2022 Annual Report

Tai LS Pasquini, MPA, PhD[1], Mahlet Mesfin[2], Julie Raskin, MA[3]

[1]CHI Research and Policy Director and HIGR Principal Investigator, [2]CHI Research and Policy Associate, [3]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

Contents

Introduction

This year, we achieved some significant milestones with the HI Global Registry (HIGR). Since 2018, patients and caregivers in the congenital hyperinsulinism (HI) community have generously shared their experiences by completing the thirteen surveys in the registry. This year, we demonstrated the power of combining deidentified individual experiences to identify patterns in the data and to tell a more complete story. These patterns are incredibly valuable to researchers, clinicians, patients, and families. Patterns can help identify trends which can inform better care, identify similarities and differences between groups of patients, and evaluate how well a particular treatment works. Deidentified data from the registry was utilized in three peer-reviewed publications, presented at medical conferences, and requested by academic and industry researchers to inform research studies and clinical trials.

This report will provide a limited snapshot of the data from launch in October 2018 through October 2022 and more information about the successes achieved in the past year. The intended audience is the HI community: people living with HI, their families, and anyone interested in HI and its related research.

About HIGR

Congenital Hyperinsulinism International (CHI) sponsors HIGR which is governed by internationally recognized HI patient advocates and experts who are members of the HIGR Steering Committee. The registry consists of thirteen surveys made up of questions about the patient's experience with HI over their lifetime. These surveys include:

- Contact information
- Demographics
- Pregnancy
- Birth
- Diagnosis
- Medication management
- Diet & feeding management
- Surgical management
- Other diagnoses
- Development
- Glucose monitoring
- Quality of life (Parent/LAR)
- Quality of life (Participant)

The respondent can update certain surveys to allow data collection over time to study the natural history of HI. These updates are made at the respondent's discretion when there is a notable change in the participant's status, such as a new address, a change in treatment, or a newly diagnosed health condition. Other surveys are meant to be completed at specific time intervals. Researchers can track responses and data over time through these longitudinal surveys. The longitudinal surveys include glucose monitoring and the two quality of life surveys. Two surveys (Pregnancy and Birth) are final after the initial submission. An international team of HI experts, including parents of children with HI, advocates, clinicians, and researchers, created the survey questions.

HIGR data is stored on the secure cloud-based IAMRARE™ Platform developed and hosted by the National Organization for Rare Disorders (NORD). The IAMRARE™ Platform was created with input from patients, caregivers, and government stakeholders to ensure a safe and user-friendly system for study participation.

About the 2022 Annual Report

This report includes high-level data elements. Many of the data elements included in previous annual reports were well covered in the 2022 peer-reviewed publications. Individuals are encouraged to review these documents or contact the HIGR staff to access additional data that is of interest to readers or researchers. We also summarize each of these articles in Section 3 of this report.

Each graph or chart includes the number of participants who provided information related to each element. The variation in the number of individual responses is the result of three factors: 1) the majority of surveys and questions are optional, 2) some questions are dependent on a ' 'respondent's answers and the individual's unique natural history, and 3) participants/respondents complete surveys at their own pace. For each element reported, the number of participants is listed as "n" followed by an equal (=) sign and the count of participants in that chart or graph.

The investigators carefully consider the sample size and acknowledge that less than 30 participants is a small sample size. In small samples, the results may not represent all those with the same condition. For that reason, readers are cautioned not to draw overarching conclusions about HI in smaller subgroup (less than 30 participants) reports. Data analysis of participant subgroups of 30 or more is presented with greater confidence. Due to the expressed interest in particular data points, some smaller subgroup data has been included with a notice of caution stated for those topics.

This annual report is meant to foster an active dialogue about the data with the larger community of researchers, physicians, those with HI and their family members, regulators, drug developers, and other community stakeholders. 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 serve to strengthen HIGR. You can contact the HIGR team at info@higlobalregistry.org.

About CHI

CHI is a leading nonprofit dedicated to improving the lives of children and adults living with HI. CHI provides information, resources, and support to the HI community worldwide. CHI advocates on behalf of patients for better treatments and access to care. CHI is dedicated to increasing awareness of the disorder as it leads to more timely diagnosis and the best outcomes for patients. CHI supports medical research for improved therapies, potential cures, and timely diagnosis. CHI works globally because we are stronger as an international community. Cooperation across borders fosters essential advances in medicine. To learn more about CHI, please visit https://congenitalhi.org/.

Note from the HIGR Investigators

We are so grateful for the support and participation of the entire HI community to grow and utilize HIGR data. In 2022, we had the opportunity to connect with many members of the HI community and representatives from other patient organizations related to best practices in registries and natural history studies. These conversations provided new approaches for us to think about registry engagement, data validation, and how we can support the HI research community, now and in the future.

In December 2020, CHI launched a collaborative research network. A collaborative research network (CRN) is a network of patients and families, physicians, researchers, and patient organizations working together to accelerate research and cures for a particular disease. The CHI CRN brings togethter clinicians, researchers, and patient advocates from 18 countries. The mission of the CRN is to maintain an HI collaborative research network that puts patients at the center of a strategy that leads to faster and more accurate diagnosis, drives new evidence-based treatments and cures, standardizes clinical guidelines, and facilitates increased and improved access.

In 2021 and 2022, the workstreams met virtually 42 times to identify the gaps that would form a prioritized research agenda. CRN members met in person for the first time in Lisbon, Portugal, in May 2022. During that meeting, CHI CRN members engaged as one group with members from other workstreams and corners of the world to discuss each workstream's findings and finalize the research agenda.

In each workstream, natural history studies were identified as a pressing need. HIGR surveys, alongside complementary data from physicians and CGMs, provide the most promising approach for creating and documenting the natural history of HI. Future directions for HIGR include providing more natural history for the CHI CRN. We believe the registry provides a strong foundation for supporting the work of the CRN and other research inquiries that can benefit from patient-reported data.

Protocol Objectives

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

The HIGR Steering Committee, made up of international researchers, clinicians, and advocates, drafted the protocol. HIGR functions as a natural history study, meaning HIGR will collect specific health-related and quality of life information over time from its participants to understand how HI develops, how it is treated, and how it impacts health and life. The objectives (or goals) of HIGR remain unchanged. The ultimate goal of HIGR is to advance the global understanding of HI and drive research toward better treatments and, ultimately, a cure.

The primary objectives of HIGR are:

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

The secondary objectives of HIGR are:

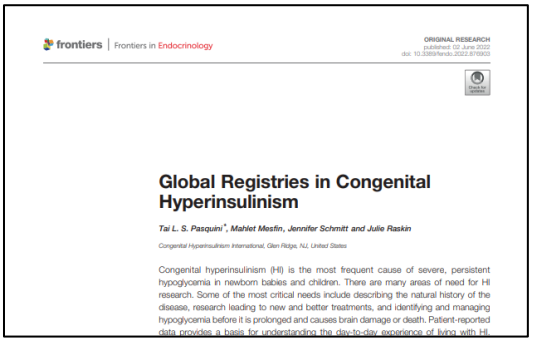
- To document the obstacles to accessing HI care, supplies, and medications.
- To measure the impact of HI and its management on patients' and caregivers' quality of life.
- To aid CHI and/or other country or region-specific HI patient organizations in identifying like genotypes or similar conditions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

HIGR 2022 – A Year in Review

Publications

In 2022, three-peer reviewed publications utilized deidentified data from HIGR. Inclusion of HIGR data in peer-reviewed medical literature suggests scholars and medical journal editors consider the data to have scientific merit. As part of the medical literature, HIGR data and analysis can be utilized and reviewed by other researchers interested in the content. In addition to research purposes, these publications are a source of information for people living with HI, clinicians of HI patients, and medical and nursing students. The addition of HIGR data in the medical literature is a noteworthy in HIGR's development because it validates patient-led patient reported HI research as a suitable resource for answering important questions related to living with HI. You can find a link to these articles on the CHI website.

Global Registries in Congenital Hyperinsulinism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ORIGINAL RESEARCH

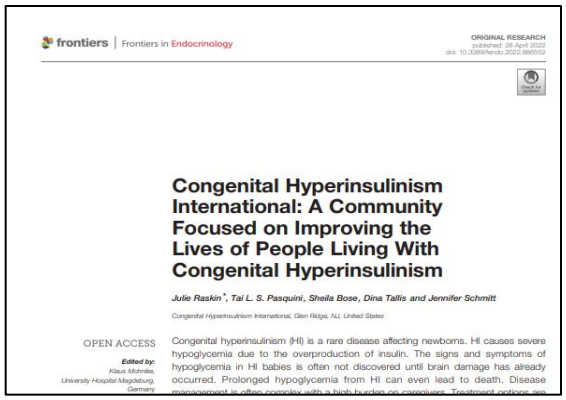
Global Registries in Congenital Hyperinsulinism

Tal L. S. Pasquini*, Mahlet Mesfin, Jennifer Schmitt and Julie Raskin

Congenital Hyperinsulinism International, Glen Ridge, NJ, United States

Congenital hyperinsulinism (HI) is the most frequent cause of severe, persistent hypoglycemia in newborn babies and children. There are many areas of need for HI research. Some of the most critical needs include describing the natural history of the disease, research leading to new and better treatments, and identifying and managing hypoglycemia before it is prolonged and causes brain damage or death. Patient-reported data provides a basis for understanding the day-to-day experience of living with HI.

