2024 Annual Report

Lauren N. Lopez, PhD[1], Julie Raskin, MA[2], Kristen E. Rohli, PhD[3],
Tai LS Pasquini, MPA, PhD[4]

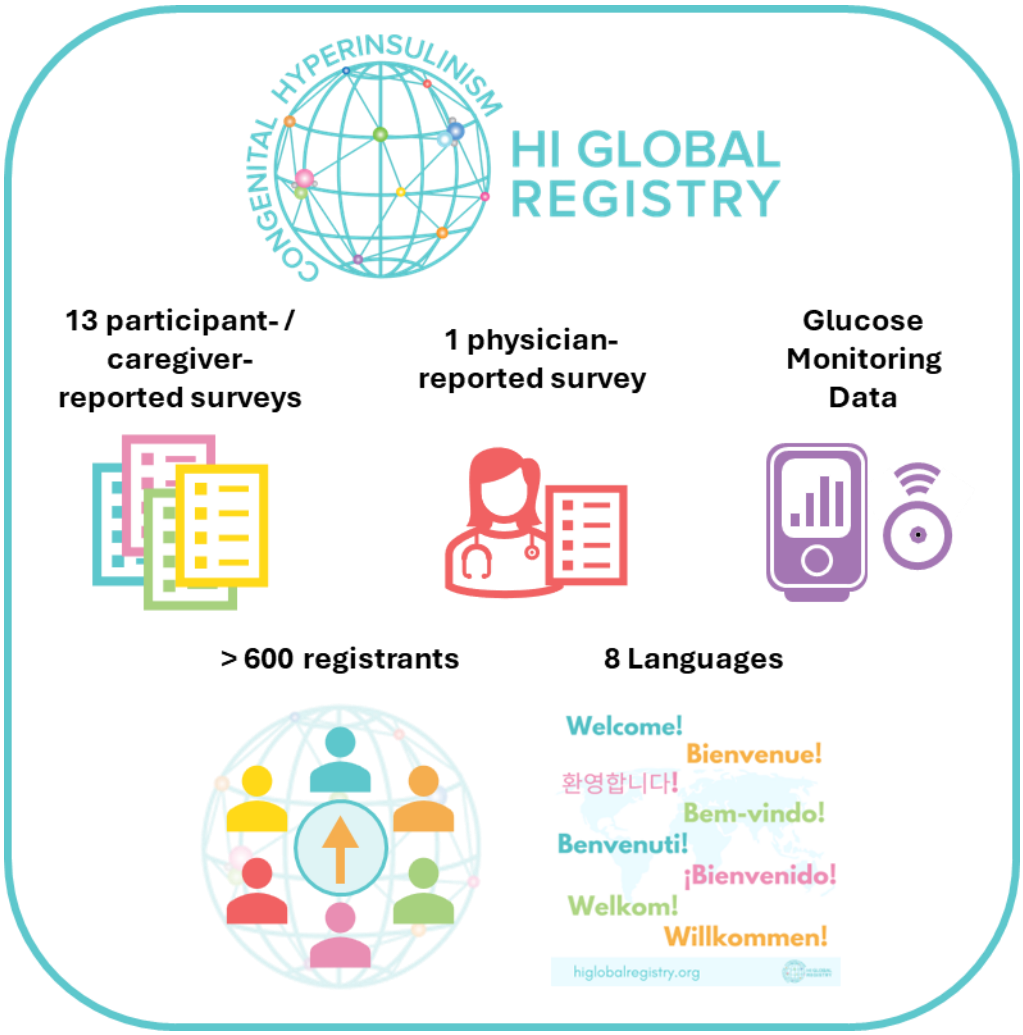
[1]CHI Registry Director and HIGR Investigator, [2]CHI Chief Executive Officer and HIGR Investigator,
[3]CHI Research Manager, [4]CHI Chief Research Officer and HIGR Principal Investigator

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

2024 has been a year filled with exciting new updates to the HI Global Registry (HIGR)! We moved to a new rare disease registry platform (Matrix, Across Healthcare) at the end of 2023, and this year we have been enjoying many new features that were made possible by the transition to Matrix, including seven new languages and the ability to collect glucose monitoring data via HIGR. HIGR registrations increased by 18% in the past year, and there were 17 different requests for deidentified HIGR data to contribute to research studies, peer-reviewed journal articles, and research grant applications. These are fantastic achievements for the HI community!



This report provides an updated sample of insights from HIGR data since the launch of HIGR in October 2018 through November 2024, as well as more information about HIGR's new features that have been added 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.

The HI Global Registry (HIGR)

HIGR is a patient-reported database of information submitted by individuals with HI and their caregivers worldwide. HIGR is developed and implemented by Congenital Hyperinsulinism International (CHI) and governed by the HIGR Steering Committee, a group of internationally recognized HI patient advocates and experts. There are thirteen base surveys to collect information about the participant's experience with HI from the initial presentation to current management, plus one physician-reported survey.

Participant-/Caregiver-reported surveys

- *Contact & Demographics*
- *MaxHIGR (participant permission form)*
- *Glucose Monitoring Management*
- *Diagnosis*
- *Other Medical Conditions*
- *Medication Management*
- *Diet & Feeding Management*
- *Development*
- *Surgical Management*
- *Pregnancy*
- *Birth*
- *Quality of Life – Participant (14+)*
- *Quality of Life – Caregiver*

Physician-reported surveys

- *MaxHIGR Physician Form*

Two surveys, *Pregnancy* and *Birth*, are final after the first submission and do not require any updates. All other surveys can be updated at the respondent's discretion when there is a notable change in the participant's contact information, health, or medical management, such as a new address, a newly diagnosed health condition, or a change in treatment. Three of these surveys are designed to be taken longitudinally to allow researchers to track changes in responses over time. Respondents are prompted to retake *Glucose Monitoring, Quality of Life – Participant,* and *Quality of Life – Caregiver* every six months, although they are welcome to complete these surveys at any time if desired.

As part of the move to the new platform, anyone who completed surveys prior to November 2023 was prompted to review all previously submitted surveys, including *Pregnancy* and *Birth*, to ensure that all questions were answered, including a few new questions that have been added. This is a one-time review that will not be necessary to do again in the future.

HIGR data is stored on the secure cloud-based Matrix Platform developed and hosted by Across Healthcare. Matrix is a shared platform connecting patients, caregivers, providers, and researchers to collect data, provide a community, and advance the goal of finding answers and discovering cures.

The 2024 Annual Report

Every year, the HIGR investigators publish a report consisting of descriptive data across key HIGR surveys to provide insights for those who share their data and for other members of the HI community. All data shown is de-identified (all personal identifiers are removed) and aggregated (data is summarized across all individuals).

Each graph or table includes the number of participants ("n") who provided information related to each data element. The variation in the number of individual responses is the result of three factors:

1) All surveys are optional, and participants/respondents can complete surveys at their own pace.
2) Between 2018 and November 2023, all survey questions were optional and respondents could skip questions for any reason. This led to a variable number of responses for every question. This has been updated as of November 2023 and most survey questions now require an answer, but respondents can select "Prefer not to answer" or "Unknown" if desired.
3) Many surveys use branching logic, where certain groups of questions are only displayed based on the respondent's answers to previous question(s). This means that not all participants will be asked to complete all questions.

A common challenge in rare disease research is small sample sizes. Data from a small group of participants may not represent the experiences of the entire population with that condition. This becomes especially true when we start to look at specific sub-populations of the whole group, such as only participants with focal disease or only those who had a pancreatectomy. For this reason, readers are advised to take caution when interpreting data presented in this report, especially since HI has many different subtypes that can vary in severity.

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.

The HIGR Research Team

CHI and the HIGR Steering Committee are delighted to announce the expansion of the HIGR research team. Kristen Rohli, PhD, joined CHI as a Research Manager in August 2024 and brings a range of professional skills to the HIGR research team; most notably, her background in pancreatic biology and genetics. You can read more about Kristen and the rest of the HIGR research team below.

Julie Raskin
Founder and CEO

Tai Pasquini, PhD
Chief Research Officer

Lauren Lopez, PhD
Registry Director

Kristen Rohli, PhD
Research Manager

Julie Raskin, Chief Executive Officer is a leader in the rare disease community with 22 years directing nonprofit programs, and 13 years serving on nonprofit and educational boards of directors. Julie is one of the original HI parent founders of CHI. Under Julie's leadership CHI has created an active worldwide community of patients, their families and caregivers, expert clinicians and researchers, and professionals in the biotech field – to fulfil CHI's mission to improve the lives of people born with congenital hyperinsulinism (HI). During her tenure, CHI has developed and launched HIGR and the CHI Collaborative Research Network, secured funding for 11 pilot research grants, organized 32 global conferences and meetings, created disease awareness information in 25 languages, provided genetic testing for those suspected of having hyperinsulinism from 63 countries, provided patient experience expertise for six biotechs, and made it possible for patients in five countries to get medication/treatment that would not otherwise be available, and led the advocacy movement for the HI community. Julie also serves on the New Jersey Rare Disease Advisory Council.

Tai Pasquini, Chief Research Officer is a rare disease patient advocate and researcher. As CHI's Chief Research Officer, she serves as the Principal Investigator for HIGR and manages the Centers of Excellence program, CHI's research program, and the Collaborative Research Network. Tai currently serves on the Massachusetts Rare Disease Advisory Council. Tai completed a PhD in Health Policy from the University of Massachusetts Amherst and her dissertation focused on issues of access and financing for rare disease patients and families. Previously, Tai worked at the National Organization for Rare Disorders (NORD) and taught undergraduate classes on the US Healthcare System and public health communications. She holds a Masters in Public Administration and a Bachelor of Arts in Communications, Legal Institutions, Economics, and Government from American University.

Lauren Lopez, Registry Director has a strong background in biomedical research and over 10 years of research experience spanning basic, translational, and clinical research. Lauren received her PhD in Cellular & Molecular Physiology from the University of Liverpool, UK in 2017, and moved to the US to complete postdoctoral research in kidney disease. She discovered her passion for serving the rare disease community during her role as a Senior Scientific Affairs Manager at AllStripes Research, and she is excited to now use her skills and experience to benefit the hyperinsulinism community. As the Registry Director, Lauren manages all aspects of the HI Global Registry including recruitment, data curation, analysis, and publications.

