# Rome Foundation Research Institute Annual Report

**For year 2024**

Prepared by: Douglas A. Drossman, MD (Executive Committee)

Magnus Simren MD, PhD (Research Director)

Jan Tack MD, PhD (Executive Committee, Director of Clinical Research Core)

Olafur Palsson Psy.D. (Co-Director, Data Management and Analysis)

Ami D. Sperber MD, MSPH (Coordinator of Epidemiologic Research)

Madhusudan Grover MD (Director, Biomarker Core)

Tiffany Taft, PhD (Data Manager)

# Part One: Background and Organization of RFRI

The Rome Foundation Research Institute (RFRI) is a subsidiary organization of the Rome Foundation, an international non-profit academic organization dedicated to improving the lives of patients with Disorders of Gut-Brain Interaction (DGBI) formerly called Functional GI Disorders. The RFRI was created in 2018 to advance the scientific understanding of DGBI by developing a semi-autonomous entity that will promote and support research in the field of DGBI. https://theromefoundation.org/research-institute-rome-foundation/

**Vision.** To be the global leader in DGBI research

**Mission.** To improve the lives of patients with DGBI through ground-breaking research

**Aim.** To increase the knowledge of the causes, identification, treatment and care of patients with DGBI.

**Implementation.** To establish an international academic research initiative with leading experts, to facilitate global DGBI research through collaboration with industry and academic partners, and with the following objectives:

- Develop a centralized data acquisition and research coordinating center.
- Serve as an international clearinghouse for investigators and industry in developing, administering, and analyzing clinical research in DGBIs.
- Develop a portfolio of current and future study protocols and an accessible database of knowledge that can be adapted to address specific questions regarding DGBIs' pathophysiology, impact, diagnosis, and treatment.

**Legal Structure and Governance.** The RFRI is governed by the Executive Committee consisting of Magnus Simren MD, PhD (Director and Chair of the Executive Committee of RFRI and Board Member of RF), Douglas Drossman MD (RF President Emeritus and CEO), and Jan Tack MD, PhD (RF President and Chairman of the Board). It is a Type I supporting organization of the Rome Foundation (RF) under Section 509(a)(3) of the US Internal Revenue Code. The corporate office is located in North Carolina, USA; therefore, the RFRI is represented by Douglas Drossman, MD (President), for legal and tax purposes.

**Organizational Structure.** Figure 1 demonstrates the organizational structure.



**Rome Foundation Research Institute**
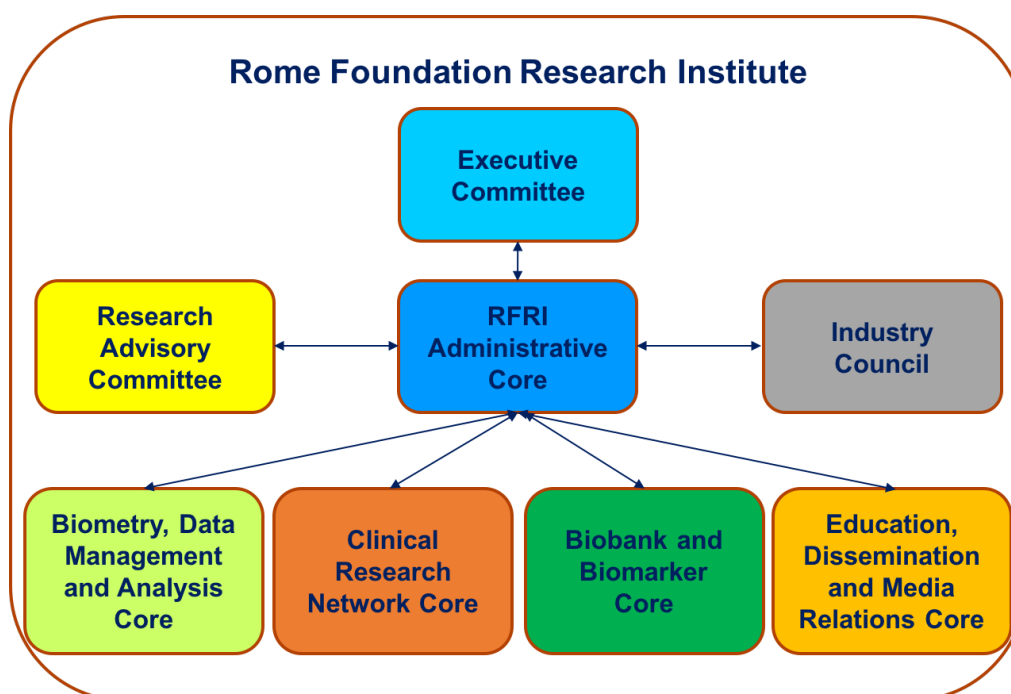
**Executive Committee (EC).** The EC (Drossman, Simren - chair, Tack) supports and directs all activities of the RFRI and is ultimately responsible for assuring that the aims and objectives of the program are achieved.