This article, published in Frontiers in Endocrinology, characterizes HI through the experience of individuals who live with it. It includes descriptive statistics on the birthing experience, hospitalizations, medication management, feeding challenges, experiences with glucose monitoring devices, and the overall disease burden to provide insights into the data in the HI Global Registry (HIGR) and demonstrate the potential areas of future research.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ORIGINAL RESEARCH

Congenital Hyperinsulinism International: A Community Focused on Improving the Lives of People Living With Congenital Hyperinsulinism

Julie Raskin*, Tal L. S. Pasquini, Sheila Bose, Dina Tallis and Jennifer Schmitt

Congenital Hyperinsulinism International, Glen Ridge, NJ, United States

OPEN ACCESS

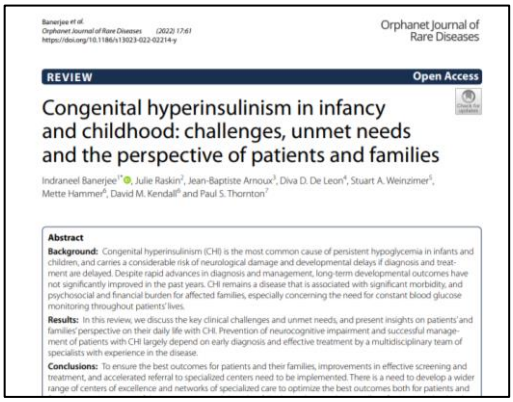
Edited by: Klaus Mohnike, University Hospital Magdeburg, Germany

Congenital hyperinsulinism (HI) is a rare disease affecting newborns. HI causes severe hypoglycemia due to the overproduction of insulin. The signs and symptoms of hypoglycemia in HI babies is often not discovered until brain damage has already occurred. Prolonged hypoglycemia from HI can even lead to death. Disease

Congenital Hyperinsulinism International: A Community Focused on Improving the Lives of People Living With Congenital Hyperinsulinism

This article, published in Frontiers in Endocrinology, describes the current challenges of living with HI, including diagnosis and disease management told from the perspective of people who live with the condition, shares family stories of life with HI, and how CHI is working to improve the lives of HI patients and their families.

Congenital Hyperinsulinism in infancy and childhood: challenges, unmet needs, and the perspective of patients and families


Banerjee et al. Orphanet Journal of Rare Diseases (2022) 17:61 https://doi.org/10.1186/s13023-022-02214-y

Orphanet Journal of Rare Diseases

REVIEW Open Access

Congenital hyperinsulinism in infancy and childhood: challenges, unmet needs and the perspective of patients and families

Indraneel Banerjee[1*], Julie Raskin[2], Jean-Baptiste Arnoux[3], Diva D. De Leon[4], Stuart A. Weinzimer[5], Mette Hammer[6], David M. Kendall[6] and Paul S. Thornton[7]

Abstract

Background: Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in infants and children, and carries a considerable risk of neurological damage and developmental delays if diagnosis and treatment are delayed. Despite rapid advances in diagnosis and management, long-term developmental outcomes have not significantly improved in the past years. CHI remains a disease that is associated with significant morbidity, and psychosocial and financial burden for affected families, especially concerning the need for constant blood glucose monitoring throughout patients' lives.

Results: In this review, we discuss the key clinical challenges and unmet needs, and present insights on patients' and families' perspective on their daily life with CHI. Prevention of neurocognitive impairment and successful management of patients with CHI largely depend on early diagnosis and effective treatment by a multidisciplinary team of specialists with experience in the disease.

Conclusions: To ensure the best outcomes for patients and their families, improvements in effective screening and treatment, and accelerated referral to specialized centers need to be implemented. There is a need to develop a wider range of centers of excellence and networks of specialized care to optimize the best outcomes both for patients and

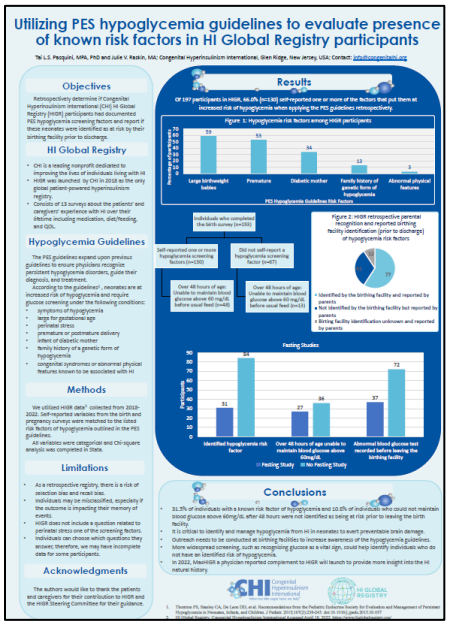
This article was published in Orphanet Journal of Rare Diseases. The perspective of families and patients with HI is published together with insights from clinical experts. In this publication, the authors Indraneel Banerjee, Julie Raskin, Jean-Baptiste Arnoux, Diva D. De Leon, Stuart A. Weinzimer, Mette Hammer, David M. Kendall, and Paul S. Thornton present the key clinical challenges and unmet needs, infused with knowledge from the patient and family perspective on daily life with HI.

Posters

Medical meetings present opportunities for professionals within a particular field to come together and learn about important topics, share new research, and network. CHI often participates in medical and

rare disease meetings to raise awareness of HI. CHI has also submitted proposals to present posters with HI research at medical meetings.

Utilizing PES hypoglycemia guidelines to evaluate presence of known risk factors in HI Global Registry participants

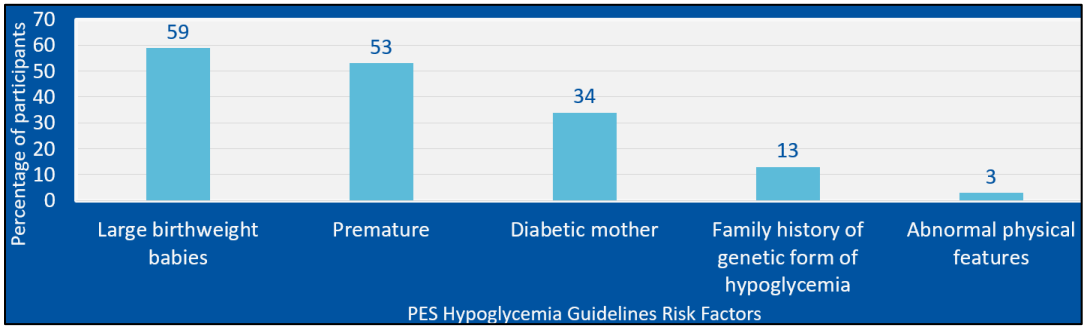


The European Society for Paediatric Endocrinology (ESPE) meeting took place between September 15 and 17th in Rome, Italy. The objective of CHI's poster was to retrospectively determine if HIGR participants had documented PES hypoglycemia screening factors[1] and to report if these neonates were identified as at risk by their birthing facility before discharge. Self-reported variables from the birth and pregnancy surveys were matched to the listed risk factors of hypoglycemia outlined in the PES guidelines. All variables were categorical, and Chi-square analysis was completed in Stata.

Of 197 participants in HIGR, 66.0% (n=130) self-reported one or more of the factors that put them at increased risk of hypoglycemia when applying the PES guidelines retrospectively.

31.5% of individuals were found to have a known risk factor of hypoglycemia and 10.8% of individuals who could not maintain blood glucose above 60 mg/dL after 48 hours were not identified as being at risk before leaving the birth facility. Identifying and managing hypoglycemia from HI in neonates is critical to avert preventable brain damage. Outreach must be conducted at birthing facilities to increase awareness of the hypoglycemia guidelines. More widespread screening, such as recognizing glucose as a vital sign, could help identify individuals who do not have an identified risk of hypoglycemia.