Kristen Rohli, Research Manager has been active in pancreatic biology research since 2016. Kristen earned her bachelor's degrees in Biochemistry and Psychology from Louisiana State University, where she conducted research on the relationship between obesity and Type 2 diabetes at Pennington Biomedical Research Center. In 2024, Kristen completed her PhD in Genetics at the University of Iowa, focusing on organelle function and the cellular environment within pancreatic beta-cells. Kristen recently joined Congenital Hyperinsulinism International as the Research Manager, she is applying her expertise to further the understanding of the genetic factors associated with HI.

Congenital Hyperinsulinism International (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. HIGR is one of several foundational programs established by CHI to support the global HI community. To learn more about CHI, please visit https://congenitalhi.org/.

HIGR Objectives

HIGR functions as a natural history study, meaning HIGR collects specific health-related and quality-of-life information from its participants over time to understand how HI is diagnosed, how it is treated, and how it impacts health and life. HIGR is conducted under a research protocol drafted by the HIGR Steering Committee (a group of international researchers, clinicians, and advocates) and approved by an Institutional Review Board (IRB). The IRB, also known in some countries as an ethics committee, 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 HIGR team, you can contact the IRB at info@northstarreviewboard.org, or toll-free at (877) 673-8439.

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 2024 – A Year in Review

HIGR moved to the Matrix platform by Across Healthcare. All HIGR data was migrated to the Matrix platform in November 2023, paving the way for exciting new features for the HIGR community.

HIGR is available in 8 languages: English, Dutch, French, German, Italian, Korean, Portuguese, and Spanish! We understand how important it is for people with HI and their caregivers to contribute their experiences with HI in the language they are most comfortable using. The expansion of HIGR surveys into more languages is part of our ongoing commitment to make it easy for everyone to participate in HI research and to create a truly international patient registry for the HI community. HIGR was translated into French, German, Italian, Korean, Portuguese, and Spanish in April 2024, and into Dutch in November 2024. CHI will continue to evaluate language needs within the HI community – if your language is not currently available, please reach out to us at info@higlobalregistry.org!

CHI launched support materials for HIGR. To reduce the barriers to participation in HIGR and make it as simple and easy as possible to find answers to questions, CHI launched various support materials for HIGR. The Guides and Tutorials page of the CHI website now contains video tutorials guiding participants and caregivers through the registration process and PDF Help Guides with screenshots to support registration into HIGR, navigate the registry, complete and update surveys, and more! Our Frequently Asked Questions (FAQs) are available as an interactive feature in English on the website and can be downloaded as a PDF in all eight languages. The FAQs and PDF Help Guides can also be accessed via the **"Resource Center"** directly within the HIGR platform.

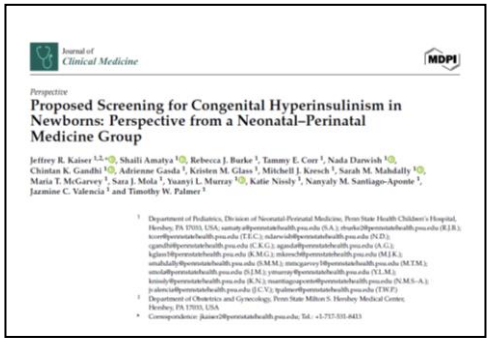
Glucose monitoring data can now be collected via HIGR! CGMs are used by many to monitor their glucose levels as part of HI treatment management, but until now, this important source of knowledge about glucose levels in people who live with HI has rarely been collected and studied outside of clinical trials. HIGR now allows participants to connect their Dexcom devices to share this incredible data source with HI researchers. The information can be paired with HIGR survey responses to help HI researchers understand how glucose management is impacted by HI type, treatment options, medications, and so much more! Learn more about sharing glucose values on the CHI website.

HIGR Data Requests and Data Sharing

HIGR data continues to grow as a valued source of scientific information within the HI research community. In 2024, HIGR data was requested for 17 different projects. These included:

- Data to support **new recommendations for hypoglycemia screening in newborns** (see new publication below)
- Data to explore **new research ideas** and to start new research projects
- Data to support **grant applications** for HI research funding
- Data to support **advocacy and awareness** at international family conferences

In May 2024, CHI Collaborative Research Network (CRN) member, Jeffrey Kaiser and a team of neonatologists published a new proposal for screening for HI in all newborns, before newborn hospital discharge. Dr. Kaiser used data from HIGR to demonstrate the limitations of current screening guidelines in correctly identifying newborns with HI.


Journal of Clinical Medicine

MDPI

Perspective

Proposed Screening for Congenital Hyperinsulinism in Newborns: Perspective from a Neonatal–Perinatal Medicine Group

Jeffrey R. Kaiser [1,2,*], Shaili Amatya [1], Rebecca J. Burke [1], Tammy E. Cox [1], Nada Darwish [1], Chintan K. Gandhi [1], Adrienne Gasda [1], Kristen M. Glass [1], Mitchell J. Kresch [1], Sarah M. Mahdally [1], Maria T. McGarvey [1], Sara J. Mola [1], Yuanyi L. Murray [1], Katie Nissly [1], Nanyaly M. Santiago-Aponte [1], Jazmine C. Valencia [1] and Timothy W. Palaser [1]

[1] Department of Pediatrics, Division of Neonatal-Perinatal Medicine, Penn State Health Children's Hospital, Hershey, PA 17033, USA; samaty@pennstatehealth.psu.edu (S.A.); rburke2@pennstatehealth.psu.edu (R.J.B.); kcox@pennstatehealth.psu.edu (T.E.C.); ndarwish@pennstatehealth.psu.edu (N.D.); cgandhi@pennstatehealth.psu.edu (C.K.G.); agasda@pennstatehealth.psu.edu (A.G.); kglass1@pennstatehealth.psu.edu (K.M.G.); mkresch@pennstatehealth.psu.edu (M.J.K.); smahdally@pennstatehealth.psu.edu (S.M.M.); mmcgarvey1@pennstatehealth.psu.edu (M.T.M.); smola@pennstatehealth.psu.edu (S.J.M.); ymurray@pennstatehealth.psu.edu (Y.L.M.); knissly@pennstatehealth.psu.edu (K.N.); nsantiagoaponte@pennstatehealth.psu.edu (N.M.S.-A.); jvalencia@pennstatehealth.psu.edu (J.C.V.); tpalaser@pennstatehealth.psu.edu (T.W.P.)
[2] Department of Obstetrics and Gynecology, Penn State Milton S. Hershey Medical Center, Hershey, PA 17033, USA
* Correspondence: jkaiser2@pennstatehealth.psu.edu; Tel.: +1-717-531-4413

"These data from the Hyperinsulinism Global Registry show that current clinical practices are not effective in screening for CHI"
Kasier et al., Journal of Clinical Medicine (2024)

In June 2024, Lapidus et al. reviewed all available epidemiological data to estimate the birth prevalence of HI and found that there were few good-quality studies that could reliably estimate HI birth prevalence around the world. The authors discussed HIGR as a future source of reliable data to estimate HI birth prevalence globally.


Hormone Research in Paediatrics

Review Article

Horm Res Paediatr
DOI: 10.1159/000539464

Received: April 10, 2024
Accepted: May 17, 2024
Published online: June 17, 2024

The Birth Prevalence of Congenital Hyperinsulinism: A Narrative Review of the Epidemiology of a Rare Disease

David Lapidus [a] Diva D. De Leon [b] Paul S. Thornton [c] Davelyn Hood [d] Jeffrey Breit [d] Julie Raskin [e] Tai L.S. Pasquini [e]

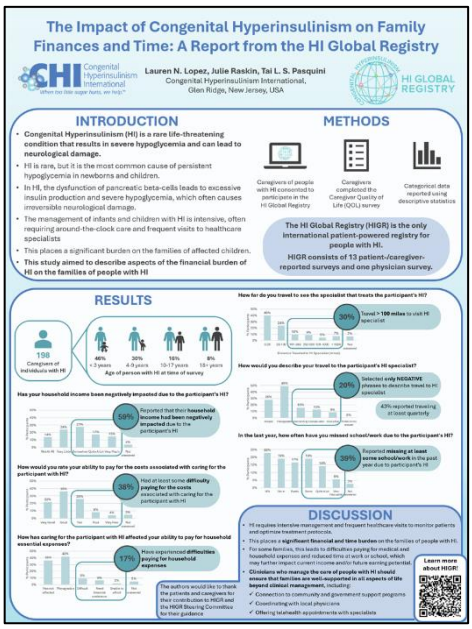
[a]LapidusData Inc., Oklahoma City, OK, USA; [b]Congenital Hyperinsulinism Center and Division of Endocrinology and Diabetes, Department of Pediatrics, The Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [c]Congenital Hyperinsulinism Center, Cook Children's Medical Center, Fort Worth, TX, USA; [d]Rezolute, Inc., Redwood City, CA, USA; [e]Congenital Hyperinsulinism International, Glen Ridge, NJ, USA

*"As its reach expands with the introduction of new languages, **HIGR may become a crucial tool in providing more reliable figures for global HI prevalence in the future.** Reliable epidemiological data on HI are urgently needed to pave the way for public health approaches, defining the impact of HI on populations, examining cost, and improving patient management"*
Lapidus et al., Hormone Research in Pediatrics (2024)

Congenital Hyperinsulinism International
When too little sugar hurts, we help.™

HI GLOBAL REGISTRY

In addition to publications in academic journals described above, conferences and meetings are another way that researchers can share their findings. Preliminary or early-stage results are often shared via posters that are presented during informal poster sessions at conferences. These provide an opportunity for researchers to talk about their work in one-on-one or small group discussions with other researchers.



HIGR data was shared with HI families and clinicians at the CHI Family Conference, and with pediatric endocrinologists and researchers at the European Society of Pediatric Endocrinology (ESPE), both in Liverpool, UK, in November 2024.