**Executive Committee**

**Douglas Drossman MD**
Executive Committee

**Magnus Simren MD, PhD**
RFRI Director
Executive Committee

**Jan Tack MD, PhD**
Executive Committee

**Responsible for assuring that the aims and objectives of the RFRI are achieved**

**Administrative Core (AC).** The AC is responsible for the oversight of the day-to-day activities of the RFRI relating to research administration and program implementation, training, education and dissemination of information, collaboration with sponsors and outside agencies, and quality control of all core programs. The AC consists of three executive committee members: the Biometry Co-Director (Shrikant Bangdiwala PhD), the data manager of the RFRI and Biometry Co-Director (Olafur Palsson Psy.D.), the Coordinator of Epidemiologic Research (Ami D. Sperber MD, MSPH), an external industry consultant who advises on collaborations with commercial organizations in the Life Sciences (biopharmaceutical, device, and diagnostics companies) Doug Levine, MD. The AC is also informed by the RAC and the Industry Council (see below)

**Research Advisory Committee (RAC).** The RAC serves as an advisory to the AC as a repository to review and revise research proposals. Currently, the RAC is composed of RF Board members who have been selected based on their academic record of scientific achievement and their ability to evaluate, conduct, and analyze scientific data related to DGBI in consideration of demographic and geographic diversity issues. RAC members are responsible for participating in the various Cores discussed below. Current RAC members include Giovanni Barbara, MD, William Chey, MD, Lin Chang, MD, Laurie Keefer, Ph.D., Brian Lacy, MD, Madhu Grover, MBBS, Samuel Nurko, MD, MPH, Max Schmulson, MD, and Ami D. Sperber, MD, MSPH. The RAC may include members external to the RF board, providing they meet the described guidelines and their participation will help serve the future needs of RFRI.

**Industry Council (IC).** The IC is advisory to the AC and comprises representatives from pharmaceutical and device companies who share the mission of and sponsor the RFRI. Members of the IC interact with the AC in an advisory capacity and review the activities of the RFRI, which may include discussion of ongoing research studies, exchange of ideas for planned initiatives, review of operations of all cores, evaluation of research data, and participation in bilateral or collaborative research studies with privileged status.

**Biometry, Data Management and Analysis Core (Biometry Core).**

The Biometry Core is responsible for providing and ensuring the standards for high-quality data management systems and quality assurance processes. It handles data collection, data management, and statistical analytic aspects for the RFRI. It works under the direction of the Executive Committee. Core members and include the core's co-directors Shrikant Bangdiwala, Ph.D. and Olafur Palsson Psy.D., who is also data manager and coordinator of activities; Tiffany Taft Psy. D. data manager, Carolyn Morris MPH, biostatistician, Ami D. Sperber MD MSPH, coordinator of epidemiologic research, and Johann Hreinsson MD, PhD, biostatistician, and study administration. This Core is also actively involved with ongoing research proposals, as discussed below.