Figure 1: Hypoglycemia risk factors among HIGR participants

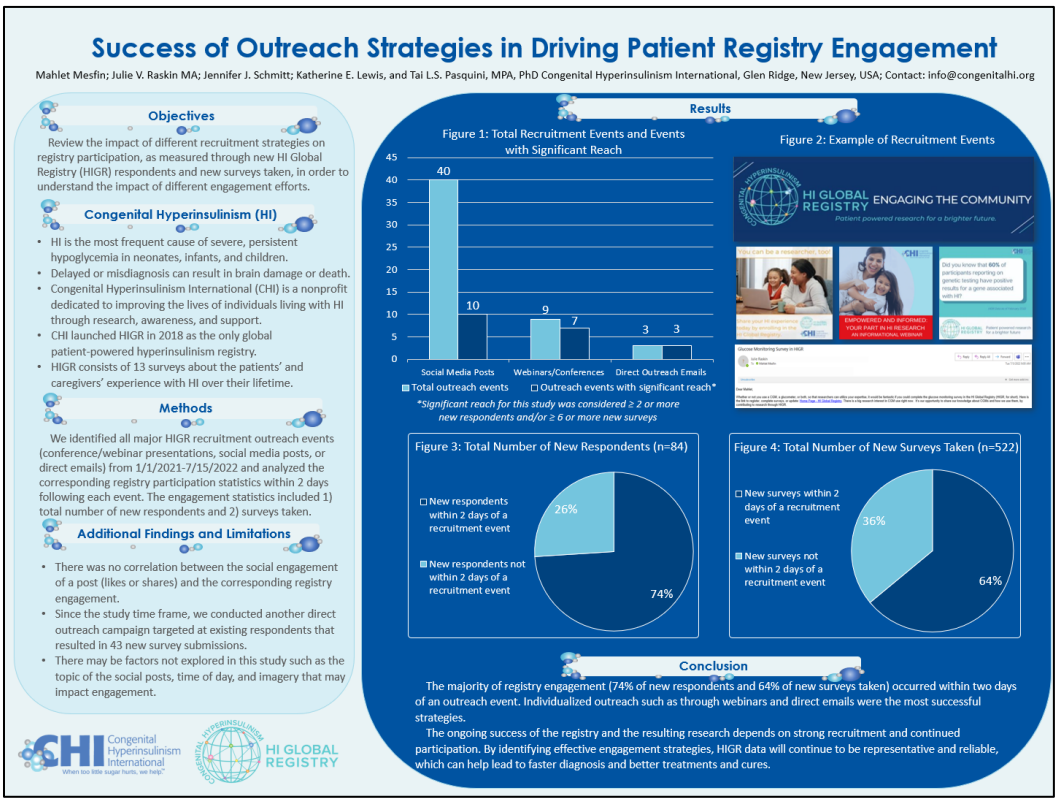


Success of Outreach Strategies in Driving Patient Registry Engagement

The National Organization for Rare Diseases (NORD) 2022 Breakthrough Summit® was held in Washington, DC, from October 17-18. The objective of this poster was to review the impact of different recruitment strategies on registry participation, as measured through new HIGR respondents and surveys taken, to understand the impact of different engagement efforts. All major HIGR recruitment outreach events were identified (conference/webinar presentations, social media posts, or direct emails) from 1/1/2021-7/15/2022, corresponding registry participation statistics were analyzed

[1] Thornton PS, Stanley CA, De Leon DD, et al. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. J Pediatr. 2015;167(2):238-245. doi:10.1016/j.jpeds.2015.03.057

within 2 days following each event. The engagement statistics included 1) total number of new respondents and 2) surveys taken.



Most registry engagement (74% of new respondents and 64% of new surveys taken) occurred within two days of an outreach event. The most successful strategies were individualized outreach, such as through webinars and direct emails. The ongoing success of the registry and the resulting research depends on strong recruitment and continued participation. By identifying effective engagement strategies, HIGR data will continue to be representative and reliable, which can help lead to faster diagnosis and better treatments and cures.

MaxHIGR

Maximizing the Utilization of the HI Global Registry (MaxHIGR) is a new project to grow and expand the research possibilities in HIGR. Through MaxHIGR, patients can add physician-provided information to HIGR, which will enhance its value and impact.

Any HI patient or caregiver who has completed the relevant HIGR surveys and is interested in participating can have their endocrinologist fill out the MaxHIGR form, which will be returned to them for upload into HIGR. MaxHIGR will add physicians' information to increase HI research opportunities by complementing patient-reported responses in the registry.

The MaxHIGR physician form adds physician-collected treatment and diagnosis details in that will complement the existing patient-provided information in HIGR. Together. MaxHIGR and HIGR are a powerful resource set for continued explorations into the natural history of HI and an understanding of the individual's and caregiver's quality of life, both essential for the development of new treatments and cures.

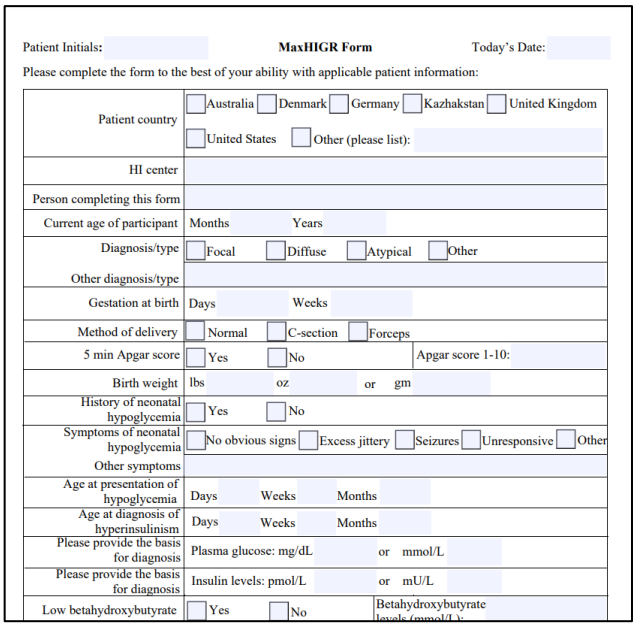
The MaxHIGR pilot project was funded through a Million Dollar Bike Ride grant awarded to Dr. Indraneel Banerjee of the University of Manchester and the Royal Manchester Children's Hospital. Researchers from leading HI institutions worldwide are partnering with Dr. Banerjee and CHI on this project.

Any respondent who has consented to participate in HIGR and has completed all relevant HIGR surveys can participate in MaxHIGR.

How can someone join?

If you are a caregiver of someone living with HI or an adult living with HI and have not already done so, register and join HIGR. If you have registered for HIGR, log in to your profile and complete all surveys.

Once you have completed all surveys, CHI will send you an email stating that you are eligible to join the MaxHIGR, which is a sub-study of HIGR. You should also see a green "More" button in your HIGR profile inviting you to join MaxHIGR. Once you click this link in your profile, you will be asked to read an informed consent document and agree to join the study. You can view a step-by-step guide here.



Patient Initials: **MaxHIGR Form** Today's Date:

Please complete the form to the best of your ability with applicable patient information:

Patient country	☐ Australia ☐ Denmark ☐ Germany ☐ Kazhakstan ☐ United Kingdom ☐ United States ☐ Other (please list):
HI center	
Person completing this form	
Current age of participant	Months Years
Diagnosis/type	☐ Focal ☐ Diffuse ☐ Atypical ☐ Other
Other diagnosis/type	
Gestation at birth	Days Weeks
Method of delivery	☐ Normal ☐ C-section ☐ Forceps
5 min Apgar score	☐ Yes ☐ No Apgar score 1-10:
Birth weight	lbs oz or gm
History of neonatal hypoglycemia	☐ Yes ☐ No
Symptoms of neonatal hypoglycemia	☐ No obvious signs ☐ Excess jittery ☐ Seizures ☐ Unresponsive ☐ Other
Other symptoms	
Age at presentation of hypoglycemia	Days Weeks Months
Age at diagnosis of hyperinsulinism	Days Weeks Months
Please provide the basis for diagnosis	Plasma glucose: mg/dL or mmol/L
Please provide the basis for diagnosis	Insulin levels: pmol/L or mU/L
Low betahydroxybutyrate	☐ Yes ☐ No Betahydroxybutyrate levels (mmol/L):

Once you have granted your consent to participate, complete the "MaxHIGR First Step" survey to choose whether you prefer to contact your physician, asking them to complete the MaxHIGR form, or prefer for CHI to contact your physician on your behalf. Once your physician completes the MaxHIGR form, they will provide you with a PDF copy that you can upload into HIGR. In your survey list, you will see the "MaxHIGR Second Step" survey, where you can upload the completed form from your physician.

Data Snapshot

Characteristics of HIGR Participants and Diagnosis

There are many areas of need for HI research, beginning with understanding the characteristics and diagnostic journeys of different patient communities. By analyzing the characteristics of HIGR participants, we can better define each type of HI patient while targeting our research to represent all patients.

HI occurs worldwide, and the global prevalence (or frequency) of HI is poorly understood. HIGR has the potential to help calculate this vital figure one day. Figure 2 shows that HIGR has participants from 51 countries. Individuals completed a total of 2,684 surveys. There is a wide range of ages among HIGR participants, from just a few weeks old to 77 years old (Figure 3). Unless otherwise noted, the data presented in this report reflects the information in HIGR as of November 1, 2022.