Title: The Impact of Congenital Hyperinsulinism on Family Finances and Time: A Report from the HI Global Registry

Presenter: Lauren Lopez, PhD, CHI Registry Director.

Conference: Annual Meeting of the European Society of Pediatric Endocrinology (ESPE) in November 2024

Key Message: For some HI families, the financial and time burden of HI leads to difficulties paying for medical and household expenses, and reduced time in school or work. Clinicians who manage the care of people with HI should ensure that families are well-supported in all aspects of life beyond clinical management.

Request Access to HIGR Data

Researchers can add patient-powered data to their HI research! Qualified researchers who sign a Data Use Agreement (DUA) may request access to de-identified data from HIGR.

Researchers can contact the CHI research team to explore ways that HIGR data could be used to support and enhance research studies in HI: info@higlobalregistry.org

Data Report

Characteristics of HIGR Participants and Diagnosis

HI occurs worldwide, and a recent study estimated the prevalence of HI to be 1 in 28,000 live births in most countries. As of November 4, 2024, HIGR has enrolled 606 participants from 60 countries. The majority of participants are from North America (55%) and Europe (24%) (Figure 1).

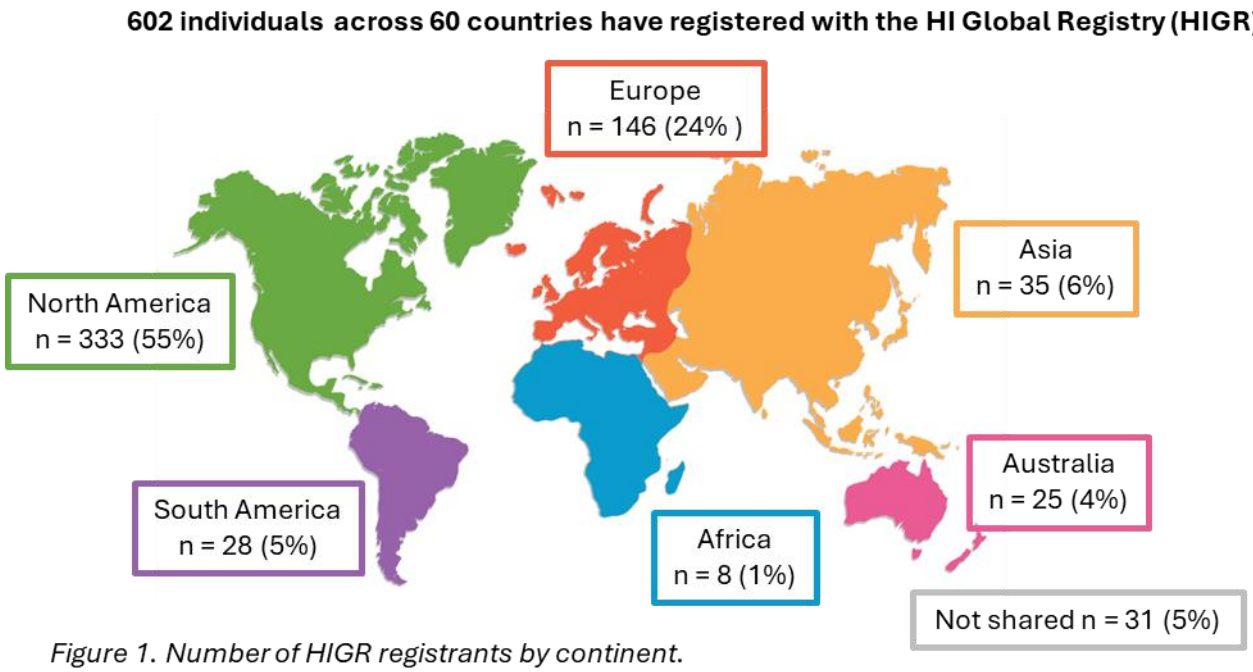


Figure 1. Number of HIGR registrants by continent.

Since the last Annual Report in 2023, 75 new individuals consented to participate in HIGR. The majority of new participants were from North America (53%) and Europe (35%).

HIGR was translated into six new languages in March 2024 (French, German, Italian, Korean, Portuguese, and Spanish) and a seventh language in November 2024 (Dutch). Since the launch of additional languages, one-third of new registrants chose to complete registration in a non-English language (Table 1).

Table 1. Contact & Demographics survey completion language by new registrants since 27 March 2024.

Language	n (%)
English	42 (67%)
French	5 (8%)
German	1 (2%)
Italian	9 (14%)
Korean	0 (0%)
Portuguese	1 (2%)
Spanish	5 (8%)
Total	**63**

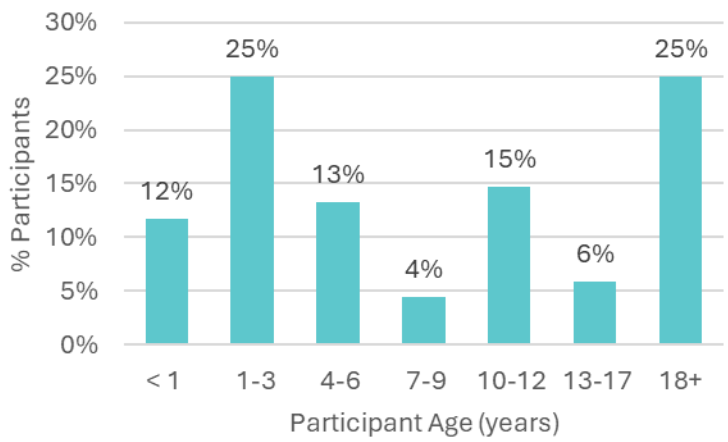


Figure 2. Participant age at time of joining HIGR (new participants in 2024 only, n = 68)

There is a wide range of ages among HIGR participants, from just a few weeks old to over 50 years old, however the majority of HIGR participants are children. Most new HIGR participants who joined in 2024 are young children, however 25% of new participants in the past year were over the age of 18 (Figure 2).

HI Type

Of the 292 participants who responded to the question on HI type, 148 (51%) indicated diffuse disease, 28 (10%) reported focal HI, and 11 (4%) reported atypical HI. Another 105 (36%) report unknown or another type of HI (Figure 3).

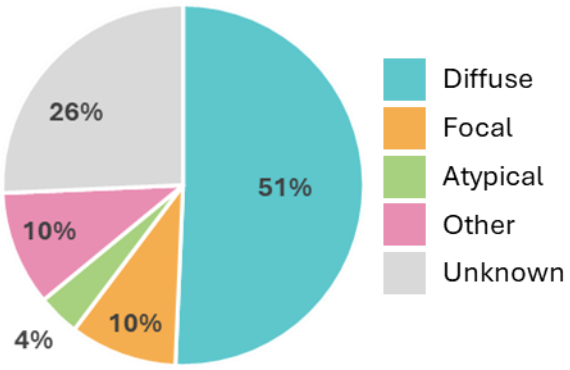


Figure 3. HIGR participants by HI type (n = 292)

Histologically, HI is classified as either focal, diffuse, or atypical, but this form of classification is not universally known for all individuals with HI. HI type may be reported as unknown because 1) the appropriate testing has not been performed to determine the HI type, or 2) because the participant or their caregiver is unaware of the HI type, even if their physician knows.

The focal form of HI typically affects an area of cells in the pancreas and can often be surgically removed. Diffuse HI is a general term that includes several forms of HI that affect the entire pancreas, including KATP (potassium channel) defects, glutamate dehydrogenase HI (GDH-HI), also known as hyperinsulinism hyperammonemia (HIHA), glucokinase HI (GK-HI), those without a known genetic cause, and others. If the tissue histology is not characteristic of either of these forms, it is considered atypical, which can include the overgrowth pattern of Beckwith–Wiedemann syndrome. For individuals who responded "Unknown" or "Other", members of the HIGR research team have been able to confirm active HI based on critical characteristics such as HI medication use or frequency of hypoglycemia.

Genetic Testing

Across all participants who answered survey questions about genetic testing (n = 293), 81% reported that they received a genetic test, and 18% did not receive a genetic test. 54% of all participants reported a positive result for a gene associated with HI across one or more genetic tests. 22% received a negative result after one or more genetic tests, and 5% had a genetic test but did not know or did not report the result (Figure 4).

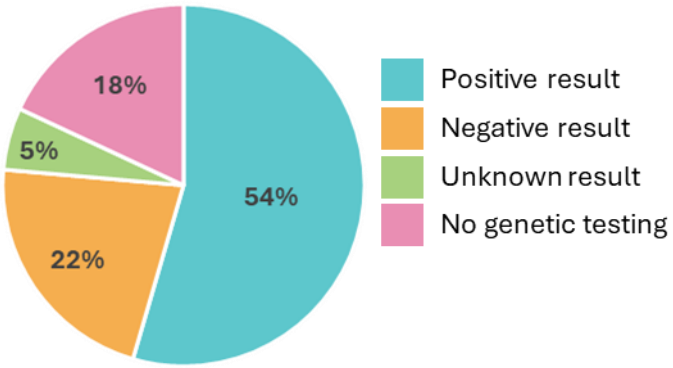


Figure 4. Genetic testing performed and results (n = 293)

Of the 236 participants who reported receiving a genetic test, 65% reported that the results were positive for a gene associated with HI (Figure 5). Of the 33% who had a negative or unknown result from the first test, 44% reported that additional genetic testing was performed. 4/34 (12%) received a positive result after additional genetic testing; 88% did not receive a genetic diagnosis after additional testing. There are many reasons why additional testing may have been performed, including tier-1 gene testing of a small number of genes expanded to panel gene testing or initial testing that occurred before new genes related to HI were identified.

