 11). The most common side effects include: changes in stool (8 participants, 42%), continued hypoglycemia (8 participants, 42%), hyperglycemia (4 participants, 21%), gallstones/gallbladder sludge (3 participants, 16%), and stomach pain or upset (3 participants, 16%). Some participants noted more than one side effect.

Figure 11. Side effects experienced by those having taken octreotide



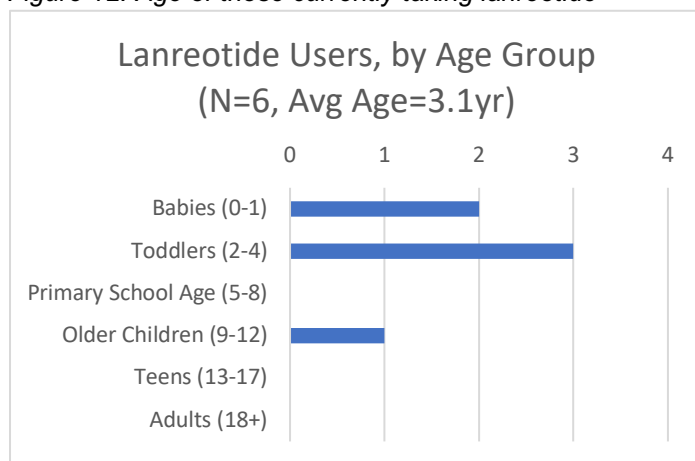
The threshold for reporting on participant glucose monitoring experience for those currently taking octreotide was not met at the time of this report.

Octreotide LAR:

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

Lanreotide:

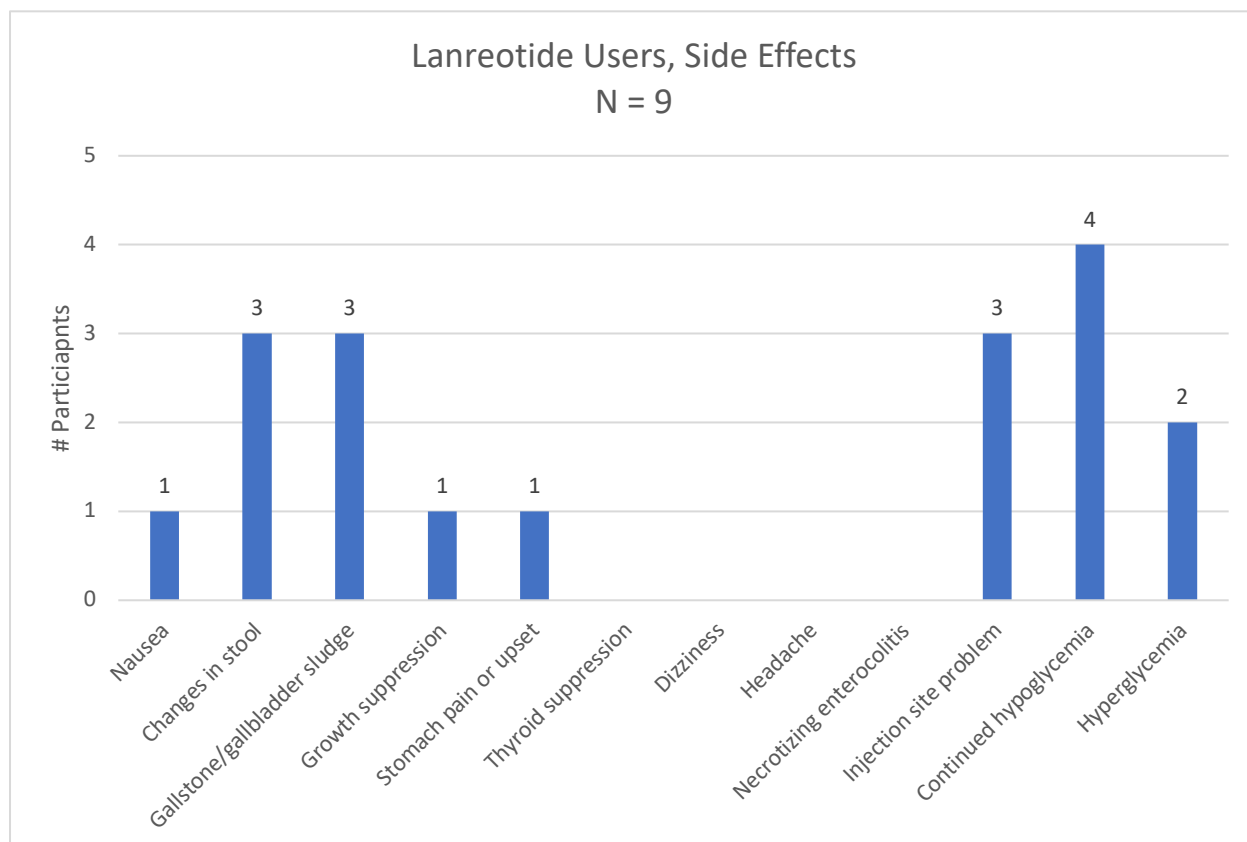
Figure 12. Age of those currently taking lanreotide



The following is a report that includes a small sample size. Of those who reported having taken lanreotide, six are currently taking lanreotide and three have taken it in the past. The average age of those currently taking lanreotide is 3.1 years old, with an age range of eight months to ten years. Figure 12 shows the breakdown by age group of those currently taking lanreotide.