Figure 2. HIGR participants by continent

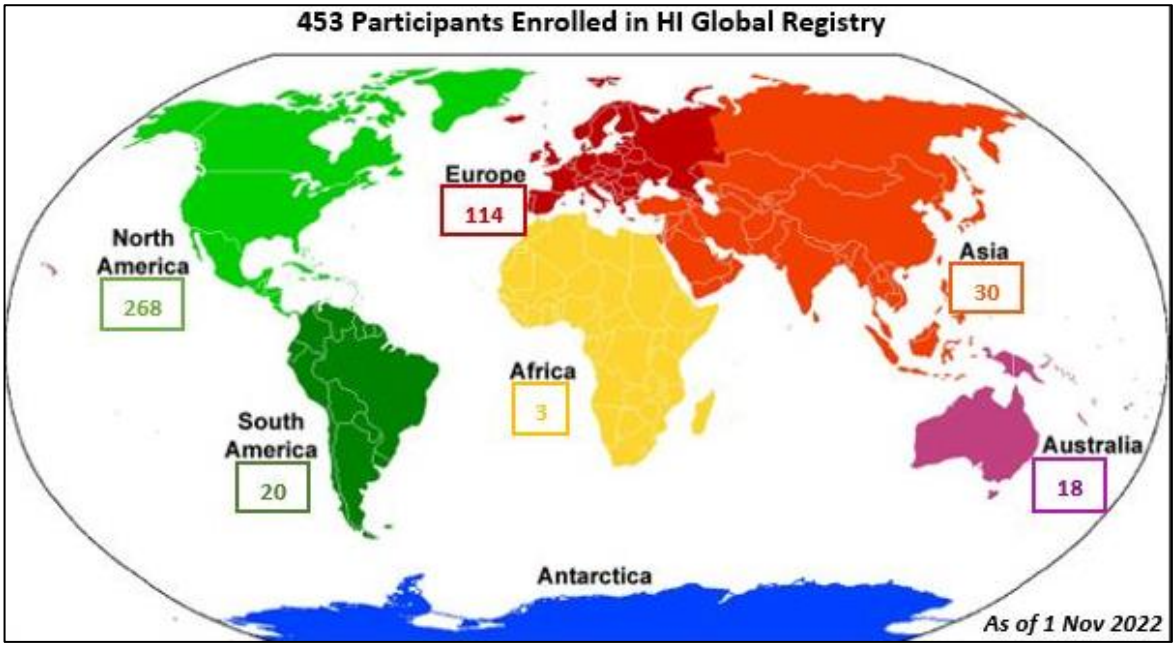


Figure 3. HIGR participants by age

Age	Participants
0-2 years	61
3-5 years	134
6-9 years	118
10-12 years	24
13-17 years	30
18+ years	86

HI Type

Diffuse HI is a general term that includes several forms of HI that affect the entire pancreas, including KATP (potassium channel) defects, glucose dehydrogenase HI (GDH-HI), also known as hyperinsulinism hyperammonemia (HIHA), glucokinase HI (GK-HI), those without a known genetic cause, and others.

Figure 4. HIGR participants by HI type

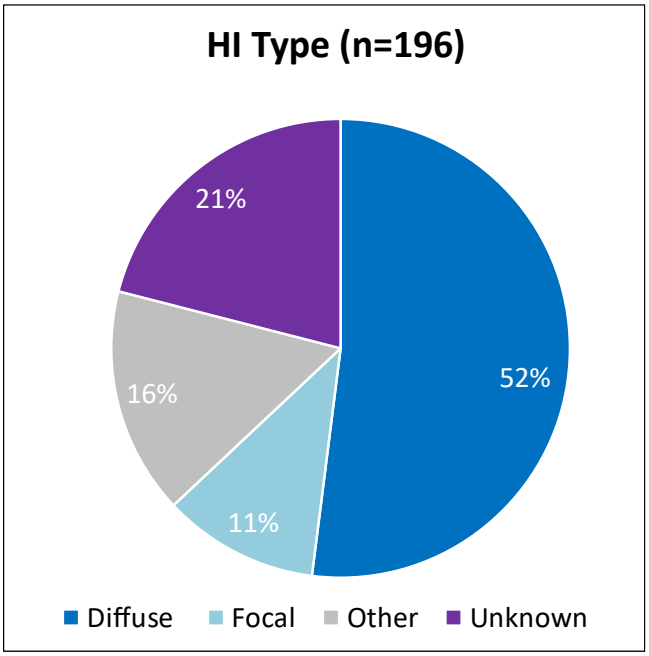
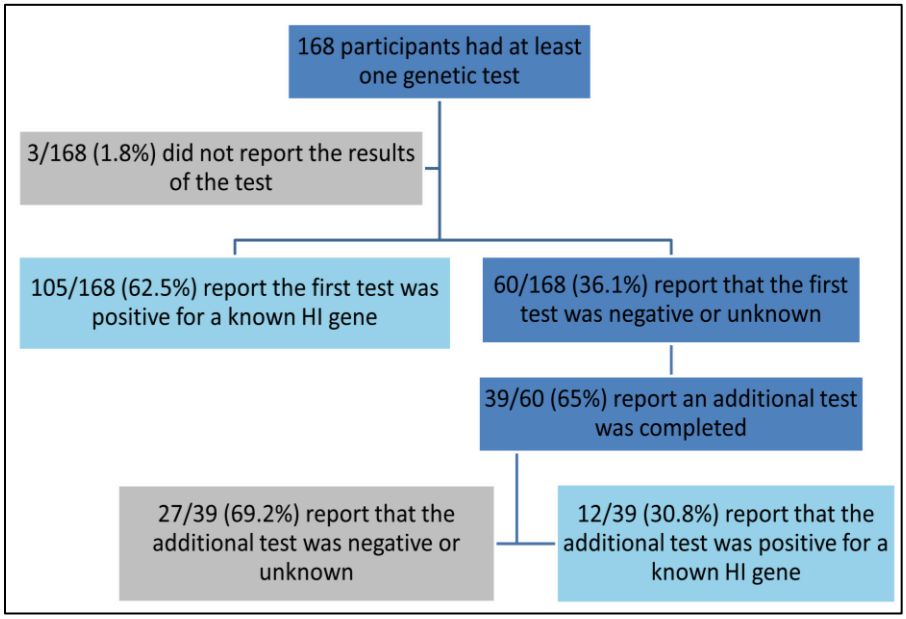


Figure 4 shows the proportion of reported HI types for 196 participants who responded to this question in HIGR. Of these participants, 102 (52%) indicated diffuse disease, and 21 (11%) reported focal HI. Another 73 (37%) report one of the other types of HI, including 9 (5%) who indicated atypical HI; 41 (21%) report an unknown type of HI; 17 (9%) report an undiagnosed status; and six (3%) report that HI is a suspected diagnosis. HIGR investigators further analyzed the individuals who reported that HI was unknown, suspected, or undiagnosed and feel confident that these individuals are likely to have HI based on responses to other questions, such as positive genetic results or reported methods of medical management.

Histologically, HI is classified as either focal, diffuse, or atypical, but this form of classification is not universally known by all patient families. The focal form of HI is typically a small area of islet cell expansion with scattered and minimal exocrine tissues included. The diffuse form involves the entire pancreas and is characterized by nucleomegaly or the enlargement of the nucleus of some islet cells. If the tissue histology is not characteristic of either of these forms, it is considered atypical. Atypical histology can include the overgrowth pattern of Beckwith–Wiedemann syndrome and the islet cell nuclear enlargement patterns localized to specific regions.

Genetics

Figure 5. Percent positive genetic testing



As seen in Figure 5, 70% of the 168 participants who had genetic testing reported a positive result for a gene associated with HI across one or more genetic tests. Of the 36% of people who had unknown or negative results on the first genetic test, 39 had a second test, and 12 of those individuals had positive results. There are many reasons why additional testing may have been performed, including single-gene testing expanded to panel gene testing or initial testing that occurred before new genes related to HI were identified.

Figure 6 displays HI genetic testing results by HI type. Of the 163 individuals who provided both their HI type and their genetic testing results, 64% tested positive for a change/mutation in HI-related genes, 29% of participants tested negative for a change/mutation in HI-related genes, and 7% had unknown results. Of those who tested positive, 65 (63%) reported diffuse HI, 18 (17%) reported focal HI, and 21 (20%) reported their HI type was either unknown, atypical, suspected, or undiagnosed. The number of people reporting positive genetics, but an unknown type underscores the need for more consistent nomenclature or names for the types of HI and a greater understanding of how the community (patients and clinicians) describe an HI diagnosis. Of those who tested negative, 17 (36%) reported diffuse HI, 2 (4%) reported focal HI, and 28 (60%) reported their HI type was either unknown, atypical, suspected, or undiagnosed.