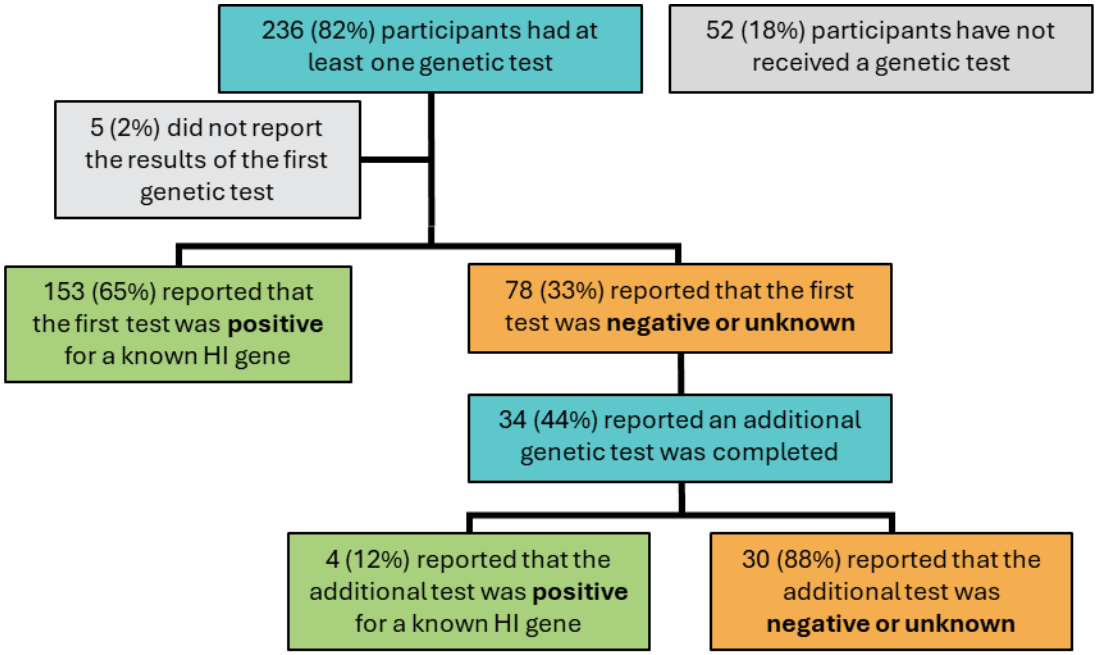


Figure 5. Flow chart showing percent positive genetic testing, for the first genetic test and any additional genetic tests.

Medication Management

223 people reported their medication use in the *Medication Management* survey. Figure 6 displays the percentage of participants who have taken each medication to treat HI, either in the past or currently. The table below the bars displays the total number and percentage of participants who have ever taken each medication. Individuals may be taking multiple medications, so the percentages will not add up to 100%.

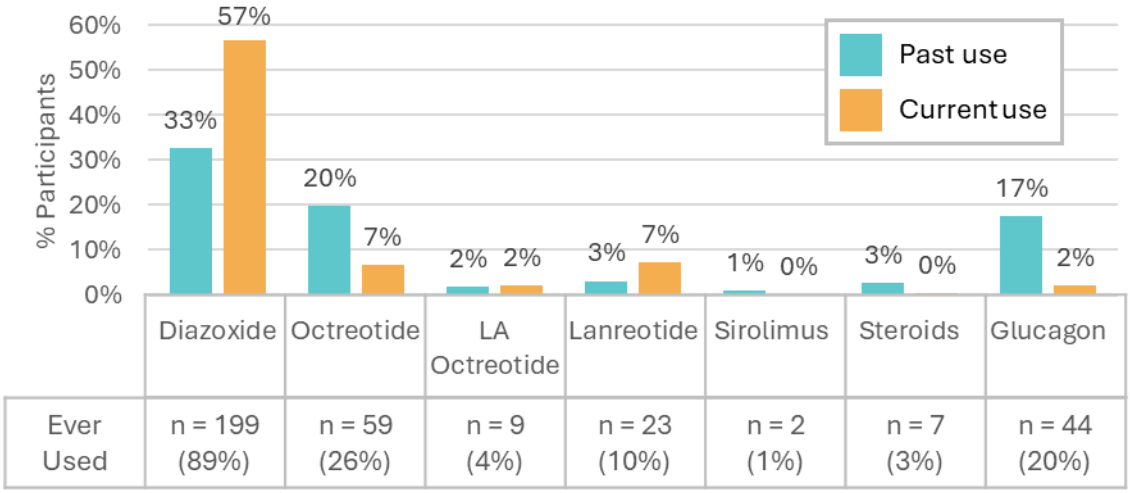


Figure 6. Medications used to treat HI currently and in the past (n = 223)

Figure 7 shows the age of participants who are currently taking diazoxide or a somatostatin analog (SSA; octreotide, long-acting octreotide, or lanreotide). 199 participants (88%) reported taking diazoxide at some point, and 126 (57%) were currently taking diazoxide at the time of completing the medications survey. 69 participants (63%) who reported they were currently taking diazoxide were under 5 years old, and 10 participants (8%) were also currently taking at least one other medication. 73 participants (41%) reported taking an SSA at some point, some participants reported taking more than one type of SSA, and 34 (47%) were currently taking an SSA at the time of completing the medications survey. 22 participants (65%) who reported that they were currently taking an SSA were under 5 years old.

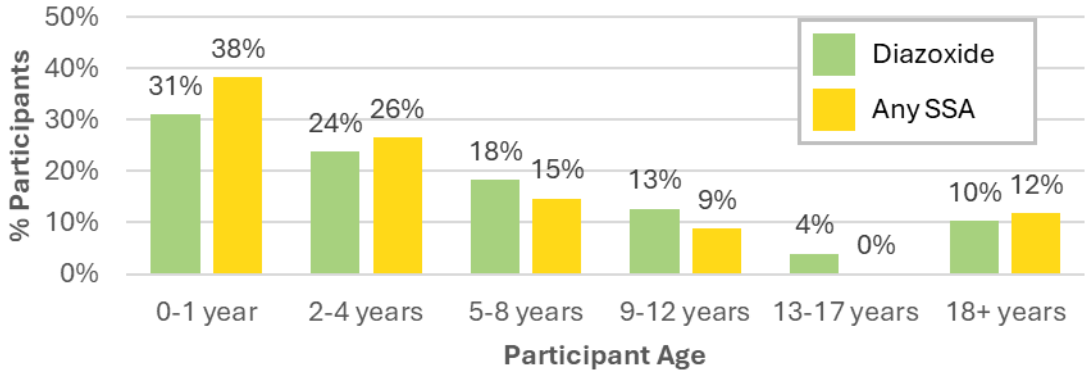


Figure 7. Age of current diazoxide (n = 126) and somatostatin analog (SSA) (n = 34) users. SSAs include octreotide, long-acting octreotide, and lanreotide.

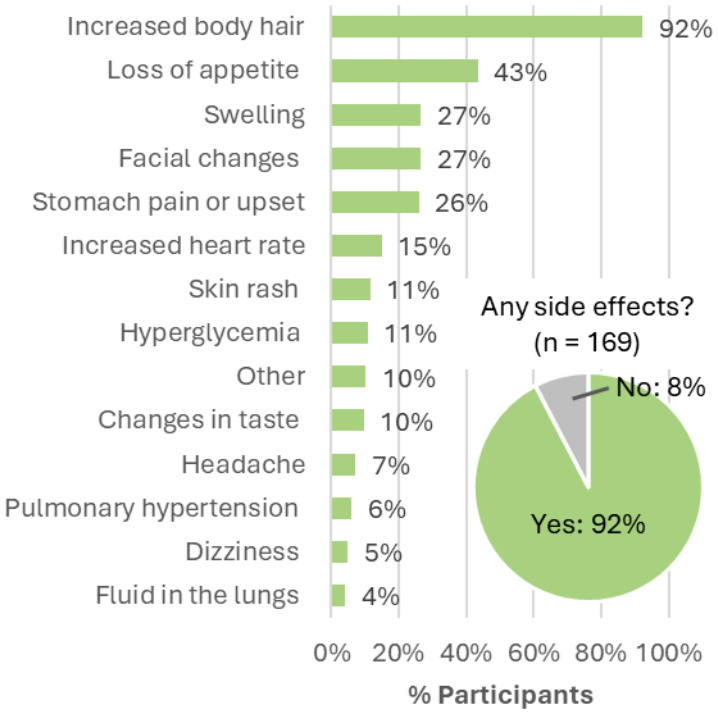


Figure 8. Reported side effects of diazoxide (n = 166). Inset pie chart: Presence of any side effect (n = 183).

Diazoxide and SSAs are all associated with multiple side effects. 92% of 183 participants reported that they had experienced at least one side effect of diazoxide. Figure 8 shows the most common side effects of diazoxide reported by 166 HIGR participants. The most frequently reported side effects for diazoxide users include increased body hair (92%), loss of appetite (43%), swelling (27%), facial changes (27%), and stomach pain or upset stomach (26%). Less commonly reported side effects of diazoxide (≤20%) include increased heart rate, skin rash, hyperglycemia, changes in sense of taste, headache, pulmonary hypertension, dizziness, and fluid in the lungs. 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, 54% of 112 individuals who currently use diazoxide and also completed the *Glucose Monitoring* survey reported continued hypoglycemia at least once per week while on diazoxide.

77% of 60 participants reported that they had experienced at least one side effect of an SSA. The most commonly reported side effects for SSA users include changes in stool (59%), stomach pain or upset (28%), gallstone/ gallbladder sludge (28%). Less commonly reported side effects (≤25%) include hyperglycemia, nausea, growth suppression, and injection site problems (Figure 9). 61% of people on an SSA reported continued hypoglycemia. Additionally, 74% of 34 individuals who currently use an SSA and also completed the *Glucose Monitoring* survey reported continued hypoglycemia at least once per week while on the SSA.

Surgical Management

Of the 224 participants who completed the *Surgical Management* survey, 26% reported that they had one or more pancreatectomies to treat HI. Of those with a known HI type, 60% of those who had a pancreatectomy had diffuse disease and 33% had focal disease (Figure 10).