Seven (78%) of those who have taken lanreotide injections (past and current) experienced some adverse effect (see Figure 13). The most common side effects include: continued hypoglycemia (4 participants, 44%), changes in stool (3 participants, 33%), gallstones/gallbladder sludge (3 participants, 33%), and hyperglycemia (2 participants, 22%). Some participants noted more than one side effect.

Figure 13. Side effects experienced by those having taken lanreotide



Six participants currently taking lanreotide reported on low blood sugar frequency, and four (67%) of those participants (all ages included) experience at least one hypoglycemic event per day.

Sirolimus:

Two participants reported taking sirolimus. Sirolimus duration of use ranged from 2-5 months for one participant and 1-2 years for the other. The threshold for reporting further analysis on the experience of these participants with this medication was not met at the time of this report.

Feeding Experience

The Diet and Feeding Management Survey collects data about past and feeding routes, schedules and potential issues. This section looks at reported feeding issues as well as the use of tube feeds to manage HI.

Figure 14 presents reported feeding issues for 60 participants who have completed the Diet and Feeding Management Survey. Results are grouped for all participants and also subdivided according to HI type. Other type of HI includes those reporting HI is suspected but not diagnosed, unknown HI type and atypical HI. Participants with diffuse HI are further subdivided into those who had a pancreatectomy and those who did not.

Of the 60 participants (all HI types and treatments included), 68% report having one or more feeding issue. Among the most commonly reported feeding issues, 84% report poor appetite or refusing to eat. Problems with texture and reflux were also commonly reported.

Figure 14. Reported feeding issues

Has the participant experienced any feeding issues on a regular basis (check all that apply)?	All participants		Diffuse			Focal	Other
	W/WO Surgery		No surgery	Pancreatectomy	Total	(4 surgery/1 no)	None had surgery
	N	%	N	N	N	N	N
No feeding issues	19	32%	9	1	10	2	6
Feeding issue(s)	41	68%	16	9	25	3	14
Poor appetite	25	42%	12	3	15	2	8
Refusing to eat	25	42%	9	4	13	2	10
Slow eating	15	25%	6	4	10		5
Overeating	7	12%	3	2	5	1	1
Uncoordinated oral skills	11	18%	4	4	8	1	2
Problems with texture	18	30%	6	5	11	1	6
Coughing	8	13%	7	4	7		1
Gagging	13	22%	5	3	8		5
Vomiting	14	23%	6	2	8	1	5
Reflux	18	30%	9	3	12	1	5
Other	2	3%					2
Total	60		25	10	35	5	20

Figure 15 shows the use of tube feeds of all types, nasogastric (NG), orogastric (OG), gastronomy button (G) and jejunostomy tube (J), in participants. Of the 60 participants (all HI types and treatments included) answering the question about routes of feeding, 57% report that tube feeding has been used to provide nutrition and/or background sugar to the participant since HI was suspected. Those with surgical interventions report the highest use of tube feeds.

Figure 15. 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
	W/WO Surgery		No surgery	Pancreatectomy	Total	(4 surgery/1 no)	None had surgery
	N	%	N	N	N	N	N
No Tube feeding	26	43%	13	0	13	2	11
Tube feeding (NG/OG/G/J)	34	57%	12	11	23	3	8
Total	60		25	11	36	5	19

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 and the outcomes of pancreatic surgery for the treatment of HI. The survey is intended for all participants, whether or not they required a pancreatectomy. As for the Other Diagnoses survey, it reports on conditions which may be associated with HI and in this section of the report we focus specifically on diabetes and pancreatic insufficiency.

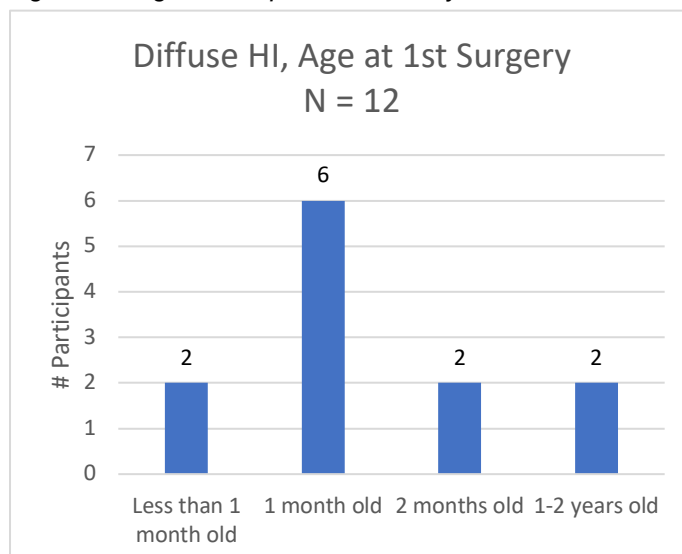
Twenty-four HIGR participants reported that a pancreatectomy was considered for the treatment of their HI, and eighteen of those 24 participants (75%) report undergoing at least one pancreatectomy. Of those eighteen that had a pancreatectomy, twelve (67%) reported diffuse HI, four (22%) reported focal HI, one reported atypical HI, and one provided no response about HI type.

