

2023 Annual Report

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Introduction

In 2023, the HI Global Registry (HIGR) reached a very important milestone: HIGR has now been active for <u>five years</u>, and in that time, over 500 participants with hyperinsulinism (HI) or their caregivers have registered to share their experiences. This is a significant achievement for the HI community, and the data provided by every single participant will help to advance HI research for better treatments, faster diagnosis, and improved outcomes for everyone affected by HI.

HIGR also moved to a new platform in 2023, and some exciting new features have been added, including six new languages, improved survey questions, integration of CGM and glucometer data, and separate registry accounts for caregivers and participants.

This report provides a sampling of insights gleaned from HIGR data since the launch of HIGR in October 2018 through November 2023, as well as more information about HIGR's new elements and functionality 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.

- Contact & Demographics
- MaxHIGR (Physician provided data)
- 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

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 will be 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.

A new survey, called *Dashboard*, was added in 2023 to help prompt respondents to think about anything notable that may have changed in recent months. Respondents will be prompted to take the *Dashboard* survey every six months. If they indicate any notable changes in the *Dashboard* survey, they will be directed to update the information in the appropriate base survey.

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 2023 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) Most questions within each survey are optional, and respondents can choose to skip questions they do not want to answer¹.
- 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.

¹ Note that most survey questions now require an answer on the new platform, but respondents will be able to select "Prefer not to answer" if desired. Only respondents who completed surveys on the old platform were able to skip questions.

The HIGR Research Team

CHI and the HIGR Steering Committee are delighted to announce the expansion of the HIGR research team. Lauren Lopez, PhD, joined CHI as the Registry Director in August 2023 and adds a range of professional skills to the HIGR research team. Lauren's knowledge base includes biomedical research, real-world data collection in rare disease, and data analysis and visualization, with a specific interest in making research results accessible to all audiences. You can read more about Lauren and the rest of the HIGR research team below.

Lauren Lopez 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. Lauren has joined Congenital Hyperinsulinism International as the Registry Director and will manage all aspects of the HI Global Registry including recruitment, data curation, analysis, and publications.

Mahlet Mesfin is a seasoned public health specialist whose career spans research, data management, and data analysis. Holding a degree in Public Health and a professional certificate in Project Management, she has experience leading engagement campaigns, managing international projects, and conducting different aspects of research, including qualitative and quantitative methods and synthesizing diverse data sets. Her hands-on experience reflects her commitment to enhancing patient outcomes and tackling intricate health challenges on a global scale.

Tai Pasquini 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.

Julie Raskin 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 a founder and the chief executive officer 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 31 global conferences and meetings, created disease awareness information in 23 languages, provided genetic testing for those suspected of having hyperinsulinism from 61 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 has recently been appointed to the New Jersey Rare Disease Advisory Council.

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. 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 2023 – A Year in Review

Platform Migration to Matrix

2023 has been a very big year for HIGR – the registry is now hosted on the Matrix platform by Across Healthcare! The move to Matrix was a huge undertaking for the HIGR staff, and we have been hard at work over the last few months preparing for the move. We announced the launch of HIGR 2.0 in November 2023, and are now delighted to share more details of the new features available for HIGR participants and their families.

- 1) New languages to expand our international reach and increase access. HIGR aims to capture the experiences of people affected by HI across the world. To reach this goal, we will be adding six new languages in 2024, making it even easier for more people to contribute their data to HI research by allowing survey completion in their native language. All surveys will be available in English, Spanish, German, French, Italian, Portuguese, and Korean. The surveys have been translated by a certified medical translation company and are now being verified by native speakers from the HI community. This is a significant development, but it is just the beginning, we plan to continue expanding into additional languages in the future.
- 2) Separate registry accounts for participants and caregivers. While the majority of HIGR surveys focus on the person living with HI, a few surveys are designed specifically for the caregivers. Families are now able to create separate accounts for participants and caregivers, allowing separation and privacy of participant and caregiver responses. Furthermore, this allows multiple caregivers to contribute to HI research by each completing their own caregiver surveys, allowing us to capture the experiences of everyone in the family.
- 3) Integration of glucometer and CGM data. Blood glucose management is an integral part of HI management for many families affected by HI, and devices such as glucometers and continuous glucose monitors (CGMs) have been an untapped source of rich data. Starting in 2024, HIGR participants will be able to pair their glucose monitoring device(s) with HIGR and contribute this data to HI research. This will provide researchers with valuable data on blood glucose levels that can be linked to other information provided in the registry, such as how HI is managed (medications, surgery, etc.), health outcomes, and participant/caregiver perspectives on quality of life. Like all data collected in the registry, data privacy and security are an important priority, and all data is deidentified for reporting and research purposes.
- 4) Improvements to surveys. We have learned a lot over the last five years, and during the transition to Matrix, we improved some of the survey questions and answer options based on feedback we received. Some key updates include:
 - New survey questions to help us better understand key topics of interest, including how comfortable parents feel leaving their child with HI with another caregiver and more specific aspects of developmental milestones
 - Improved question wording to make sure respondents know exactly what we are asking
 - Almost all survey questions now require an answer and cannot be skipped with no response; however, a *"Prefer not to answer"* option has been added for those who do not feel comfortable answering
- 5) **Physician profiles for MaxHIGR.** It is now even easier for physicians to contribute data to their patients' HIGR accounts (when requested). Starting in 2024, physicians will be able to access their own physician profiles in HIGR and will be able to complete the MaxHIGR survey online. No need to complete the paper form by hand!