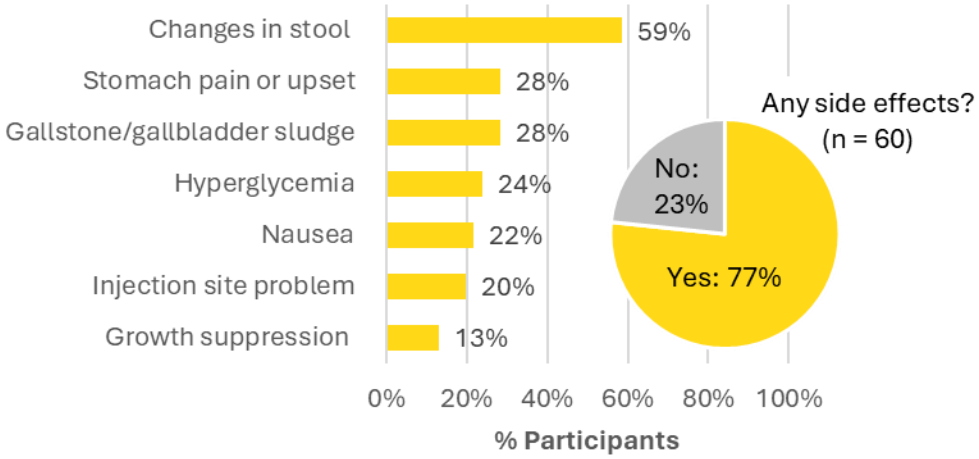


Figure 9. Reported side effects of SSAs (octreotide, long-acting octreotide, lanreotide) (n = 46). Inset pie chart: Presence of any side effect (n = 60).

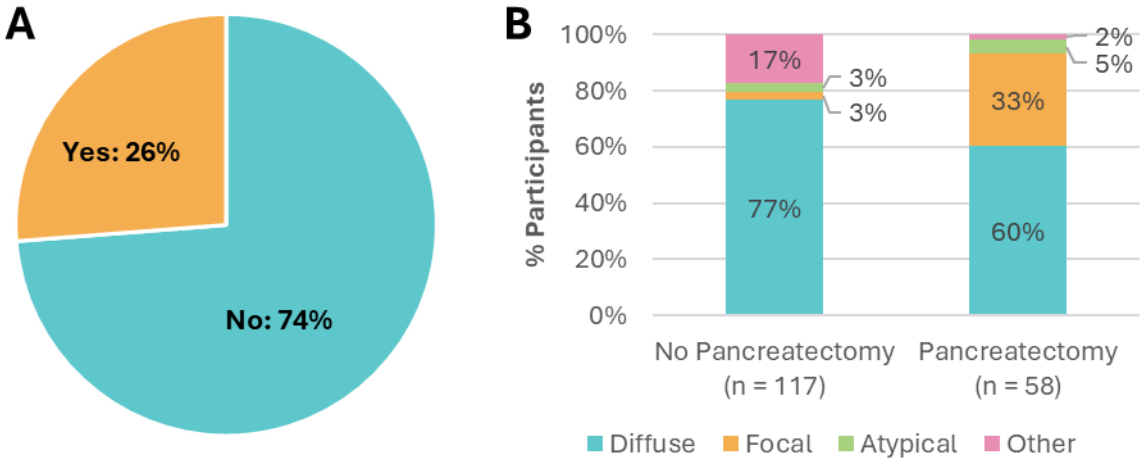
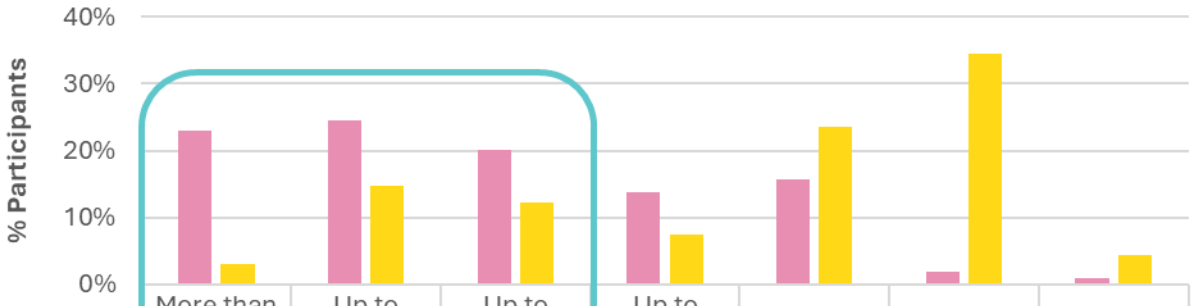


Figure 10. Presence or absence of pancreatectomy to treat HI (n = 244) and surgical status by HI type (n = 175).

Glucose Monitoring

Figure 11 presents the reported frequency of low and high blood glucose. Over 200 participants reported how frequently they experience blood sugars below 70 mg/dL (3.9 mmol/l, 0.7 g/L) and above 180 mg/dL (10 mmol/L, 1.8 g/L). Note that n = 56 participants who reported that HI had resolved or that they had been diagnosed with diabetes have been excluded from this analysis. Of the remaining participants, 68% report experiencing lows at least once per week, and 30% experience highs at least once per week.



	More than once a day	Up to once a day	Up to once a week	Up to once a month	Infreq-uently	Never	Unknown
Hypoglycemia (Lows, n = 204)	23%	25%	20%	14%	16%	2%	1%
Hyperglycemia (Highs, n = 203)	3%	15%	12%	7%	24%	34%	4%

Figure 11. Frequency of hypoglycemia (lows, n = 204) and hyperglycemia (highs, n = 203).

Feeding Issues

Figure 12 shows the presence and current status of feeding issues reported by 237 participants who completed the *Diet & Feeding* survey. 65% of participants reported having experienced feeding issues.

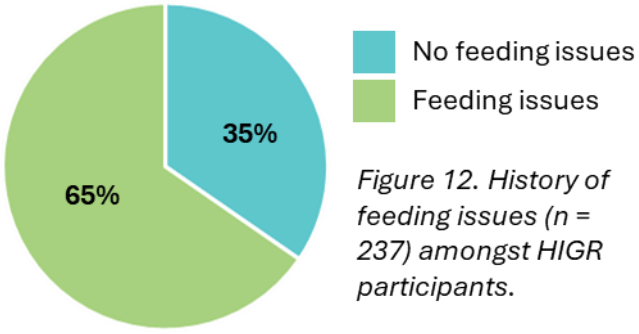


Figure 12. History of feeding issues (n = 237) amongst HIGR participants.

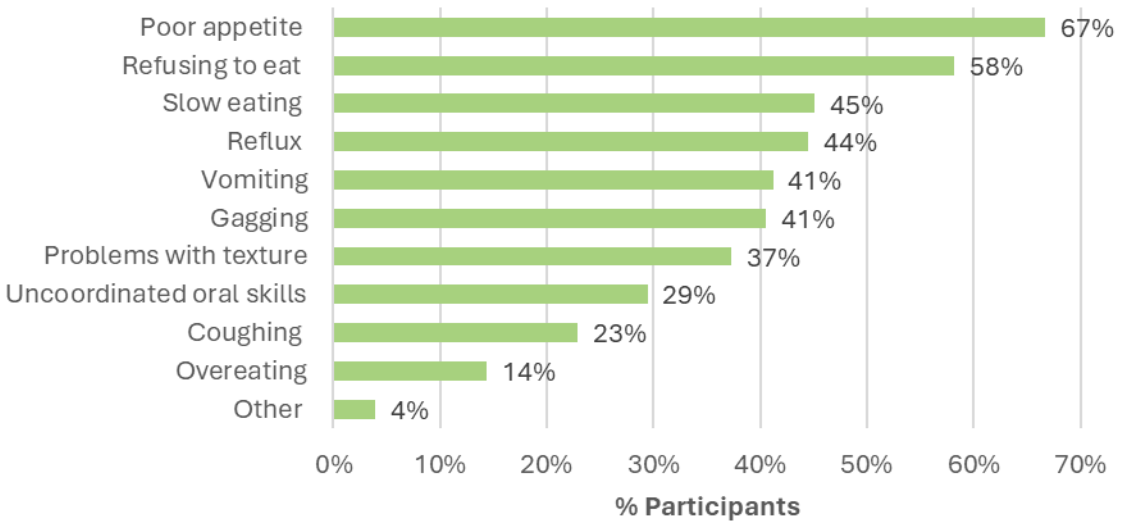


Figure 13. Feeding issues ever experienced (n = 153).

153 participants specified the feeding issues they had experienced. The most common feeding issues reported were poor appetite (67%), refusing to eat (58%), and slow eating (45%). Reflux, vomiting, gagging, problems with texture, and uncoordinated oral skills were each reported by over 25% of the participants (Figure 13).

Figure 14 shows the reported age of participants when feeding issues resolved. Of 55 participants who reported that feeding issues had resolved, 31% resolved within the first year of life, and 84% resolved in early childhood (6 years and under). Of the 90 participants who reported that feeding issues were not fully resolved, 71% were aged six years old and younger, 17% were aged seven to 12 years, and 12% were 13 years and older.