Focal:

Five participants in HIGR report having focal HI. Four of those participants underwent at least one pancreatectomy, and one of the four required a second pancreatectomy. The reported participant age when the pancreatectomy was performed was less than one month old, one month old, five months old, and between 1-2 years old. The total amount of pancreas removed in focal participants, whether in a single surgery or combined for the participant requiring a second pancreatectomy, was evenly split between less than 25% (two participants) and between 25-49% (two participants). Due to the small sample size and young age of these participants, long-term outcomes are not included in this report.

Diffuse:

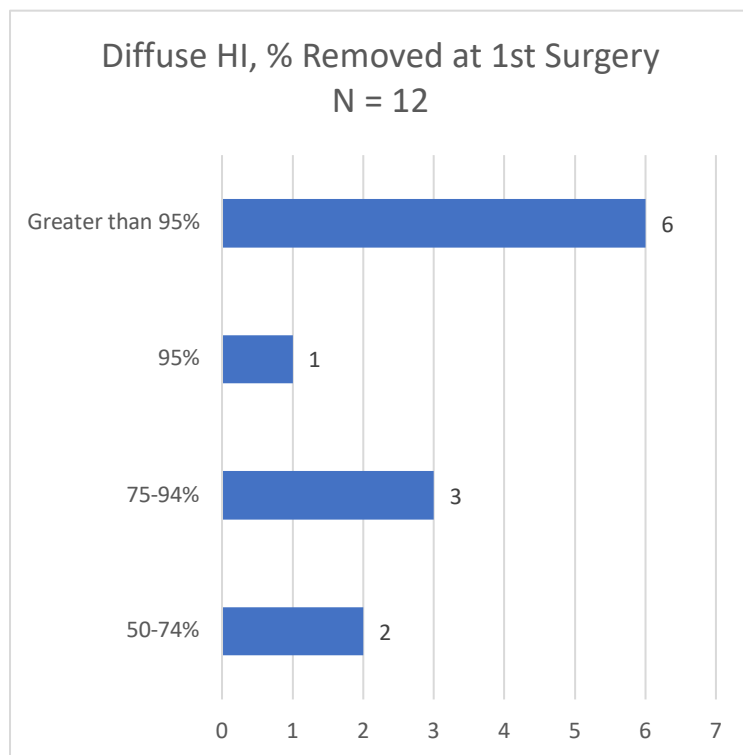
Figure 16. Age of first pancreatectomy in diffuse HI



Twelve participants that reported having at least one pancreatectomy have diffuse disease. At the moment of reporting, the age range of this group is seventeen months to 25 years old, with two-thirds under thirteen years old and one-third thirteen years or older. Figure 16 shows that of the twelve participants reporting diffuse HI and having undergone a pancreatectomy, eight (67%) had their first surgery during the first month of life; two (17%) had

their surgery during the second month of life and another two (17%) had surgery between 1-2 years old.

Figure 17. Percent of pancreas removed at first surgery in diffuse HI participants



In this group seen in Figure 17 of diffuse HI participants who underwent a pancreatectomy, seven (58%) reported at least a 95% pancreatectomy and five (42%) had less than 95% of their pancreas removed during their first surgery. Four participants (33%) required at least a second or subsequent pancreatectomy. Of those four participants, three (75%) had an initial pancreatectomy of less than 95%. One participant reported requiring a third pancreatectomy. Ten participants (83.3%) of this group report having a total of at least 95% of their pancreas tissue removed.

Four of the twelve of those with diffuse HI having undergone a pancreatectomy report having diabetes. Three of the four reporting a diagnosis of diabetes report being at least ten years old when diabetes was diagnosed. One participant reports diabetes developed in infancy shortly after undergoing a subtotal pancreatectomy. All but one of the remaining eight participants with diffuse HI, having undergone a pancreatectomy, and who do not report having diabetes, have not reached adolescent age. The lower percentage of diabetes currently reported in this group is not unexpected because it is reported that nearly all patients that undergo a subtotal pancreatectomy ultimately go on to develop insulin-dependent diabetes by adolescence (Bertrand, J Diabetes Care, 2011).