Publications

Last year, three articles using HIGR data were published in peer-reviewed academic journals. That represented a huge success for HIGR as publication in academic journals is a major step in sharing research findings with the wider community of HI clinicians and researchers. This year, HIGR data continues to have an impact through these publications, and together, all three articles have been viewed or downloaded over 17,000 times!

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*Ranking based on the Altmetric Attention Score. All stats are accurate as of December 11, 2023

Hormone Research in Paediatrics	Consensus Statement	
	Horm Res Paediatr DOI: 10.1159/000531766	Received: November 1, 2022 Accepted: May 16, 2023 Published online: July 14, 2023
International C	Suidelines for the Management of	
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This year, HIGR data played a role in influencing the International Guidelines for the Diagnosis and Management of Hyperinsulinism. The guidelines were drafted by an international team of 17 experts, including the Principal Investigator of the HI Global Registry, Tai Pasquini. HIGR data informed several aspects of the guidelines, including the percentage of people with HI who experience feeding issues and the significant prevalence of excessive hair growth as a side effect of diazoxide.

Posters

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 presented at two scientific conferences this year.

Title: Natural History of the Hyperinsulinism Hyperammonemia Syndrome – A Multicenter Retrospective Review Incorporating Patient-centered Data

Presenter: Elizabeth Rosenfeld, MD. Pediatric endocrinologist and recipient of the 2021 Million Dollar Bike Ride grant, which funded this work.
Conferences: 1) Hyperinsulinism — Novel Genes, Drugs and Guidelines, Children's Hospital of Philadelphia Hyperinsulinism Center, April 2023
2) Pediatric Endocrine Society (PES), May 2023
Key Message: Diazoxide dose requirement tends to decrease as patients age. However, most require treatment into adulthood. Presentation with seizure and initial misdiagnosis with epilepsy is common.

Title: Neurologic Outcomes of HI Global Registry Participants

Presenter: Tai Pasquini, MPA, PhD. Principal Investigator of the HI Global Registry and Chief Research Officer at CHI.

Conference: Hyperinsulinism — Novel Genes, Drugs and Guidelines, Children's Hospital of Philadelphia Hyperinsulinism Symposium, April 2023 **Key message**: The early identification of HI and timely appropriate care is critical to prevent brain damage and subsequent neurologic damage. The administration of glucose or dextrose following an initial abnormal blood glucose value did not prevent subsequent neurologic damage in a large subset of HIGR participants. This underscores the importance of following HI guidelines for care and management and the need for better treatments.





Data Brief

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 important figure one day. As of November 6, 2023, HIGR has enrolled 512 participants from 57 countries. The majority of participants are from North America (59%) and Europe (25%) (Figure 1).



512 participants across 57 countries enrolled in the HI Global Registry (HIGR)

Figure 1. Number of HIGR participants by continent.

There is a wide range of ages among HIGR participants, from just a few weeks old to over 50 years old (Figure 2). The majority of HIGR participants are children, and the most common age at the time of joining HIGR is 1-3 years old.



Figure 2. Age of participants at the time of joining HIGR vs current age.

HI Туре

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.

Of the 259 participants who responded to the question on HI type, 129 (50%) indicated diffuse disease, 26 (10%) reported focal HI, and 11 (4%) reported atypical HI. Another 93 (36%) report unknown or another type of HI (Figure 3).



Figure 3. HIGR participants by HI type (n = 259).