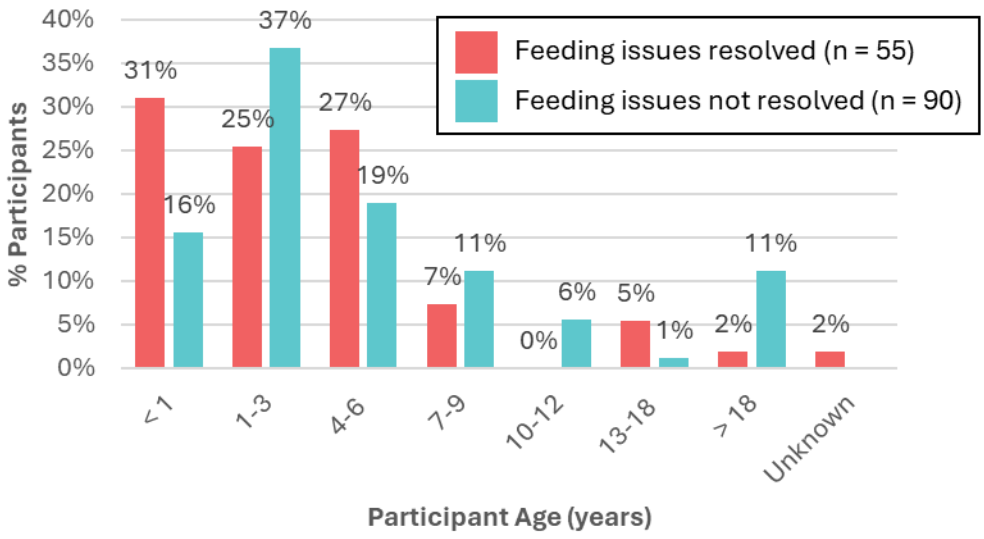


Figure 14. Age of participants when feeding issues fully resolved (red; n = 55), and current age of participant at report of feeding issues not fully resolved (blue, n = 90)

Neurological Disorders

Of the 180 individuals who reported on other medical conditions, 81 (45%) reported that the participant was diagnosed with one or more neurological conditions. Of the 81 participants with a neurological condition, the most common was epilepsy (35%), followed by attention-deficit/hyperactivity disorder (ADHD, 33%), learning disability (27%), autism spectrum disorder (ASD, 23%), and anxiety disorder (23%). Less common neurological disorders included migraine / headache disorder, language disorder/auditory processing disorder, intellectual disability, and cerebral palsy (Figure 15). This is likely an underestimate of the prevalence of neurological disorders within individuals with HI due to the younger age of most HIGR participants. Of those who reported no neurological disorders, 61% were aged six years old or younger.

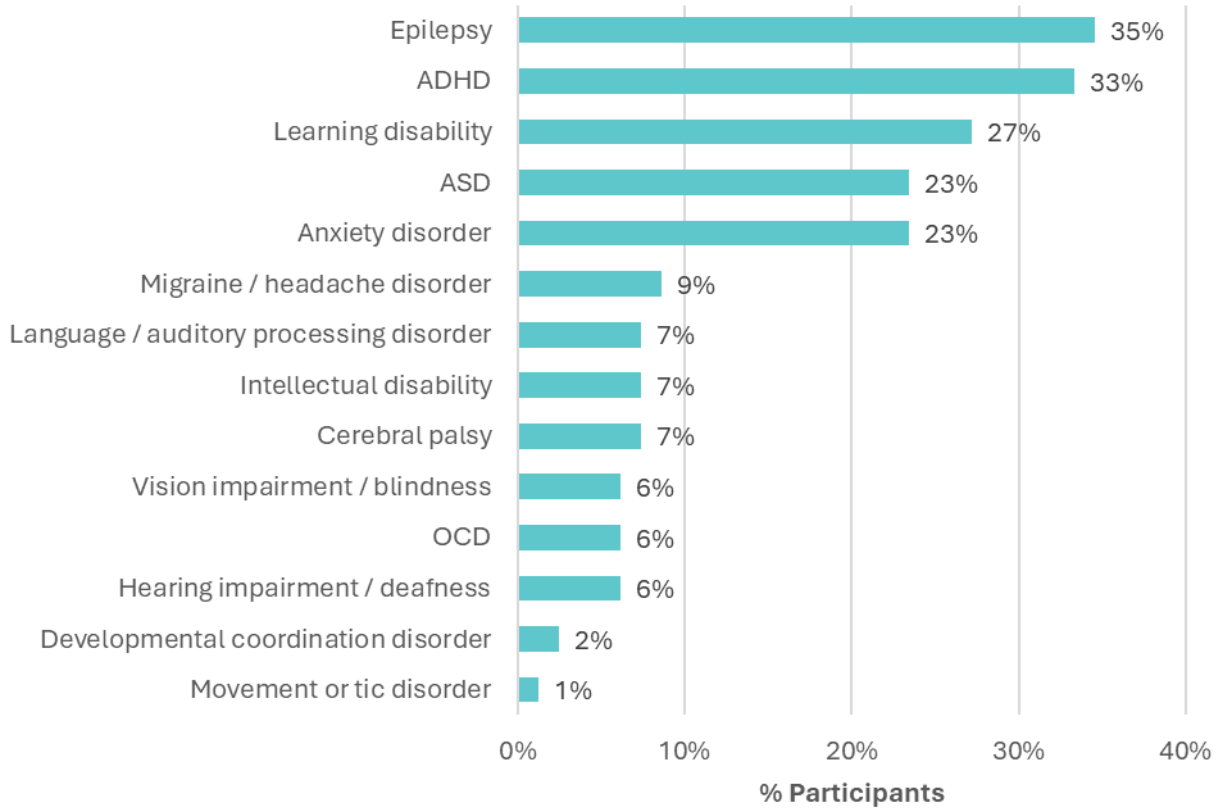


Figure 15. Neurological conditions reported by participants (n = 81).
Neurological condition labels have been shortened. Options presented to survey respondents were: Epilepsy; Attention-deficit/Hyperactivity disorder (ADHD); Learning disability (in reading, written expression, mathematics, or other specified impairment); Autism Spectrum Disorder (ASD); Anxiety disorder; Migraine/Headache disorder; Language disorder / Auditory Processing Disorder; Intellectual disability; Cerebral palsy; Vision impairment / Blindness; Obsessive Compulsive Disorder (OCD); Hearing impairment / Deafness; Developmental coordination disorder; Movement or tic disorder.

Developmental Delay

Of 235 participants who completed the *Development* Survey, 110 (45%) participants reported that they had experienced delays in reaching developmental milestones (Figure 16). Figure 17 shows the percentage of participants who reported delays in each milestone area listed. Please note that many participants reported delays in more than one milestone area. Areas that most participants were delayed in were gross motor and language skills. 68% reported that they had experienced delays in gross motor milestones, such as sitting, crawling, or walking. 59% reported delays in language, speech, or communication milestones. Around one-third of respondents indicated that the participants had experienced delays in an area that was not listed in the survey, and the majority of these (70% of respondents who selected "other" and 24% of the total group) described feeding issues. While feeding is not typically categorized as a developmental milestone, the prevalence of comments in this section highlights the importance of feeding issues to the community of HIGR participants.

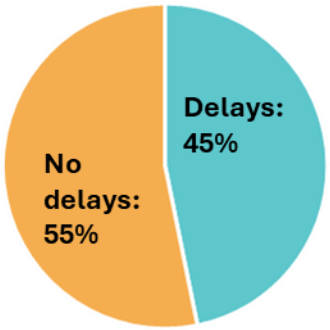


Figure 16. Presence of delays in reaching developmental milestones (n = 235)

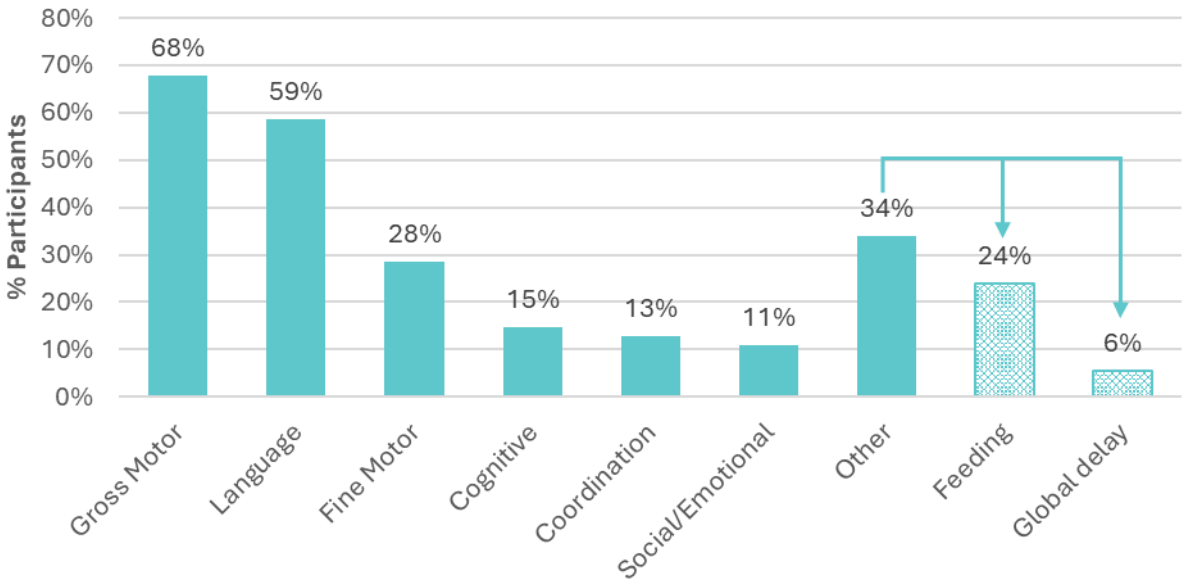


Figure 17. Developmental areas with reported delays in milestones (n = 109). Feeding and global delays represent common themes described in open text for the "Other" category.

Burden of Disease

The Direct Costs of Hyperinsulinism

The majority of families within the HIGR community are experiencing financial difficulties as a result of HI. 63% of 204 caregivers reported that their household income had been impacted due to HI, and 39% reported that they were struggling to some degree to pay for the costs associated with HI (Figure 18). HI is a complex medical condition often requiring expensive medications or surgical procedures, specialized equipment, and around-the-clock care. For many families, medical insurance does not cover many of these direct expenses. Furthermore, the highly specialized nature of the care that is required by people with HI, especially younger children, often makes it necessary for one parent to focus on caregiving, which may lead to a loss of income or earning potential (such as a missed promotion).