Three of those with diffuse HI having undergone a pancreatectomy report having pancreatic insufficiency (PI). Two of the three reporting being diagnosed with PI began taking pancreatic enzymes during infancy within months of their last pancreatectomy. One participant reported a diagnosis of PI and began taking pancreatic enzymes between 15-19 years old, many years after the pancreatectomy.

Medical Management Elected:

Twenty-four participants report that a pancreatectomy was considered by the medical team and family for the treatment of HI (all HI types, known and unknown, included in this count); of those, six participants report opting for medical management rather than undergoing a pancreatectomy. The six that did not have a pancreatectomy report either genetic tests consistent with KATP channel defects or unknown genetics, are non-diazoxide responsive, and/or require tube feeds for background glucose supplementation. The average age of those medically managed in this subgroup is currently 8.3 years old, with ages ranging from two to 23 years old.

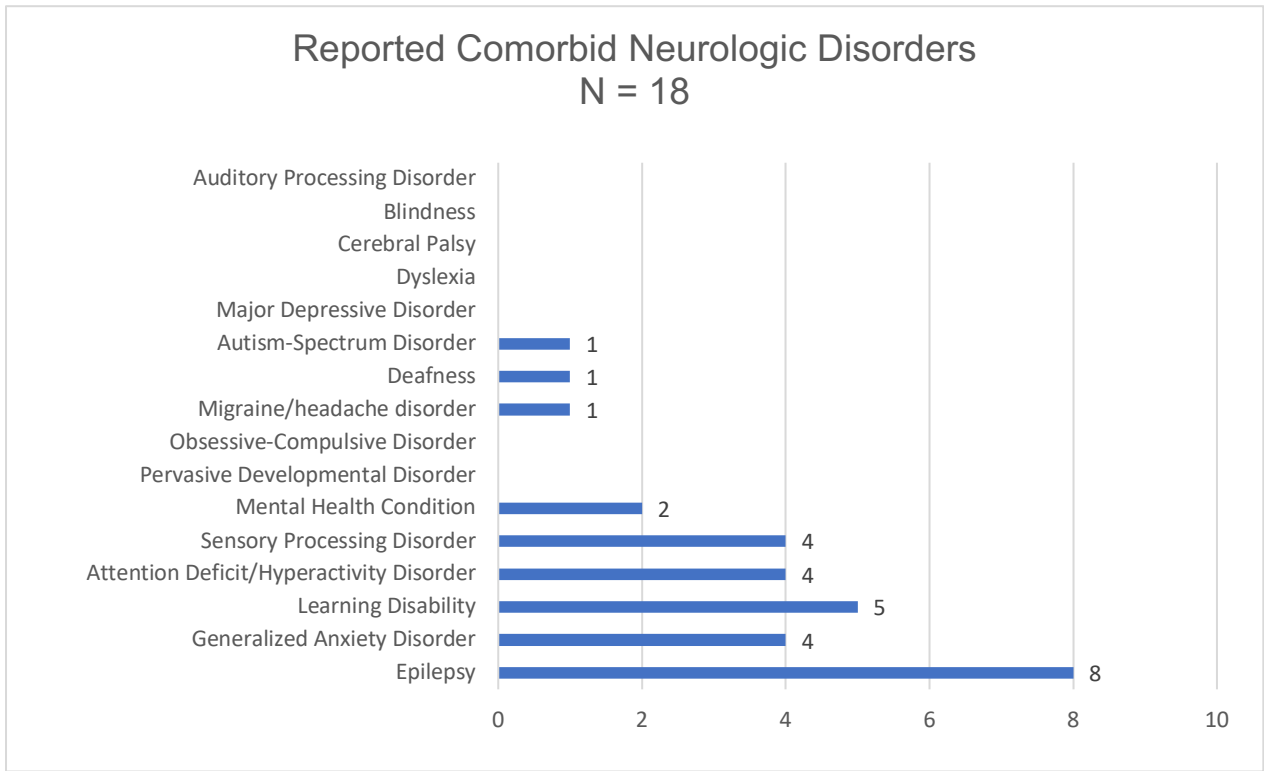
Neurologic Outcomes

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

Neurologic Disorder

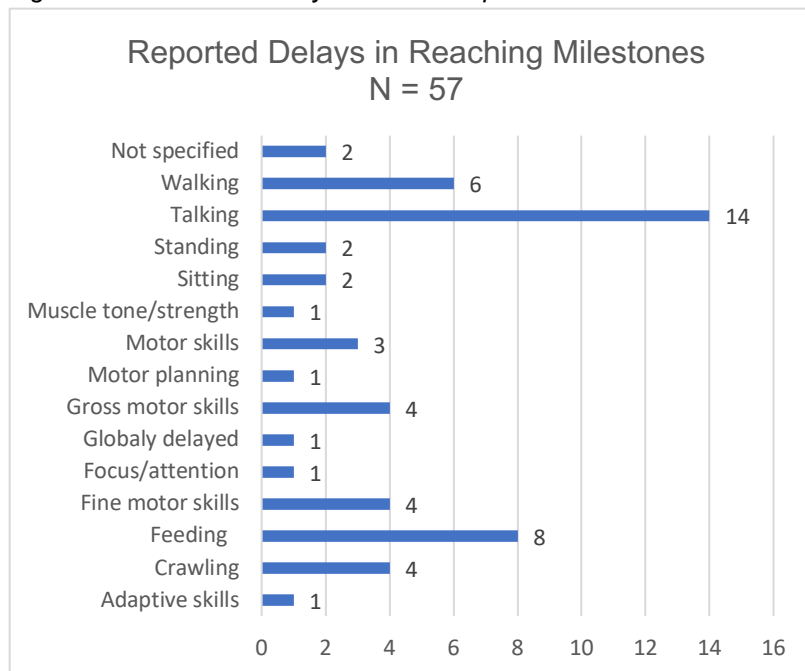