Figure 6: HI genetic testing results by HI type

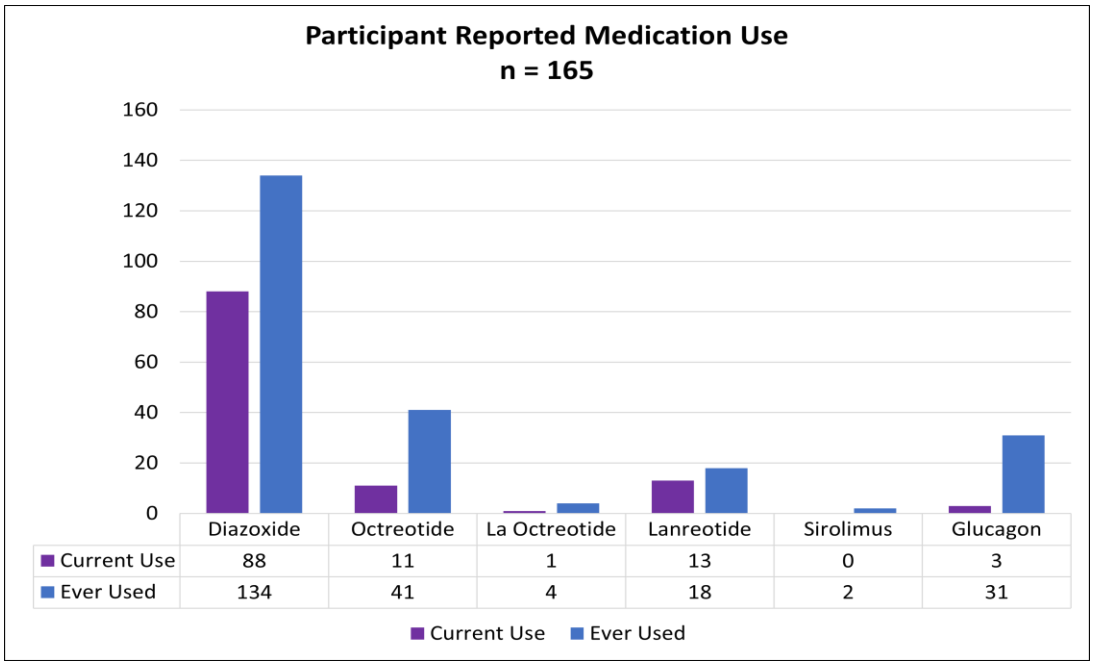
HI Genetic Testing Results			
HI Type	**Positive for change/mutation in HI-related gene(s)**	**Negative for change/mutation in HI-related gene(s)**	**Unknown**
Diffuse	65	17	6
Focal	18	2	1
Unknown	11	17	1
Other	10	11	4
Total	**104**	**47**	**12**

**The "other" category includes participants with atypical, HI suspected, or undiagnosed types.*

Medication and Surgical Management

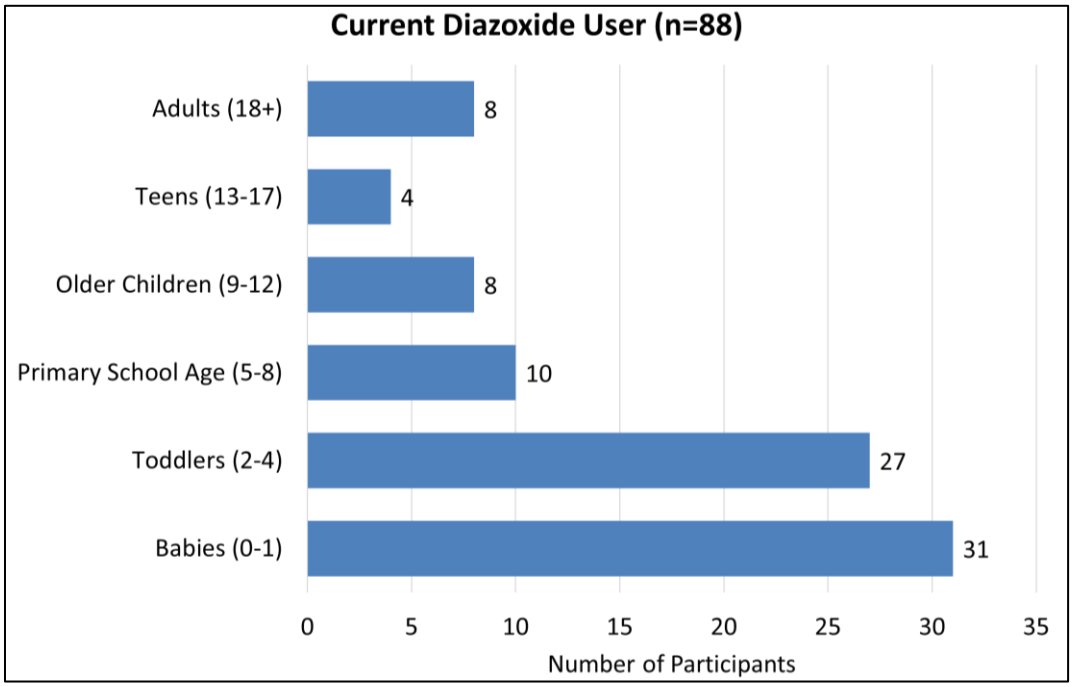
The survey regarding the medical management of HI gathers data on medication the participant has taken to treat HI. A total of 165 people completed the medication experience survey. Figure 7 displays the medications participants reported ever and currently using. It is possible that individuals are on multiple medications.

Figure 7: Medical management



Of the 134 participants who reported having taken diazoxide, 88 participants (66%) are currently taking diazoxide, and 46 (34%) have taken it in the past. The average age of those currently on diazoxide is seven years old, ranging from one month to 44 years old. Figure 6 shows the breakdown by age group of those currently taking diazoxide. Fifty-eight participants (66%) who report that they are currently taking diazoxide are under five years old.

Figure 8. Age of those currently taking diazoxide



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

Figure 9 displays the most commonly reported side effects among individuals who took diazoxide or octreotide. The most frequently reported side effects for diazoxide users include increased body hair (85%), loss of appetite (36%), swelling (25%), stomach pain or upset stomach (23%), and facial

changes (22%). Less commonly reported side effects of diazoxide (≤15%) include changes in taste, headache, dizziness, skin rash, racing heartbeat (tachycardia), fluid in lungs, and hypertension. Other than the available response options, participants also reported severe nausea, vomiting, fluid retention, scrotal swelling, thrombocytopenia (low platelet count), and congestive heart failure. Additionally, 25% of individuals reported continued hypoglycemia.

The most commonly reported side effects for octreotide users include changes in stool (34%), stomach pain or upset (24%), hyperglycemia (21%), and gallstone/gallbladder sludge (18%). Less commonly reported side effects (≤13%) include nausea, growth suppression, and injection site problem. A total of 42% of people on octreotide reported continued hypoglycemia.

Figure 9: Side effects experienced by those having taken diazoxide and octreotide

Side effects	Diazoxide (%)	Octreotide (%)
None	4 (3)	10 (26)
Loss of appetite	47 (36)	N/A
Stomach pain or upset	30 (23)	9 (24)
Changes in sense of taste	11 (8)	N/A
Increase in growth of body hair	111 (85)	N/A
Headache	8 (6)	0 (0)
Dizziness	5 (4)	0 (0)
Skin rash	10 (8)	N/A
Facial changes	28 (22)	N/A
Swelling (hands, feet or both)	32 (25)	N/A
Racing heartbeat (tachycardia)	19 (15)	N/A
Fluid in the lungs	6 (5)	N/A
Pulmonary hypertension	8 (6)	N/A
Hyperglycemia	10 (8)	8 (21)
Nausea	NA	5 (13)
Changes in stool	N/A	13 (34)
Gallstone/gallbladder sludge	N/A	7 (18)
Growth suppression	N/A	2 (5)
Thyroid suppression	N/A	0 (0)
Necrotizing enterocolitis	N/A	0 (0)
Injection site problem	N/A	3 (8)
Other	9 (7)	0 (0)
Total	**130**	**38**

As seen in figure 10, 62 (38%) of 163 participants reported that a pancreatectomy was considered for the treatment of their HI. A total of 61 participants provided a response on whether a pancreatectomy was performed for the treatment of their HI, with 48 (79%) of these participants indicating a pancreatectomy was performed.

Figure 10. Surgical experience

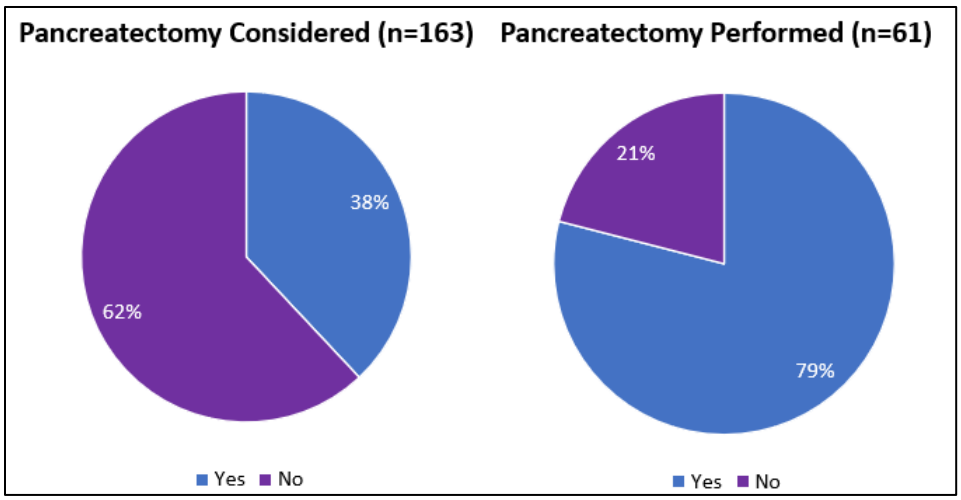


Figure 11 displays the surgery status and medications used by HI type. Of the 44 participants who report undergoing a pancreatectomy, 25 (57%) report diffuse HI, 15 (34%) report focal HI, and 4 (9%) report their HI was either unknown, atypical, suspected, or undiagnosed. Of 126 participants reporting diazoxide use, 83 (66%) report currently using diazoxide to treat their HI. Of these 83, 49 (59%) report diffuse HI, and 34 (41%) report another form. Additionally, of 48 participants reporting SSA (octreotide, la octreotide, or lanreotide) use, 22 (46%) report currently using some form of SSA to treat their HI. Of these 22 participants, 15 (68%) report diffuse HI, 4 (18%) report focal HI, and 3 (14%) report their HI was either unknown, atypical, suspected, or undiagnosed.