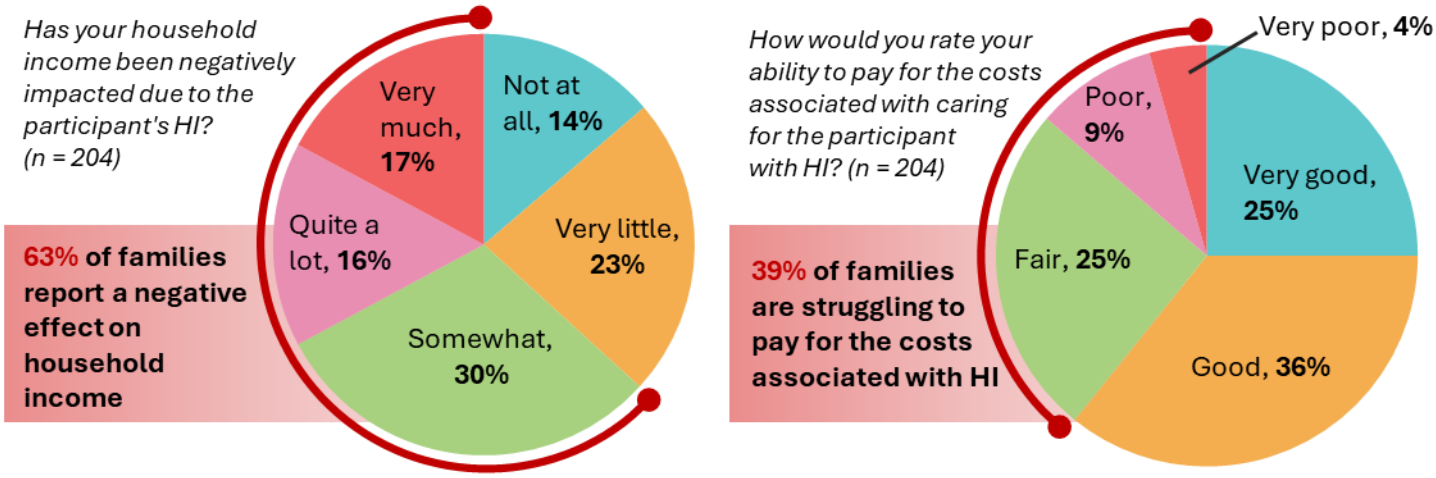


Figure 18. Insights into the effects the direct costs of HI has on families.

The Indirect Costs of Hyperinsulinism

The indirect costs of HI will look very different for different families: for one family, the burden of tube feeding may have a major impact on the ability to take family days out or travel for vacation, whereas, for another family, the fear of hypoglycemia may be the biggest source of stress and anxiety, leading to sleepless nights and pressure on mealtimes.

One example of an indirect cost of HI is reflected in the caregivers' ability to trust others to care for their loved one with HI. The ability to step away from caretaking responsibilities is an important aspect of life for all parents, and even more so for families of children with complex medical needs. Data from HIGR shows that caregivers of younger children (0 – 9 years) more frequently respond that they never or seldom feel comfortable allowing others to care for the participant, whereas caregivers of older children (10 – 17 years) were more likely to respond with greater comfort levels (quite often, very often, or always).

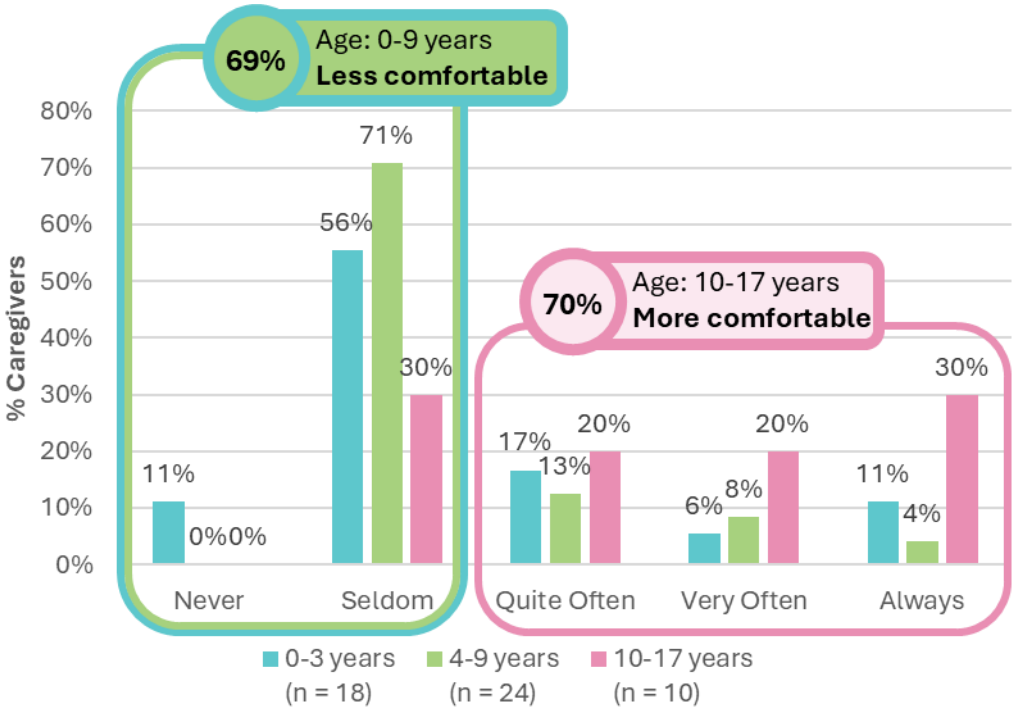


Figure 19. Caregiver comfort level when allowing others to care for the participant without you being present (i.e. babysit) (n = 52)

This data represents just a small sample of the insights that can be gathered from survey responses in HIGR. There is so much more that we can learn from those who have chosen to share their personal experiences of life with HI. We encourage every individual with HI and their caregivers to complete all HIGR surveys. Each survey tells us something difference about life with HI, and it is important for families to complete all surveys to tell the full story and ensure that their unique experiences are captured.

MaxHIGR

Maximizing the Utilization of the HI Global Registry (MaxHIGR) is a project that was launched in September 2022 to grow and expand the research possibilities of HIGR. For HIGR participants who agree to involve their physician in HIGR, MaxHIGR provides a way for physicians to share medical information about patients directly within the registry, which will enhance its value and impact.

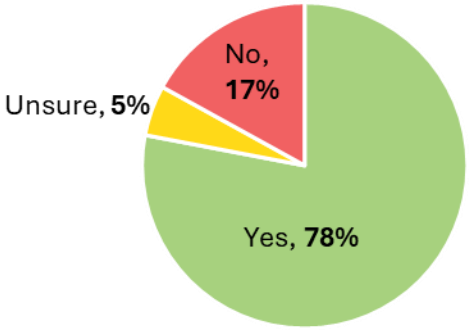


Figure 20. Permission granted for HIGR staff to contact the participant's physician (n = 100).

Participants or Caregivers are asked if they would like to participate in MaxHIGR through a survey on their dashboard. Of the 100 individuals who have completed the survey, 78% provided permission for HIGR staff to contact their physician to complete the MaxHIGR Physician Form (Figure 20). 5% of individuals said they were unsure and requested more information about MaxHIGR. HIGR staff then reached out to each individual to provide more information and answer questions. Respondents who indicate interest are asked to provide contact information for their endocrinologist, and US residents are asked to sign a HIPAA authorization form. HIGR staff will then contact the participant's physician to request that they complete the MaxHIGR physician form. 56 email requests were sent to physicians, of which 38% have returned a completed MaxHIGR Physician Form (Figure 21).

The MaxHIGR physician form adds physician-provided treatment and diagnosis details 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.

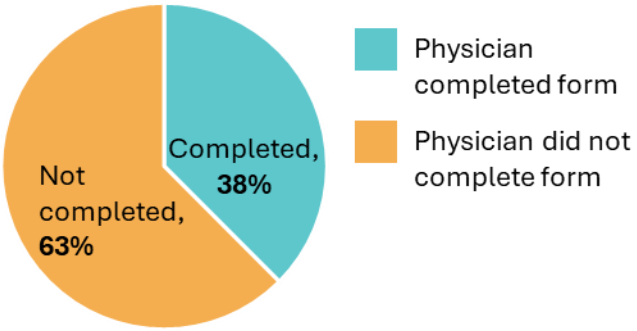


Figure 21. MaxHIGR Physician Form completion status (n = 56)

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 in 2020. Researchers from leading HI institutions worldwide are partnering with Dr. Banerjee and CHI on this project.

Comparison of Physician Responses vs Participant/Caregiver Responses

One of the goals of MaxHIGR is to provide physician-reported data to supplement and reinforce participant-/caregiver-reported data and fill in missing data on medical details that the participant or their caregiver might not know. For this reason, we plan to conduct a thorough analysis of physician vs participant/caregiver responses to various questions throughout the surveys. This project is currently in an early stage, but we are excited to share some early insights in this Annual Report. Here, we will share data on the physician and participant/caregiver (Pt/Cg) agreement on an objective fact from the medical history (HI type) and a more nuanced topic (feeding issues).

20 participants received a completed MaxHIGR Physician survey. We compared the physician and Pt/Cg reported responses to questions about birth weight and feeding issues (Table 2).

Table 2. Comparison of questions across physician- and participant-/caregiver-reported surveys.

Analysis	Survey	Respondent	Question
HI Type	MaxHIGR	Physician	Diagnosis/Type.
	Diagnosis	Participant or Caregiver	What type of congenital hyperinsulinism diagnosis has the participant been given?
Feeding issues	MaxHIGR	Physician	Has the participant experienced any feeding difficulties?
	Diet & Feeding	Participant or Caregiver	Has the participant experienced any feeding issues on a regular basis?

HI Type

Agreement between responses: 75% of Physician-Pt/Cg pairs agreed on the participant's HI type (Figure 22). All pairs either both reported "diffuse" or both reported "unknown" or "other".

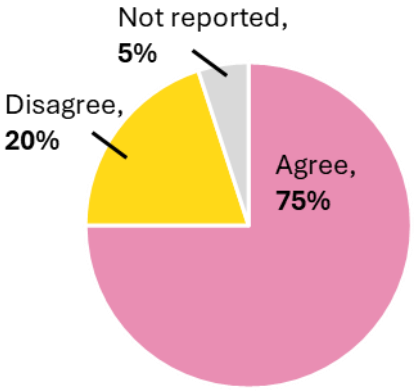


Figure 22. Agreement on participant's HI type.