Eighteen (32%) of the 57 participants who completed the Other Diagnoses survey report having been diagnosed with a neurologic disorder. Epilepsy is the most commonly reported neurologic disorder, accounting for eight (44%) of those who report having a neurologic disorder. Figure 18 shows the other diagnoses reported. Some participants noted more than one disorder.

Figure 18. Reported neurologic disorders



Developmental Delay

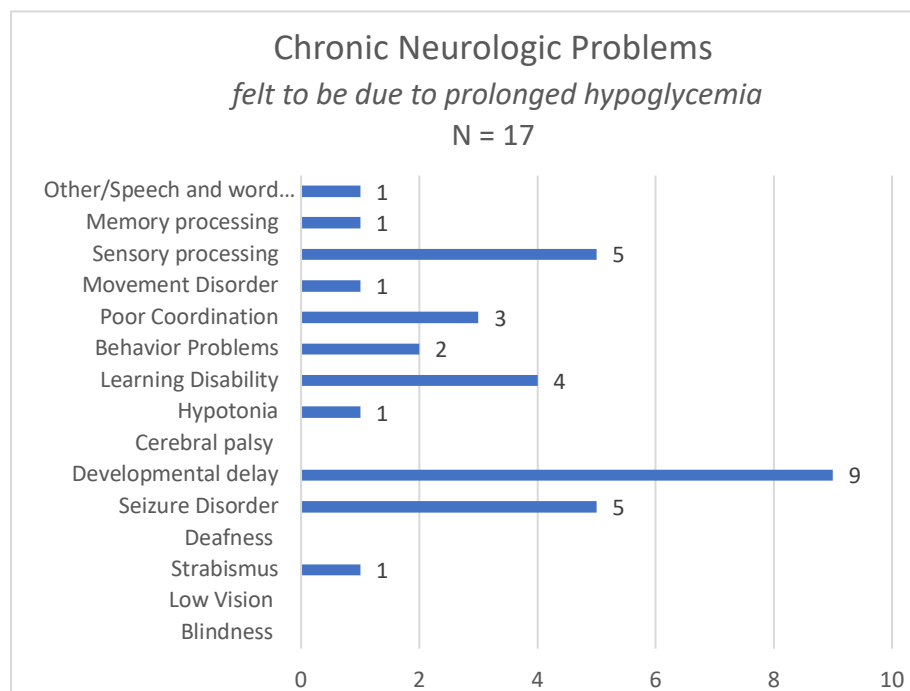
Figure 19. Milestone Delays in HI Participants



Of 57 participants who completed the Developmental survey, 26 participants (46%) report delays in reaching developmental milestones, including fourteen participants (25%) reporting delays in talking, eleven participants (19%) for motor-related skills, eight participants (14%) in feeding, and six participants (11%) in walking. Some participants noted more than one delay. Figure 19 shows all reported milestone delays.

Reported Neurologic Problem Felt to be Due to Prolonged Hypoglycemia

Figure 20. Reported chronic neurologic problems felt to be due to prolonged hypoglycemia



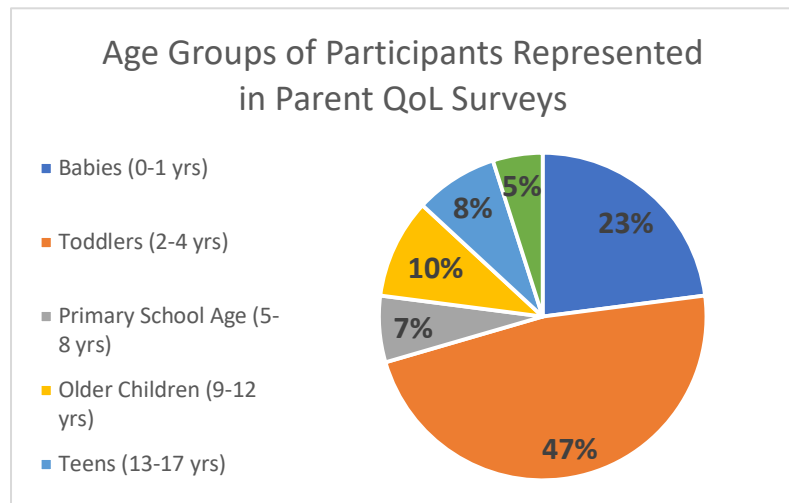
Seventeen (30%) of 57 participants report having a chronic neurologic problem which they feel is due to prolonged hypoglycemia. Figure 20 shows the list of neurologic problems reported by participants in this Developmental Survey question. Some participants noted more than one neurologic problem.