## Rome Foundation Research Institute
## Administration and Biometry Staff



**Douglas Drossman MD**
Executive Committee
CEO Rome Foundation

**Magnus Simren MD, PhD**
RFRI Director
Executive Committee

**Jan Tack MD, PhD**
Executive Committee
President Rome
Foundation

**Ami Sperber MD, MSPH**
Coordinator of
Epidemiologic Research

**Tiffany Taft PsyD**
RFRI Data Manager

**Johann Hreinsson MD**
Biostatistician

**Shrikant I. Bangdiwala PhD**
Director of Statistics

**Olafur Palsson PsyD**
RFRI
Data Manager

**Madhu Grover MBBS**
Biobank Director

**Carolyn Morris MPH**
RFRI
Biostatistician

**Clinical Research Network Core (Research Core).**

The Research Network Core is responsible for providing the infrastructure and maintaining the standards for clinical investigative studies involving epidemiological, clinical outcomes, and treatment studies. It is directed by Jan Tack, MD, PhD, and members include Laurie Keefer, PhD, Samuel Nurko, MD, Ami D. Sperber, MD, MSPH Lin Chang, MD, and William Chey, MD. This Core serves as a clearinghouse for research and is responsible for identifying and selecting study centers. This includes a) responsibility for large-scale multicenter studies, b) clinical trials of new and existing treatment interventions, c) organizing and conducting clinical trials of non-pharmacological interventions, d) developing and validating patient-reported outcomes (PROs) for DGBI, e) coordinating with the biometry core the development of operations of deep clinical phenotyping including demographic, Rome criteria, psychometric and clinical questionnaires, f) reviewing seed grant and large scale research proposals, and g) maintaining and coordinating, under the direction of the Biometry Core, a pool of leading investigators and special population resources.

**Development of the Biobank and Biomarker Core.**

To perform multinational, multicenter studies that will identify diagnostic and predictive biomarkers of relevance for patients with DGBI, the RFRI created this Core to determine optimal sampling and storing procedures for bio-samples in multicenter settings. Madhu Grover MBBS and Magnus Simren MD co-chair this core in close collaboration with the members of the Executive Committee and the Biometry Core. Logistical and regulatory issues prevented us from creating a central biobank. Therefore, participating research centers in the multicenter studies will store their samples locally according to predefined specifications. When agreed upon, the centers will ship their samples for analysis. Detailed Standard Operating Procedures (SOPs) guide the collection and storage of fecal, urine, blood, saliva samples, and tissue biopsies. This includes details regarding sampling, equipment needed, storage, and transportation. In addition, separate SOPs for esophageal, gastroduodenal, and colonic biopsies have been developed. Information about available samples and storage conditions for each subject will be entered into a database and linked with clinical phenotyping data available for that subject in the RFRI Investigator Platform (see below). Hence, the Biobank and Biomarker core planning is done in close collaboration with the Biometry Core.

The biobank and biomarker core will appoint additional members based on their expertise depending on the needs in research projects.

**Education, Dissemination and Media Relations Core (Education Core)**. The Education Core serves primarily to ensure quality control in disseminating research knowledge accumulated by the RFRI and to support its translation into clinical practice. The Core members are Douglas Drossman MD (director), and Tanya Murphy (Executive Director of the RF). This Core assures that the information provided by the RFRI to external organizations, media, journals, and other printed and digital publications is scientifically based, unbiased, and non-commercial. The Core also monitors media, publications, and other communications from external sources (e.g., news bureaus, scientific organizations, and industry) to ensure the information provided about the RFRI's work is accurate, scientifically based, and unbiased.

# Part Two: Activities of the RFRI for 2024

**Introduction.** Over the past several years, the RFRI developed and consolidated the infrastructure with further refinement of the biometry and biobank cores, creating a database of investigators, and developing and launching the RFRI Investigator Platform (RFRI-IP) to obtain clinical phenotyping data from our research sites. We also engaged in several existing and planned research studies. These have included multiple Rome Foundation Global Epidemiology Study data analysis projects, completion of the Domino clinical trial and implementation of the ROBOT studies, collaborative studies with Danone Nutricia Research to study gas-related symptoms and diet in the general

population and prevalence and impact of sub-diagnostic gastrointestinal symptoms, and consultations concerning prospective projects with other pharmaceutical companies.

Finally, we are most pleased to have Ironwood Pharmaceuticals as a diamond sponsor and Takeda Pharmaceuticals as a gold sponsor. What follows is a detailed description of these activities.

# Infrastructure Development

## Development and launch of the RFRI Investigator Platform (RFRI-IP) for clinical phenotyping

The RFRI-IP is a custom-designed, secure Internet-based data collection system. The RFRI Investigator Platform (RFRI-IP) will be used across all the research sites in the rapidly growing Global Research Network (see below) to collect detailed and uniform clinical phenotyping data on large panels of patients with DGBI. At many research sites, the patients in this phenotyping database will also have associated bio-samples (these will be our ROBOT project sites), and it will be possible to link findings from those bio-samples to their phenotyping data. The RFRI-IP was launched in April of 2022 at the Gothenburg, Sweden site, where it has been successfully piloted, and several clinical sites have since joined the network and started data collection, with several additional sites in in Asia, Latin America, Europe, and the U.S. preparing to start data collection in 2025.