Disagreement between responses: 20% of pairs disagreed on the participant's HI type. In half of the pairs, the physician reported "diffuse" and the Pt/Cg reported "unknown", and in the other half, the physician reported "atypical" and the Pt/Cg reported "diffuse".

Missing data: 5% of pairs were missing data on HI type from either the physician, the Pt/Cg, or both. In one case, the physician-reported data filled in a gap missing from an uncompleted participant survey and reported focal disease.

Knowing the type of HI that an individual has often helps guide treatment options. For example, focal disease can often be cured via surgical removal of the focal lesion. It is common for many individuals with HI to not know their HI type. HI type can only be confirmed via 18-F DOPA imaging or histological evaluation of the tissue after pancreatectomy. As such, many individuals may not have received the appropriate testing to definitively diagnose the HI type. In addition, there are many different ways to characterize HI, and HI type (diffuse, focal, or atypical) is just one way. HI can also be defined by

genetics or diazoxide-responsiveness. There are, therefore, many pieces of information that, together, characterize each individual's disease and guide the most appropriate treatment options for them.

Feeding Issues

Agreement between responses: 45% of Physician-Pt/Cg pairs agreed on the history of feeding issues (either both said "yes" or both said "no"; Figure 23). In 75% of these cases, the physician described the feeding issues, but generally described fewer feeding issues than the Pt/Cg described. This may be partially explained by the fact that the physician was provided with an open-text box to freely describe feeding issues, whereas the Pt/Cg was provided with pre-defined feeding issues that they could select, in addition to a free text box for any additional issues.

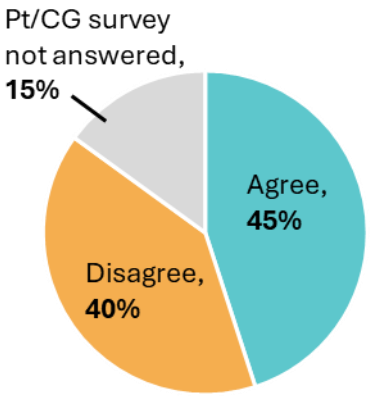


Figure 23. Agreement on history of feeding issues.

As an example, one physician reported that the patient experienced "*oral aversion, vomiting*", whereas the Pt/Cg selected nine separate issues from the Diet and Feeding survey: poor appetite, refusing to eat, slow eating, uncoordinated oral skills, problems with texture, coughing, gagging, vomiting, and reflux.

Disagreement between responses: 40% of pairs disagreed on the history of feeding issues. For 30% of the pairs, the physician either explicitly reported no feeding issues or skipped the question, whereas the Pt/Cg reported feeding issues. In all but one case, the Pt/Cg-reported data described at least three feeding issues. For 10% of the pairs, the physician reported feeding issues but the Pt/CG reported no feeding issues. In each of these cases, the physician described feeding issues that the Pt/Cg had not reported. In one example, the physician reported *"Appetite affected on diazoxide. Breakfast especially challenging"*, but the Pt/Cg reported that the participant had no feeding issues. This discrepancy was not due to a difference in the age at which the surveys were completed. This may represent an education gap in terms of which challenges are clinically considered to be feeding issues.

Physician filled the gap in missing Pt/Cg data: 15% of Pt/Cg responses were unavailable because the respondent did not complete the Diet & Feeding survey. In all of these cases, the physician-reported data filled in this gap and provided insight into the participant's history of feeding issues that was missing from the participant survey.

Feeding issues are common in HI but may be under-recognized by some physicians; either not recognizing the full extent of feeding issues or not recognizing the presence of issues at all. There are many reasons why this may occur such as physicians placing a higher focus on other issues during clinical visits (e.g. glycemic control), or due to families downplaying feeding issues and not discussing them with their physician. This is an area of the HI experience that requires much more research to fully understand.

Glucose Monitoring Data

In November 2024, HIGR enabled the collection of glucose monitoring data from Dexcom continuous glucose monitors (CGMs). This program is currently in its early stages and we encourage all members of the HI community who use a Dexcom CGM to share their values with HIGR. Information about glucose monitoring has the potential to tell us so much about the true day-to-day impact of HI on the lives of people in this community. CGM information can be paired with HIGR survey responses to help HI researchers understand how glucose management is impacted by HI type, treatment options, medications, and so much more! This feature is currently available for Dexcom CGM users (all Dexcom generations), and we are actively working to add glucometers and more CGM devices. We are excited to share more updates about this in 2025!

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 sub-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 (the HI patient or their legal, authorized representative (parent/guardian) if the patient is a minor or unable to register due to cognitive difficulties). As of November 2024, 606 individual participants were registered with HIGR. This represents an 18% increase from last year! This number does not include caregivers who created an account but did not add a participant with HI.

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 themselves have HI and also have a child with the condition.

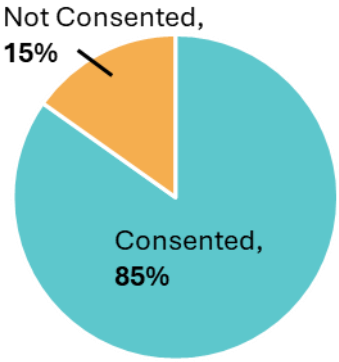


Figure 24. HIGR registration by consent status (n = 606).

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. Of the 606 registered participants, 514 participants (85%) have been consented (Figure 24). This includes 84 adults with HI who had the capacity to consent to research themselves (14%) and 430 adults and children who were consented by a caregiver (71%).

During consent, respondents must agree to be contacted for registry purposes as part of the consent process and to participate in HIGR. They can opt-in to be notified of potential clinical trials and for future networking opportunities within the international HI community. The respondent can update the contact permissions at any time.

Stage 3 is when a respondent submits at least one survey. Currently, 365 participants (68% of all consented participants) have at least one completed survey (Figure 25).

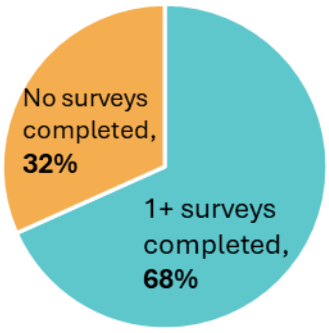


Figure 25. HIGR survey completion status (n = 514).

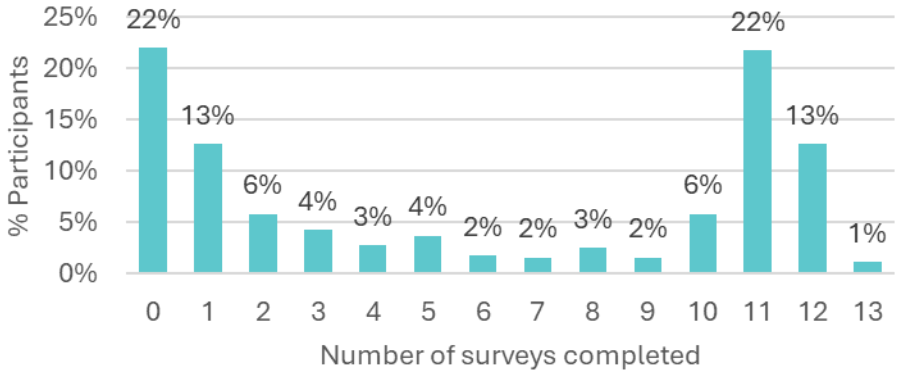


Figure 26. Number of surveys completed per consented participant (n = 514).

Stage 4 is when a respondent completes all relevant surveys. The *Participant QOL* survey is only available to participants aged 14 and above, and the *Caregiver QOL* is only available to caregivers of a participant, so depending on who the respondent is, 12-13 surveys must be completed and submitted to achieve full participation in HIGR. Of the 512 registered participants, 41% have successfully completed 10 or more surveys (Figure 26). The MaxHIGR participant survey (interest form to provide permission for CHI staff to contact the participant's physician) currently has the lowest completion rate across all surveys. This is largely influenced by its more recent launch date compared to other surveys, and indicates a need for further engagement with individuals who have not interacted with the registry recently. 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

HIGR is a patient-powered research tool, and patient-powered research tools are only as strong as the patients who power them! The continued participation of people with HI and their families is now more important than ever. We know from the data that participants have provided in HIGR that HI is a complex condition, and people with HI often experience changes in symptoms and their management over time. It is so important to make sure that your voice and your experiences are updated and included in HIGR reports. Your participation is what strengthens HIGR and HI research.

Examples of social media posts from various engagement campaigns throughout 2024.

Closing Statement

This has been another year of impressive growth for HIGR! We have increased registrations by 18% compared to last year, added seven new languages, started collecting data from continuous glucose monitors, and shared data with many people connected to the HI community. In 2025, we will focus on further expanding participation in HIGR and encouraging full survey completion from all participants and caregivers. Your ongoing participation remains as important as ever: we encourage participants and caregivers to complete and update their surveys and physicians to complete the MaxHIGR Physician form when requested. Thank you!

Acknowledgments

The HIGR 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 have been possible without the dedication of HIGR participants and their families, 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.

HIGR Steering Committee

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.

- Sandra Melo (Portugal)
- María Paz Oviedo (Paraguay)
- Irene Promoussas (Austria)
- Ulrike Seyfarth (Germany)
- Lora Van Arsdell-Bartocci (USA)
- Dr. Jean-Baptiste Arnoux (France)
- Dr. Indi Banerjee (UK)
- Dr. Henrik Christesen (Denmark)
- Dr. Antonia Dastamani (UK)
- Dr. Diva D. De León-Crutchlow (USA)
- Dr. Raphael Del Roio Liberatore Jr (Brazil)
- Dr. Sarah Flanagan (UK)
- Dr. Klaus Mohnike (Germany)
- Dr. Pratik Shah (UK)
- Dr. Charles Stanley (USA)
- Dr. Paul Thornton (USA)

HIGR Sponsors

HIGR has received funding through the HIGR Corporate Sponsors: Rezolute, Zealand Pharma, and Hanmi; the LightCure Consortium Project funded by the European Union (101080327); and many individual and foundation donors. The HIGR investigators are very grateful to all our sponsors for making this patient-powered research possible.