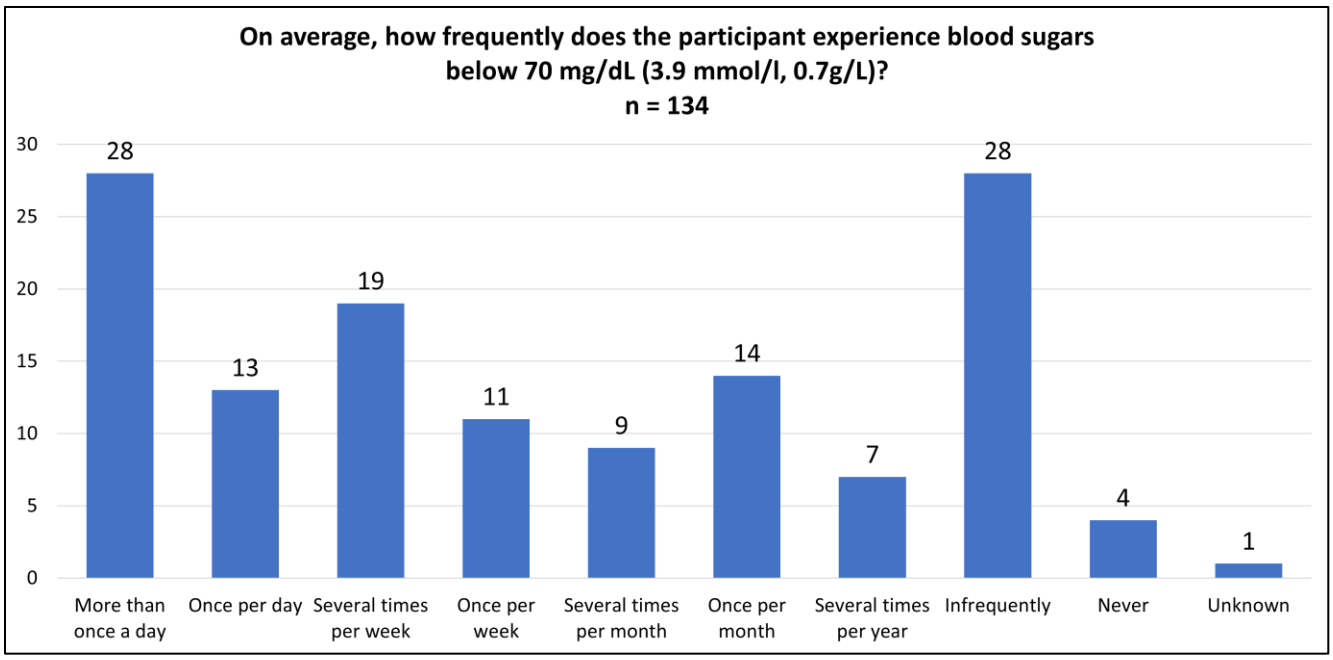
Figure 11. Disease management and surgery, by HI type

	Surgery (n=150)		Diazoxide Use (n=126)		SSA Use (n=48)	
HI Type	**Yes**	**No**	**Ever**	**Currently**	**Ever**	**Currently**
Diffuse	25	60	69	49	33	15
Focal	15	1	10	0	6	4
Other	4	45	47	34	9	3
Total	**44**	**106**	**126**	**83**	**48**	**22**

Glucose Monitoring

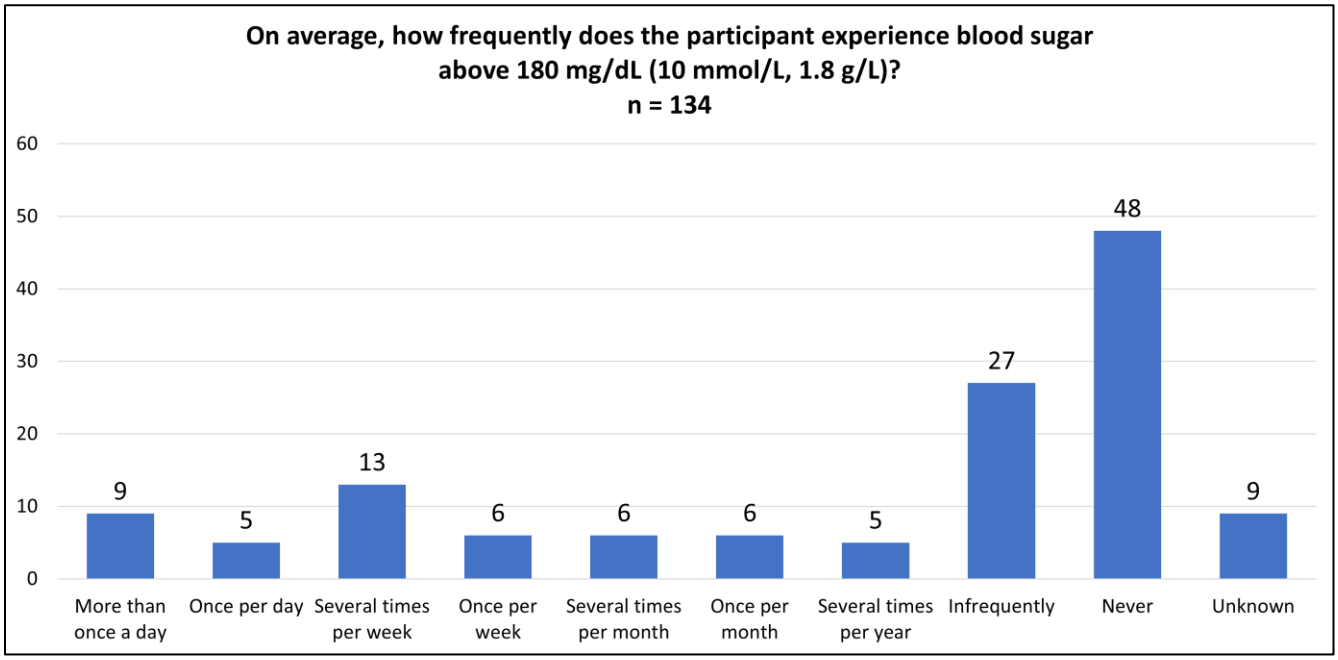
Figure 12 presents the reported frequency of low and high blood glucose by HI type. A total of 134 participants reported how frequently they experience blood sugars below 70 mg/dL (3.9 mmol/l, 0.7g/L) and above 180 mg/dL (10 mmol/L, 1.8 g/L). Of these participants, 71 (53%) report experiencing lows "more than once a day," "once per day," several times per week," or "once per week."

Figure 12: Frequency of blood glucose below 70 mg/dL



Additionally, 33 (25%) participants report experiencing highs "more than once a day," "once per day," several times per week," or "once per week."

Figure 13: Frequency of blood glucose above 180 mg/dL



Feeding Issues

Figure 14: Reported feeding issues

Has the participant experienced any feeding issues regularly (check all that apply)?	All Participants n (%)
No feeding issues	49 (31)
Feeding issue(s)	109 (69)
Poor appetite	68 (43)
Refusing to eat	65 (41)
Reflux	48 (30)
Slow eating	46 (29)
Problems with texture	43 (27)
Vomiting	43 (27)
Gagging	40 (25)
Uncoordinated oral skills	30 (19)
Coughing	23 (15)
Overeating	14 (9)
Total	**158**

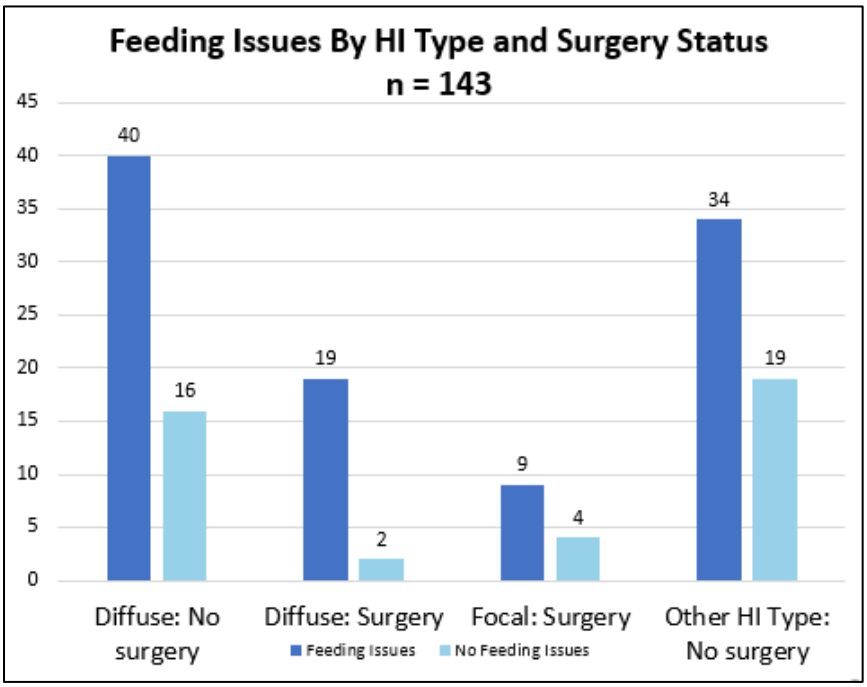
Figure 14 presents reported feeding issues for the 158 participants who have completed the Diet and Feeding Management Survey. Of those, 143 also provided information on their HI type and surgery experience; the subgroup analysis is in Figure 15. The "Other" type of HI (n=53) includes undiagnosed, unknown, and atypical HI.