The use of the RFRI-IP online data collection system is expected to quickly create an unprecedented, extensive central clinical research database that can be used to (a) rapidly invite sets of patients with well-known characteristics to participate in specific research studies;  (b) conduct analyses for research papers by site investigators, individually or in collaboration, and by the RFRI or commissioned by sponsors; and (c) assess feasibility and provide pilot information for grant applications and sponsored projects. Additionally, questionnaire data collected in the unified phenotyping are automatically scored by the computer system and instantly available for use in clinical encounters, and thus clinically valuable for doctors and patients at each participating site.

All patient data collected using the RFRI-IP is strictly de-identified and HIPAA and GDPR-compliant. To minimize costs and demands on staff at the clinical research sites, data collection is predominantly self-administered by patients, utilizing easy-to-use web-based assessment that works on any computer device and in any web browser. The primary patient evaluation method is the self-completion of questionnaires by patients at home prior to clinic visits or via computer tablets in the waiting rooms. The assessment is fully mobile-device compatible, so patients can use their mobile phones to complete the assessments if preferred. Staff-assisted entry and paper questionnaires are only used in exceptional circumstances if needed.

The patient phenotyping assessment consists of an initial 25-30 min. patient-completed questionnaire and a shorter assessment (5-10 min.) in return clinic visits. It is primarily designed to update information on clinical status in the database. These patient-completed assessments are supplemented with limited information from the medical record added by the research site staff.

The phenotyping dataset collected on each participating patient, stored and available for queries and research use in the RFRI central database, includes the following:

• Demographic questions.

• Clinical diagnoses.

• Responses to the Rome IV Diagnostic Questionnaire with scoring for 22 different DGBI diagnoses.

• Frequency and severity of current GI symptoms.

• Co-morbid GI and non-GI medical conditions.

• History of GI-relevant medical tests, medical procedures and surgeries.

• Psychological symptom and quality of life scores.

• Prescription and non-prescription medications used; and

• Self-management methods used by the patient for GI symptoms.

The availability and nature of bio-samples from each patient (with summary of findings if the samples have been analyzed) is recorded in the central RFRI database along with the phenotyping data.

**Creation of the Global Research Network**. An essential part of carrying out the mission of the RFRI is the establishment of an active Global Research Network of leading and highly productive investigators in the DGBI domain. The network will coordinate its research efforts to produce compatible clinical datasets with detailed patient phenotyping, and many of the sites will also collect associated bio-samples on their DGBI patients. The network will operate with a sufficiently uniform research methodology to make large multicenter and multinational research studies quicker and more efficient to implement than previously possible. The early sites in the network will include some of the world's top DGBI centers.

The first two sites in the Global Research Network are:

- University of Gothenburg, Sweden (PI: Magnus Simren, MD, PhD)

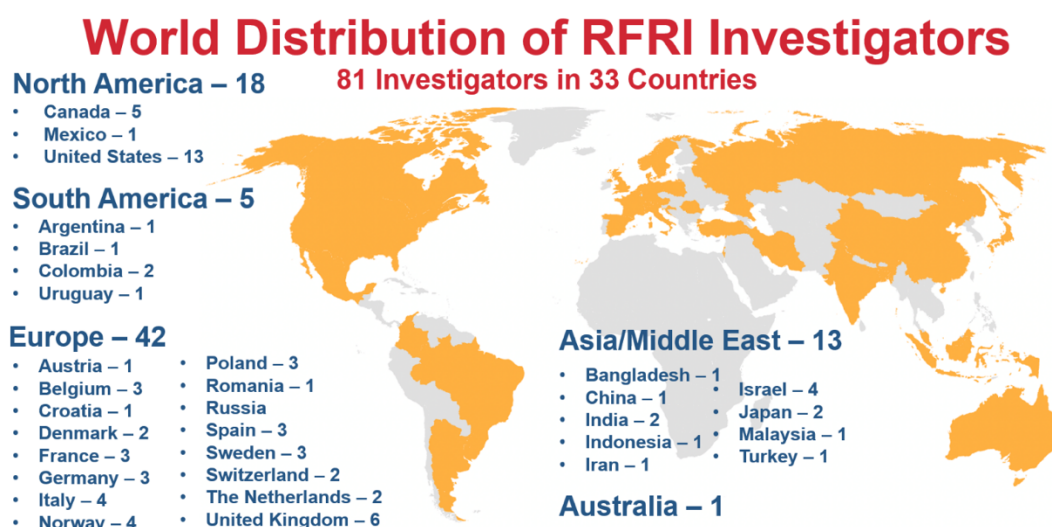- Mayo Clinic, Rochester, Minnesota, USA (PI: Madhu Grover MBBS)