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 cells in the pancreas (islet cells) that multiply in number and can often be surgically removed. The diffuse form involves the entire pancreas and is characterized by 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. 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. It is also possible that individuals respond "Unknown" because their child has not had a PET scan yet or their doctor doesn't use the words diffuse to describe their condition. Additional education for the patient community and consistency among the HI community for how we categorize the types of HI will help us to further identify these types moving forward.



Figure 4. Genetic testing performed and results (n = 259).

Genetic Testing

Across all participants who answered survey questions about genetic testing (n = 259), 82% reported that they received a genetic test, and 16% did not receive a genetic test. 54% reported a positive result for a gene associated with HI across one or more genetic tests. 21% received a negative result after one or more genetic tests, and 7% had a genetic test but did not know or did not report the result (Figure 4). Of the 211 participants who reported receiving a genetic test, 64% 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, 28% reported that additional genetic testing was performed. Only 3/29 (11%) received a positive result after additional genetic testing; 85% 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

195 people reported their medication use in the *Medication Management* survey. Figure 7 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 7. Medications used to treat HI currently and in the past (n = 195).



Figure 8. Age of current diazoxide (n = 110) and octreotide (n = 18) users.

Figure 8 shows the age of participants who are currently taking diazoxide and octreotide. 172 participants (88%) reported having taken diazoxide at some point, and 110 (56%) 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 8 participants (7%) were also currently taking at least one other medication. The second most common medication reported was octreotide. 55 participants (28%) reported having taken octreotide at some point, and 18 (9%) were currently taking octreotide at the time of completing the medications survey. 13 participants (72%) who reported that they were currently taking diazoxide were under 5 years old, and 5 participants (28%) were also currently taking at least one other medication.



Figure 9. Side effects of diazoxide (n = 155). Inset pie chart: presence of any side effects (n = 213)

Diazoxide and octreotide are both associated with multiple side effects. 98% of 213 participants reported that they had experienced at least one side effect of diazoxide. Figure 9 shows the most common side effects of diazoxide reported by 155 HIGR participants. The most frequently reported side effects for diazoxide users include increased body hair (91%), loss of appetite (41%), swelling (25%), stomach pain or upset stomach (25%), and facial changes (23%). Less commonly reported side effects of diazoxide (≤20%) include increased heart rate, skin rash, changes in taste, headache, dizziness, fluid in lungs (pulmonary hypertension), 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, 53% of individuals reported continued hypoglycemia at least once per week while on diazoxide.

The most commonly reported side effects for octreotide users include changes in stool (42%), stomach pain or upset (30%), hyperglycemia (24%), and gallstone/gallbladder sludge (24%). Less commonly reported side effects (≤20%) include nausea, growth suppression, and injection site problems (Figure 10). 58% of people on octreotide reported continued hypoglycemia. Of the 14 individuals who are currently taking octreotide and provided information related to how often they experience low-blood sugars, 71% reported that they have hypoglycemia once per day or multiple times per day.



% Participants Figure 10. Side effects of octreotide (n = 33). Inset pie chart: presence of any side effects (n = 44)

Surgical Management

Of the 203 participants who completed the *Surgical Management* survey, 27% reported that they had received one or more pancreatectomies to treat HI. Of those with a known HI type, 58% of those who had a pancreatectomy had diffuse disease, and 24% had focal disease (Figure 12).



Figure 12. Percentage of participants who received a pancreatectomy to treat HI (n = 203) and surgery status by HI type (n = 157).

Glucose Monitoring

Figure 13 presents the reported frequency of low and high blood glucose. A total of 188 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). Of these individuals, 13 reported that they currently have diabetes and were excluded from this analysis. Of the remaining participants, 63% report experiencing lows at least once per week, and 29% experience highs at least once per week.



Figure 13. Frequency of hypoglycemia (lows) (n=175) and hyperglycemia (highs) (n = 173).

Feeding Issues

Figure 14 shows the presence and current status of feeding issues reported by 196 participants who completed the *Diet & Feeding* survey. 73% of participants reported having experienced feeding issues.





139 participants specified the feeding issues they had experienced. The most common feeding issues reported were poor appetite (63%), refusing to eat (58%), and reflux (47%). Slow eating, vomiting, gagging, problems with texture, and uncoordinated oral skills were each reported by over 25% of the participants (Figure 15).

Figure 15. Feeding issues ever experienced (n = 139).



179 participants provided information on both surgery status and the presence or absence of ever having feeding issues (Figure 16). Of those who had a pancreatectomy (n = 43), 79% had experienced at least one feeding issue, and of those who did not have a pancreatectomy (n = 136), 70% had at least one feeding issue.

Figure 16. Presence of feeding issues by pancreatectomy status (n=179).