Of the 158 participants (all HI types and treatments included), 109 (69%) reported having one or more feeding issues. The most-reported feeding issues were poor appetite (43%) and refusing to eat (41%). Over a quarter of the participants who answered this question reported reflux, difficulty with texture, vomiting, and slow eating.

Seventy-seven participants reported diffuse HI, 27% of those individuals had a pancreatectomy, and 90% of those with diffuse HI and a pancreatectomy reported feeding issues. Among the individuals who had diffuse disease and did not have surgery, 71% of participants reported feeding issues.

Regular feeding issues were also reported for 69% of participants with focal disease and 64% of those reporting other types of HI. Of individuals who reported that they had surgery for focal HI, 20% said that their feeding issues had resolved.

Figure 15: Reported feeding issues by HI type and surgery status



Respondents said that the participant's feeding issues resolved within the first year of life (32%), 1-3 years of age (27%), 4-6 years of age (27%), 7-9 years of age (7%), and over the age of 9 (7%).

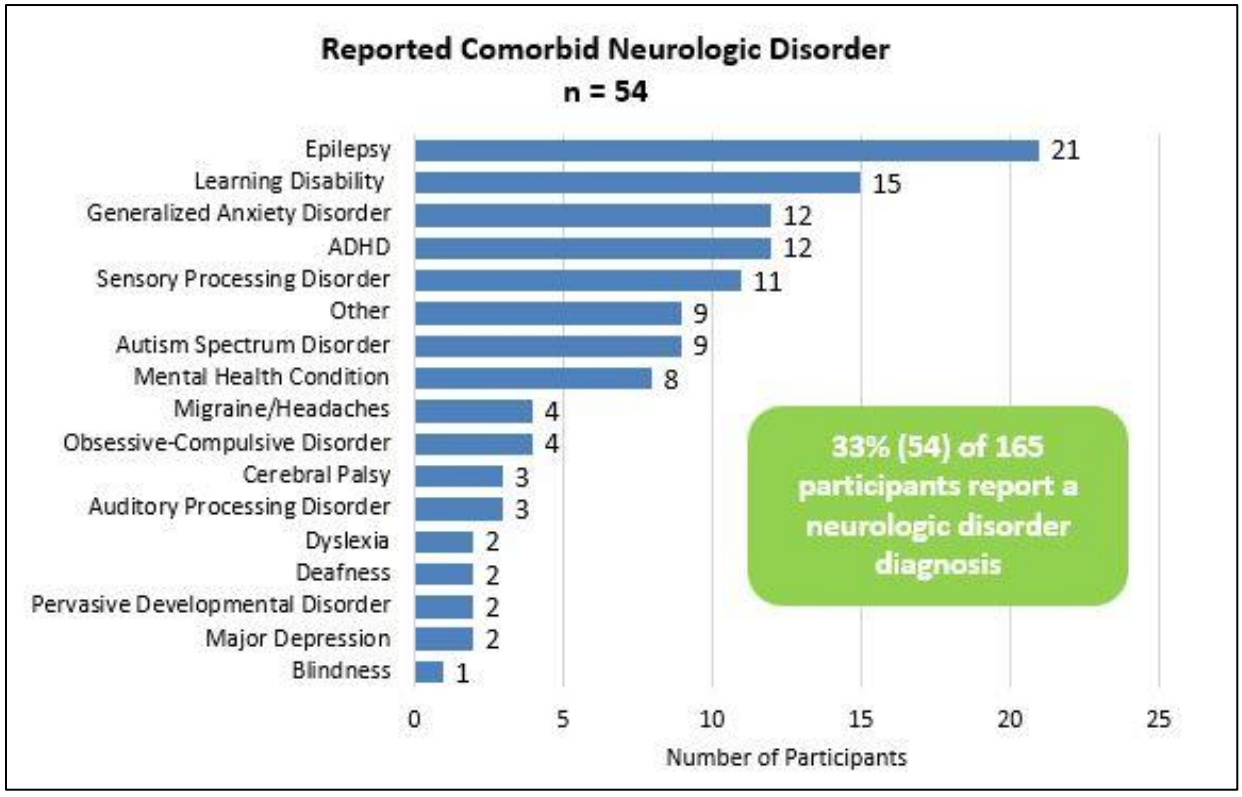
Figure 16: Age feeding issues resolved

At what age did the participant's feeding issues resolve?	All Participants n (%)
Within first year of life	13 (32)
1-3 years old	11 (27)
4-6 years old	11 (27)
7-9 years old	3 (7)
10-12 years old	0 (0)
13-18 years old	3 (7)
Total	**41**

Neurologic Disorders

Fifty-four (33%) of the 165 respondents who completed the Other Diagnoses survey report that the participant was diagnosed with one or more neurologic disorders. Epilepsy is the most reported neurologic disorder, accounting for 13% of participants who completed the other diagnoses survey. Figure 17 shows the other neurologic diagnoses reported. The most frequently reported neurologic diagnoses included learning disability (9%), generalized anxiety disorder (7%), ADHD (7%), and sensory processing disorder (7%). The "other" category includes participants with suspected, but not yet confirmed, diagnoses, including those listed above and visual, motor, and/or neurocognitive issues of a more general nature.

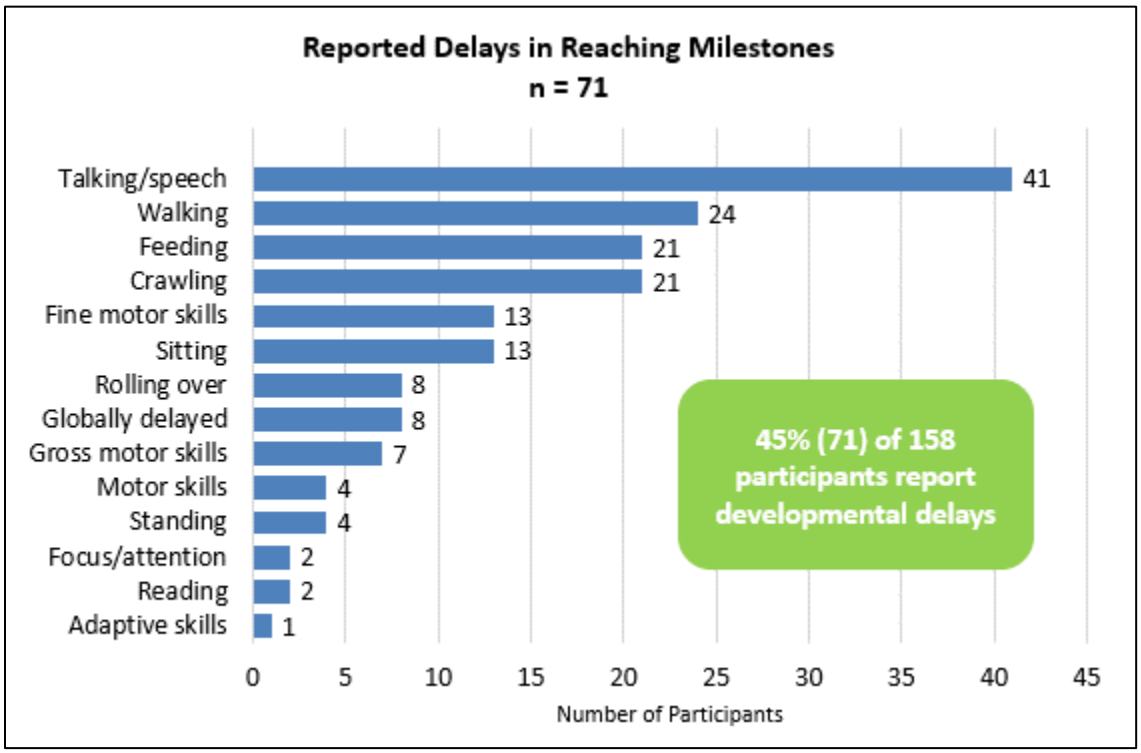
Figure 17: Reported neurologic disorders



Developmental Delay

Of 158 participants who completed the Developmental Survey, 71 (45%) participants reported delays in reaching developmental milestones. Delays reported include 41 (26%) participants report delay in talking; 24 (15%) in walking; 21 (13%) in feeding; 21 (13%) in crawling; 13 (8%) in sitting; and 13 (8%) in fine motor skills. Some participants reported delays in more than one milestone.