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 21. Participant ages as of February 16, 2019 represented in Parent QOL

Sixty-one parents of participants (only one parent for each participant) completed the Parent Quality of Life (QoL) survey. Figure 21 shows the age groups of the participants reflected in the QoL surveys in this report. As of February 16, 2019, the youngest child reflected in this QoL report is seven weeks; the oldest is 29 years old.



Parent Health

48% of parents of participants of all age groups report that their physical health has suffered from having a child with an HI-related condition.

69% of parents of participants of all age groups report that their mental health has suffered from having a child with an HI-related condition.

Family Planning, Relationships and Household Income

40% of HI parents of participants of all age groups report choosing not to have additional children, and another 27% report delaying having additional children. 58% of surveyed parents of all participant age groups report that having a child with HI strengthened their relationship with their partner; however, 30% reported a negative impact, including 5% who reported their relationship ended. 38% of parents of participants all age groups report that having a child with HI has negatively impacted their household income quite a lot or very much.

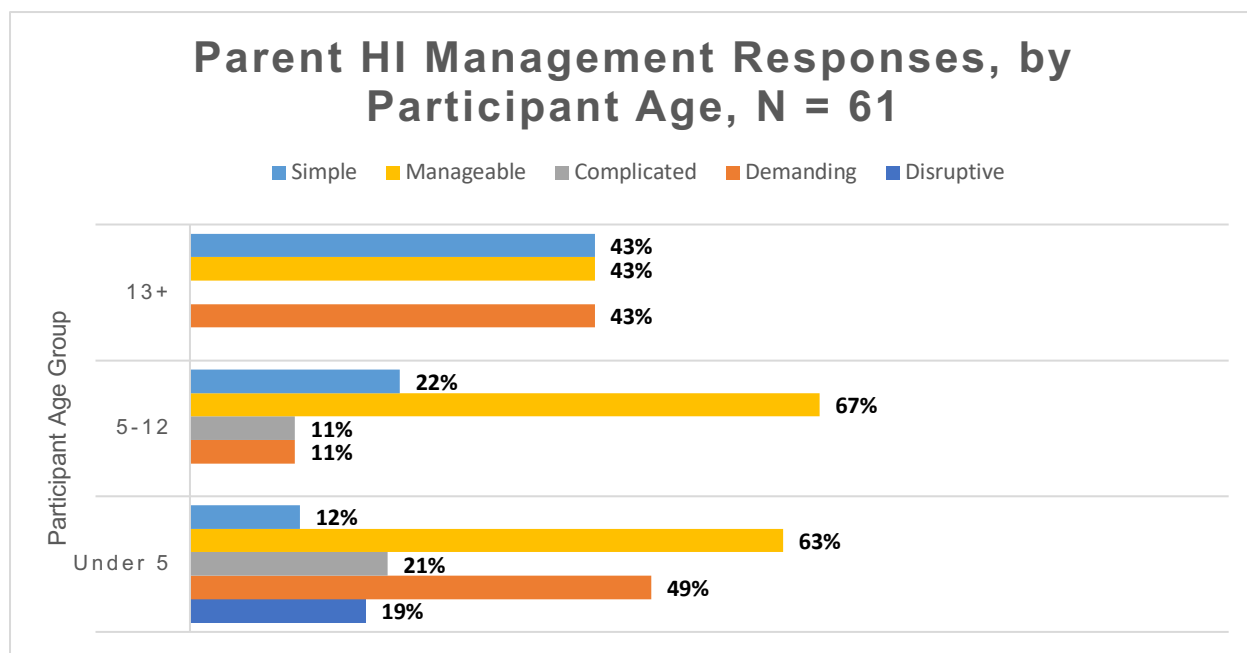
Management of HI

Figure 22 shows the various responses parents gave to describe the management of HI. Parents could select more than one response to this question. Parents of children with HI in each age group, including the adult age group still report the management of HI can be “demanding”. 49% of parents of children under five (N=43), 11% of parents with children 5-12 years old (N = 9), and 43% of parents with children thirteen or over (N=7) selected “demanding”.

Eight parents reported finding the management of their child's HI “disruptive”; 100% of those reporting disruptive were parents of children under five.

More parents of older participants select “simple” to describe the management of HI than parents of younger children. While only 12% of parents of children under five selected “simple”; 22% of parents of children 5-12 and 43% of parents of children thirteen and older selected “simple”.