Figure 17 shows the reported age of participants when feeding issues resolved. Of 46 participants who reported that feeding issues had resolved, 33% resolved within the first year of life, and 85% resolved in early childhood (6 years and under).



Figure 17. Age of participants at the time when feeding issues resolved, or the current age of participants with unresolved feeding issues.

Neurological Disorders

Of the 208 respondents who completed the *Other Medical Conditions* survey, 61 (29%) reported that the participant was diagnosed with one or more neurological conditions. Of the 61 participants with a neurological condition, the most common was epilepsy (39%), followed by autism spectrum disorder (ASD, 30%), learning disability (30%), attention-deficit/hyperactivity disorder (ADHD, 28%) and anxiety disorder (26%). Less common neurological disorders included cerebral palsy, obsessive-compulsive disorder (OCD), headache/migraine, language disorder, and vision and hearing impairments (Figure 18).



Figure 18. Neurological conditions reported by participants (n = 61). Neurological condition labels have been shortened to save space. Options presented to survey respondents were: Epilepsy; Autism Spectrum Disorder (ASD); Learning disability (in reading, written expression, mathematics, or other specified impairment); Attention-deficit/Hyperactivity disorder (ADHD); Cerebral Palsy; Obsessive Compulsive Disorder (OCD); Migraine/Headache disorder; Language disorder / Auditory Processing Disorder; Hearing impairment / Deafness; Vision impairment / Blindness.

Developmental Delay

Of 191 participants who completed the Development Survey, 88 (46%) participants reported that they had experienced delays in reaching developmental milestones (Figure 19). Figure 20 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. 62% reported that they had experienced delays in gross motor milestones, such as sitting, crawling, or walking. 56% 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 (80% of respondents who selected "other" and 28% of the total group) described feeding issues. While feeding is not typically categorized as a developmental milestone, the prevalence of comments



Figure 19. Presence of delays in developmental milestones (n = 191).

in this section highlights the importance of feeding issues to the community of HIGR participants.



Figure 20. Developmental areas with reported delays in milestones (n = 86). "Feeding" represents a common theme described in the "Other" category.

Burden of Disease

Capturing the daily impact of a disease can be incredibly challenging, but it is necessary to gain a better understanding of what it is like to live with HI and to help make improvements in the ways that families are supported. This can include improvements that help with the daily management of the disease, policies that can make it more affordable to treat rare diseases, or helping to measure the benefit of a new treatment. Often, "burden of disease" estimates by researchers simply capture the direct costs, such as medical bills. However, it is important to think about all the different ways the individual living with HI and their family are impacted, including indirect costs, like days missed from work or school, and the impact on overall quality of life.

In HIGR, we have two quality-of-life surveys that aim to capture what it is like to live with or care for someone with HI. However, the burden of HI and its impact on daily life is much broader and is captured throughout other surveys in the registry. For example, the number of times a day that a person is checking their glucometer or the way families may have to plan their day around mealtimes are directly related to quality of life and the overall impact of HI. The HIGR team would like to share more about this overall burden of disease and learn more from the HI community about how they feel their lives are impacted. Therefore, we have added new questions to the surveys to start to dig deeper into aspects of life with HI that have not yet been fully researched and would like to hear from you all in 2024 to help us further define what the burden of HI really means to the community.

The Direct Costs of Hyperinsulinism

The majority of families within the HIGR community are experiencing financial difficulties as a result of HI. 62% of 187 caregivers reported that their household income had been impacted due to HI, and 41% of 184 caregivers reported that they were struggling to some degree to pay for the costs associated with HI (Figure 24). 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 24. Insights into the effects the direct costs of HI has on families.

The Indirect Costs of Hyperinsulinism

The indirect costs of HI are very difficult to measure, and HI impacts so many aspects of life that it is impossible to summarize all indirect costs in one statement. The indirect costs will also 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. We cannot assume what the biggest challenges are for each family, which is why the HIGR team wants to hear from you! We will provide even more opportunities for you to share your experiences in 2024!

This data represents just a small taste 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 all caregivers to complete the *Caregiver Quality of Life* survey and ensure that their unique experiences are captured.

Information for Clinicians and Researchers

MaxHIGR

Maximizing the Utilization of the HI Global Registry (MaxHIGR) is a new project 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.

Participants or Caregivers are asked if they would like to participate in MaxHIGR through a survey on their dashboard. 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.

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.

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.