Figure 18: Milestone delays in HI participants



Registry Recruitment and Engagement

The registry's success depends on the engagement and broad participation of the HI community. This section provides information on the registry recruitment steps and engagement efforts this year. HIGR engagement is continuous. In research, data becomes more meaningful as the sample size (the number of participants) increases. With more participants answering more surveys over time, reports will include additional aspects of the HI experience with more meaningful comparisons across groups.

Stages of Recruitment

HIGR recruitment has been defined in four stages to help track respondent utilization of the system and identify strategies to assist individuals in completing all surveys.

Stage 1 is registration on the registry platform at www.higlobalregistry.org. The registration process includes basic identifying information provided by the respondent (HI patient or their legal, authorized representation (parent/guardian) if the patient is a minor or unable to register due to cognitive difficulties). As of November 2022, 506 respondents have enrolled in the registry. 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 understand how HI affects individuals throughout their lives. If you agree to let HIGR staff contact you for occasional reminders, it will help ensure you are an active HIGR participant.

(2) **For a possible clinical trial, the participant may qualify to participate** – CHI will never share your information with a clinical trial sponsor or anyone else. If you select yes to this preference, the CHI staff will notify you of clinical trial opportunities and will send you information about the opportunity to participate. Choosing to be contacted does not commit you to participate in the trial.

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

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

The respondent can update the contact permissions at any time.

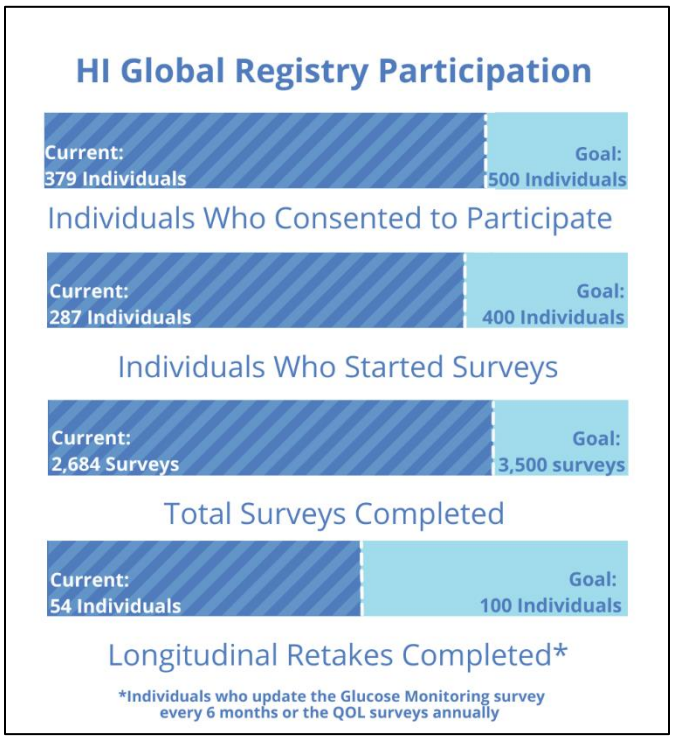
Stage 2 is when respondents, HI patients, or their legally authorized representatives (LAR) consent to participate in the HIGR study. The respondent must first add the participant (the person living with HI). A respondent may add multiple participants, for example, if they have two children living with HI or if they have HI and also have a child with the condition. Next, the respondent will review the consent documentation to participate 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, 506 registered respondents have added 455 participants (59 adults, 396 minors); 379 participants (83%) have completed the consent process, allowing access to the survey questions.

Stage 3 is when a respondent submits at least one survey. Currently, 280 participants have completed at least one survey (62% of all enrolled participants). Each survey asks questions related to different aspects of HI. They utilize a branching logic, so you will not be asked irrelevant questions within a survey. However, we invite you to visit and complete every survey, even if it does not seem relevant to you at 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 essential to complete the surgery survey to inform us that it was not recommended or was not performed and why. Researchers cannot make assumptions about survey questions left blank and rely on you to tell your whole HI story.

Stage 4 is when a respondent completes all relevant surveys. Depending on the participant's age, 12-13 surveys must be completed and submitted to achieve full participation in HIGR. A complete set of surveys is the best way to evaluate HI and make the desired cross-comparisons for more thorough reporting. When participants do not complete all the included surveys, they will likely be excluded from deeper analysis of that topic.

Engagement

Figure 19. HIGR participation, by category



CHI has employed various engagement strategies to help grow HIGR. HIGR data was disseminated through peer-reviewed publications and was displayed at three conferences (CZI Rare as One Convening, the European Society for Pediatric Endocrinology Conference, and the National Organization for Rare Diseases Summit). The HIGR team also presented data at the CHI Family Conference in Italy (September 2022) and the CHI Family Meet-Up in California (June 2022).

In 2022, CHI launched a new HIGR engagement campaign to increase new and existing respondent engagement by June 2023. The goal is to increase the number of individuals who consent to participate, individuals who have completed surveys, the total number of surveys taken, and longitudinal retakes. Figure 19 reflects the current standings for each category as of November 2022.

Social media is essential for connecting with patients and sharing information about the registry. As part of our HIGR engagement campaign, CHI started

highlighting a survey of the month to highlight each survey's unique value and importance. Figure 20 includes examples of the survey of the month social media posts.

Figure 20: Sample text from survey of the month social posts

Survey	**Sample post**
Diagnosis	Share what your or your child's experience obtaining a diagnosis was like so we can help better understand and promote the importance of timely and accurate diagnosis.
Medication Management	This survey helps researchers understand what medications most people with HI take and how effective they are. This provides comparisons of treatment experiences and may highlight the need for new treatment options.
Diet and Feeding Management	Completing this survey helps researchers understand the diet and feeding routines of HI patients and the complications that occur for some.
Developmental	The developmental survey provides insight into how HI affects developmental milestones and behaviors.

Figure 21. Examples of HIGR engagement campaign graphics

Looking Forward

2022 has been a year of growth for HIGR and HI-related research HIGR is now utilized as a research tool, and the activity has built a strong foundation for an HI natural history study reported by those who live with the disease. However, to continue to grow this important tool, it will take a commitment from everyone in the community. We want to encourage patients and caregivers to participate by taking and updating surveys, and we encourage doctors to complete the MaxHIGR form.

Looking forward, the HIGR team is working on ways to include new types of data in the registry, including CGM data and other quality of life tools. This information will provide valuable insight into the ongoing challenges of managing hypoglycemia and the impact of HI on families living with this condition. In 2023, we are also anticipating platform upgrades which should facilitate a better user experience and will enable the inclusion of additional languages into the registry.

Many people may have initially joined HIGR when it launched in 2018; our wish is that those who first joined will continue to share their experience and update information, especially related to diet and feeding, medication, developmental outcomes, and glucose monitoring so that we can tell a complete story of living with HI.

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

We look forward to growing HIGR and realizing more of the objectives outlined in the study protocol! We are so grateful for the support of the entire HI community as we develop the registry and realize our shared goals of better treatments, access to care, and, ultimately, a cure!

Acknowledgments

The CHI registry team would like to take the opportunity to thank everyone who has made it possible to conduct this important research and present its findings.

This work would not be possible without the dedication of the HIGR respondents and participants, who have generously given their time to complete surveys and contribute their data. We are very grateful to the entire HI community for its continual support of HIGR and for helping us raise awareness of this critical initiative. The authors would also like to thank the CHI Board of Directors for supporting HIGR and its growth. The investigators wish to express our appreciation to the HIGR Steering Committee, who volunteer their expert advice and guidance to ensure the success of the HIGR research program.

HIGR Steering Committee Members:

Sarah Dearman – United Kingdom

Ciara Grace – United Kingdom

Sandra Melo – Portugal

María Paz Oviedo – Paraguay

Irene Promoussas – Austria

Abigail Ridler – United States of America

Ulrike Seyfarth – Germany

Lora Van Arsdell-Bartocci – United States

Dr. Jean-Baptiste Arnoux – France

Dr. Indi Banerjee – United Kingdom

Dr. Henrik Christesen – Denmark

Dr. Antonia Dastamani – United Kingdom

Dr. Diva D. De León-Crutchlow – United States of America

Dr. Raphael Del Roio Liberatore Jr – Brazil

Dr. Sarah Flanagan – United Kingdom

Dr. Klaus Mohnike – Germany

Dr. Pratik Shah – United Kingdom

Dr. Charles Stanley – United States of America

Dr. Paul Thornton – United States of America

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