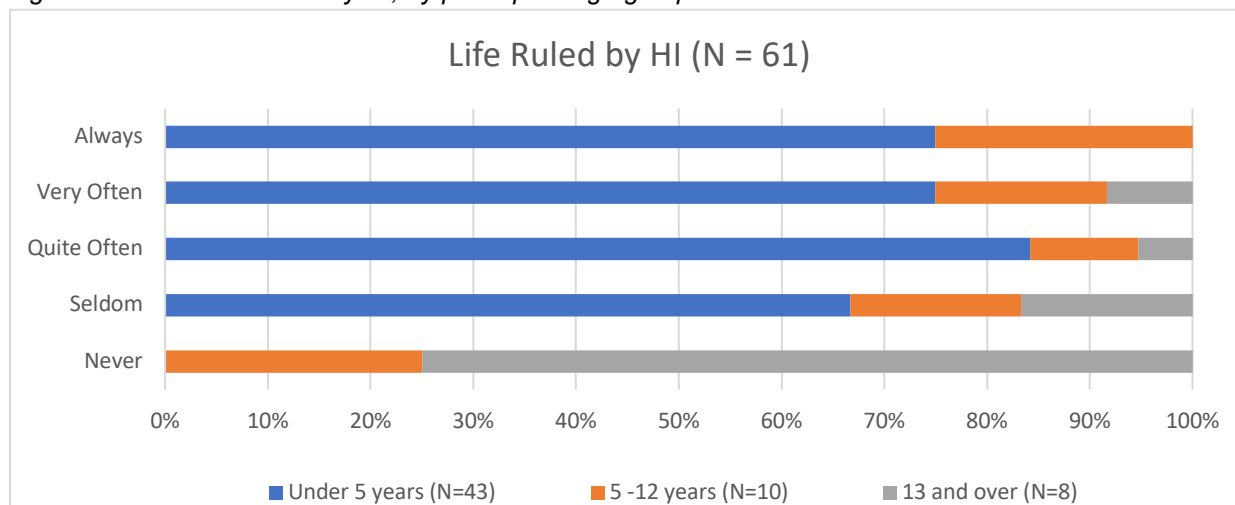
Figure 22. Parents’ responses to management of HI, by participant age group



General Quality of Life

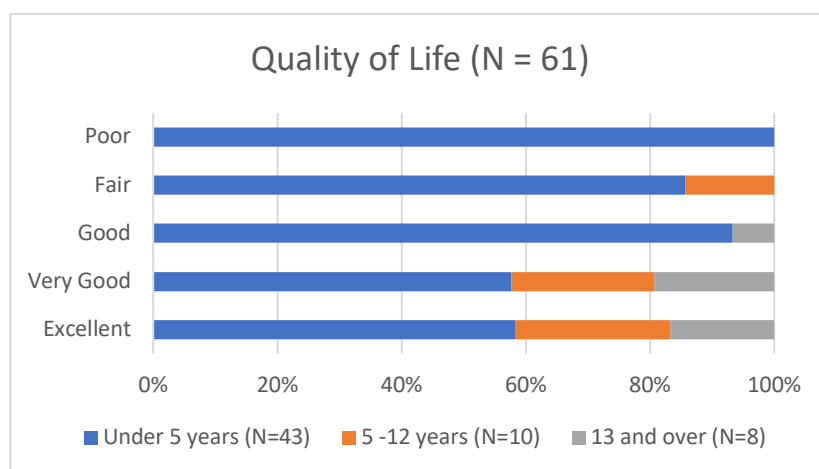
Fewer parents of older children report feeling their lives are ruled by HI. 72% of HI parents of children under five years old report they quite often, very often or always feel their lives are ruled by HI; this number decreases to 60% of HI parents of children aged 5 - 12 years and again to 25% for HI parents of children aged thirteen years and older. Figure 23 show the various responses of parents to this question by participant age group.

Figure 23. Parent life ruled by HI, by participant age group



Regardless of age group, all parents worry to some extent about their children. Fewer parents of older children report worrying about their child quite often, very often or always. 95% of parents of children under five years old, 90% of parents of children 5-12 years of age and 75% of parents of children thirteen years and older report worrying at least quite often.

Figure 24. General quality of life reported by parents, by participant age group



The general quality of life of an HI parent (see Figure 24) does appear to improve as children get older. 84% of HI parents of kids under five rank their QoL as good, very good or excellent; 90% of HI parents with children 5-12 years old and 100% of HI parents with children thirteen years old and older.

Discussion

This early glimpse into the high level data collected by HIGR between the date of its launch in October 2018 and mid-February 2019 lays the groundwork for an HI natural history study reported by those who live with the disease. However, due to the early nature of participation and limited number of full-survey responses, the reader should be 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 information as an introduction into the early data, addressing some of the topics frequently discussed by key HI community stakeholders.