Patient Initials:	MaxHIGK Form Today's Date:
Please complete the form to the	e 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	Ves No
hypoglycemia	
hypoglycemia	No obvious signs Excess jittery Seizures Unresponsive Other
Other symptoms	
Age at presentation of	Days Months Years
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):
Confirmatory glucagon test	Yes No
Syndromes	Beckwith-Wiedemann Rubinstein Taybi Kabuki Turner Sotos Costello Fanconi Other
Other syndromes	
Other co-morbidities at presentation	Yes
Describe co-morbidities	
Diabetes	Yes No
Describe diabetes	

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: <u>info@higlobalregistry.org</u>

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 <u>www.higlobalregistry.org</u>. 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). During the platform transition from NORD to Matrix, HIGR staff reviewed registry accounts and decided not to migrate accounts where the respondent had signed up but never added a participant (n = 97, 18%). As a result, a total of 512 participants were migrated to Matrix in November 2023. This includes 95 adults with HI who have registered for their own HIGR accounts (19%) and 417 adults and children who were registered by a caregiver (81%).

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. 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 512 registered participants, 433 participants (85%) have been consented (Figure 23). This includes 68 adults with HI who had the capacity to consent to research themselves (16%) and 365 adults and children who were consented by a caregiver (84%).



Figure 23. HIGR Registration by consent status (n = 512).

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, 330 participants (64% of all enrolled participants) have at least one completed survey (Figure 24).

Stage 4 is when a respondent completes all relevant surveys. The *Participant QOL* survey is only available to participants aged 14 and above, so depending on the participant's age, 11-12 surveys must be completed and submitted to achieve full participation in HIGR. Of the 512 registered participants, 30% have successfully completed all relevant surveys (11-12 surveys) (Figure 25).





Figure 24. Number of participants with at least 1 survey completed (n = 512).

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.

Figure 25. Number of surveys completed per participant (n = 512).

Figure 26 shows the completion rate per survey based on the number of participants who were eligible for the survey (*Participant QOL*, n = 124 eligible; all other surveys, n = 512 eligible). *Pregnancy* and *Diagnosis* have the highest completion rates (54% and 50%, respectively), and *Participant QOL* has the lowest completion rate (30%).



Figure 26. Completion rates for each registry survey. Data is displayed as a percentage of those eligible to complete the survey – only participants over the age of 14 are eligible for the Participant QOL (n = 124); all participants are eligible for all other surveys (n = 512)

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.

Moving HIGR to a new platform is the ideal opportunity for participants and their families to re-engage with HIGR. The launch of HIGR on the Matrix platform occurred together with HIGR's fifth birthday and the milestone of reaching 500 registrations, which paved the way for some fun social media content to help raise awareness of HIGR. Together, these posts received 192 likes and nine shares on social media, helping to raise the profile of HIGR.



Examples of social media posts to promote the launch of HIGR on Matrix and celebrate five years of HIGR.



Examples of social media posts for the "We Win Together" campaign".

In addition to engagement surrounding the launch of HIGR on Matrix, CHI has employed various other engagement strategies in 2023 to help grow HIGR. The "We Win Together" campaign was designed to create comradery and highlight the team effort of participating in HIGR. We highlighted the power of "I" by encouraging everyone to say the following statement: "I am on Team CHIbra, and I participate in HIGR". When your individual experience is combined with other participants, it moves research forward for everyone.

The value of HIGR data in HI research was demonstrated this year at several scientific conferences and meetings. HIGR data was presented in the form of research posters at two scientific conferences: Hyperinsulinism — Novel Genes, Drugs and Guidelines, a symposium hosted by Children's Hospital of Philadelphia (CHOP) in April, and the annual Pediatric Endocrine Society (PES) conference in May 2023. The HIGR research team also presented HIGR data at the CHI Collaborative Research Network meeting in Lisbon, Portugal, in December, and the data presented informed small group discussions on newborn screening, CGM guidelines, and advocacy.

Conclusion

HIGR celebrated its fifth birthday and the huge milestone of 500 registrants this year, but this really is only the beginning of our vision for how HIGR can impact HI research. The HIGR research team has many exciting plans in store for 2024, including the launch of six new languages, the integration of glucometer and CGM data, programs to encourage new registrations and ongoing participation for existing users, and new ways for HIGR participants to engage with the wider HI community and advocate for HI research.

Your ongoing participation remains as important as ever: we encourage patients 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.

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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.

- Sarah Dearman (UK)
- Ciara Grace (UK)
- Sandra Melo (Portugal)
- María Paz Oviedo (Paraguay)
- Irene Promoussas (Austria)
- Abigail Ridler (USA)
- 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)
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HIGR Sponsors

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