One of the guiding tenets of this project is to be as transparent and inclusive as possible. Even before this report was created, the HIGR system platform has been producing data charts and graphs for participants to see. Those who have consented to participate in HIGR and submitted surveys can see data charts and graphs of many of the questions based on the compiled responses from all participants. These auto-generated graphs appear once a minimum of ten responses to a given question have been submitted and are an excellent source of information for participants. With this early data available to participants, the investigators decided to broaden this principle and share some of the early findings with the entire community of people interested in HI. The early data appears to align with some known features of the disease and its community: (1) the incidence of HI is global, occurring on every continent; (2) HI is not only a disease of the young; (3) there are many types of HI including those from known and unknown genetic causes; and (4) HI occurs together with a number of syndromes.

We can also begin to describe some facets of life for the participants who responded to the surveys and their families. For the group of participants that have responded: (1) feeding issues are very common; (2) adverse effects are frequently experienced for those taking currently available medication such as diazoxide, octreotide (and its long-acting formulations) and sirolimus; (3) hypoglycemia, the main problem caused by HI, is still a common feature of life for many who are receiving currently available treatments. A sizable number of those on HI medications (with and without a pancreatectomy) still experience hypoglycemia at least once a week; while a smaller group experiences hypoglycemia on a daily basis.

The small data pool on neurological issues is consistent with what is currently in the literature with respect to frequency. As reported above, almost half of the participants who have completed surveys on development, have experienced delays in reaching developmental milestones.

This report also demonstrates that life can feel ruled by the HI condition and its management, particularly for parents of younger children. While cause and effect is not specifically addressed here, one can easily imagine how the constant need to be

prepared to rapidly respond to blood sugar levels, frequently dipping so low that brain damage is a very real possibility, would lead to feeling ruled by HI.

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. However, HIGR also gives back to participants with real-time, up-to-date graphs that participants receive when they complete surveys. With consent, HIGR also provides those who enroll the opportunity to choose to network with other HI participants who share similar characteristics (regional or disease-specific) as well as to learn about clinical trials and research studies for which the participant may qualify. In the future, HIGR has the potential to give a great deal more back to the HI community by supporting current research, generating new insights into HI, driving new research for treatments and cures, supporting the success of clinical trials, and guiding standards of care from a patient and family-centered perspective.

HIGR is currently available 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 as well. With time, additional languages, better mobile integration, and more participants fully completing all available surveys, HIGR will truly reflect the global HI story. The HIGR team is actively pursuing the addition of other languages and encourages all those who are comfortable in English to enroll and complete the relevant surveys.

The future of HIGR depends on continuing to involve and include the HI community. 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.

The foundation for a HI natural history study has been established with the launch of HIGR. As participation grows, the pool of HI data will become increasingly more significant. The investigators intend to initiate an annual reporting process with more complete study data beginning in early 2020.

A key reason for sharing the data from early HIGR responses is 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.

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The authors would like to take the opportunity to thank everyone who made it possible to conduct this important research and present its findings to date in our first report. It has been a pleasure to work with everyone, and we are excited to share the current results and future discoveries.

To start, 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 authors would also like to thank Jacqueline Kraska, CHI's Registry and Research Director, for her commitment and assistance bringing this vital research program to fruition. Thank you to the CHI Research and Development Committee and HIGR Steering Committee who volunteer their invaluable expert advice and guidance to ensure the success of the HIGR research program.

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Key Words and Terminology

In order to provide background for reading this report, key terms that are frequently used are defined below.

- **HIGR** is the shortened name for the HI Global Registry Study, sometimes also just called the Registry.
- **Congenital Hyperinsulinism** is shortened to **HI**.
- The **Participant** is the patient (the person with HI). In this report “participants” refer to both adult participants and legally authorized representatives (LAR) reporting on behalf of minors or dependents
- The **Respondent** is the individual who completes the surveys, and can either be the participant or his or her parent, guardian or legally authorized representative (LAR).
- **LAR** is the shortened name for legally authorized representative who is legally authorized to input the data on behalf of the participant.
- The **Sponsor** (Congenital Hyperinsulinism International, CHI) is the organization responsible for the initiation, management, and financing of the HI Global Registry.
- **Investigators** are researchers who conduct the HI Global Registry Study, including producing de-identified reports, evaluating requests for de-identified data from third parties (such as, researchers, advocacy partners, biotechnology firms doing relevant work), and ensuring the safety and ethics of the HI Global Registry, in accordance with the Institutional Review Board (IRB) approved study documents. The investigators are also the authors of this report.
- The **HIGR Research Team** includes the Research Director, Investigators and other personnel who support the operations of the Registry.
- The **HIGR Steering Committee** is a collection of international HI representatives that provides oversight and expertise to the design and operation of the Registry from the patient, parent and clinical professional perspectives [<https://congenitalhi.org/hi-gr-steering-committee/>].
- An **Institutional Review Board** (IRB) is an appropriately constituted group that has been formally designated to review research to assure the protection of the rights and welfare of the human subjects. To accomplish this purpose, IRBs use a group process to review research protocols and related materials (e.g., informed consent documents and investigator brochures).