Several other sites will join the Global Research Network within the next year and start collecting data via the RFRI-IP into the uniform central database. Early additional sites in the network are likely to include the following:

- University of Bologna, Italy (PI: Giovanni Barbara, MD)

- University of Rouen, France (PI: Chloé Melchior, MD)

- A network of UK sites coordinated by Imran Aziz, MD, Sheffield

- National University of Singapore (PI: Kewin Siah, MD)

- University of Michigan, USA (PI: William Chey, MD);

- University of California Los Angeles, USA (PI: Andrea Shin MD, Lin Chang, MD);

- Stony Brook University (PI: Olga Aroniadis, MD)

- University of Texas in Austin (PI: Mohammad Bashashati, MD)

- Cleveland Clinic, USA (PI: Anthony Lembo, MD)

- University of California San Diego, USA (PI: David Kunkel, MD)

- Washington University, USA (PI: Greg Sayuk, MD)

- University of Pittsburgh Medical Center, USA (PI: David Levinthal, MD)

- University of Miami, USA (PI: Morgan Sendzischew Shane, MD)

- Cedars Sinai, USA (PI: Chris Almario, MD)

- Queen's University School of Medicine, Canada (PI: Steve Vanner, MD, MSc)

- KU Leuven, Belgium (PI: Jan Tack, MD, PhD);

- Monash Malaysia Microbiome Research Centre (PIs: Deborah Chiew,MD, Chua Kee Hua, MD, Justin Lee, MD)

- International Digestive/Spleen-Stomach Databases, China

- Universidad Nacional Autónoma de México (UNAM), Mexico (PI: Max Schmulson, MD)

- University of Bologna, Italy (PI: Giovanni Barbara, MD)

- University of Rouen, France (PI: Chloé Melchior, MD)

- A network of UK sites coordinated by Imran Aziz, MD, Sheffield

- A network of Asian sites coordinated by Kewin Siah, MD, Singapore

- 

With more than a dozen sites anticipated to be fully operational in the research network during 2025, the network will be able to start offering unique research opportunities of interest to sponsors and industry based on the coordinated data collection. We fully expect the number of sites in the RFRI Global Research Network to grow further over the next few years, as numerous DGBI investigators worldwide have shown great interest in participating in RFRI Global Research Network. A survey among Rome-affiliated DGBI researchers in late 2020 resulted in 81 investigators in 33 countries who have either confirmed participation in the network or expressed strong interest in joining it (see figure 1).

**Figure 1 – RFRI investigators by country location**



## World Distribution of RFRI Investigators
### 81 Investigators in 33 Countries

**North America – 18**
- Canada – 5
- Mexico – 1
- United States – 13

**South America – 5**
- Argentina – 1
- Brazil – 1
- Colombia – 2
- Uruguay – 1

**Europe – 42**
- Austria – 1
- Belgium – 3
- Croatia – 1
- Denmark – 2
- France – 3
- Germany – 3
- Italy – 4
- Norway – 4
- Poland – 3
- Romania – 1
- Russia
- Spain – 3
- Sweden – 3
- Switzerland – 2
- The Netherlands – 2
- United Kingdom – 6

**Asia/Middle East – 13**
- Bangladesh – 1
- China – 1
- India – 2
- Indonesia – 1
- Iran – 1
- Israel – 4
- Japan – 2
- Malaysia – 1
- Turkey – 1

**Australia – 1**

**Rome Foundation Global Epidemiology Study (RFGES), Data Analysis and Publication Status (Box #1) in the flow diagram below).**

The global study was initiated in 2013 with its Executive Committee, a group of 13 leaders in the field who developed the study design and methodology. The primary aims of the RFGES were to a) conduct an extensive multinational epidemiological study of all the DGBIs, b) to obtain reliable regional and local estimates of DGBI prevalence, to evaluate the reasons for differences among regions by collecting data on multiple potentially associated factors, and c) to generate hypotheses to advance further our understanding of the pathophysiology of IBS and the other DGBI. Secondary aims were to: a) generate a database that can serve as a source of data mining and be integrated with other similar databases in the future and b) establish a network of DGBI experts with a track record of research collaboration on a global scale. A tertiary aim is to develop a repository of translated versions of the Rome IV adult diagnostic

questionnaire in multiple languages, including linguistic validation (cognitive debriefing) and cultural adaptation.

In all, 33 countries participated in the study. The participating countries and the data collection method in each country are depicted in this map – See Figure 2

**Figure 2 – Countries participating in Global Epidemiology Study**
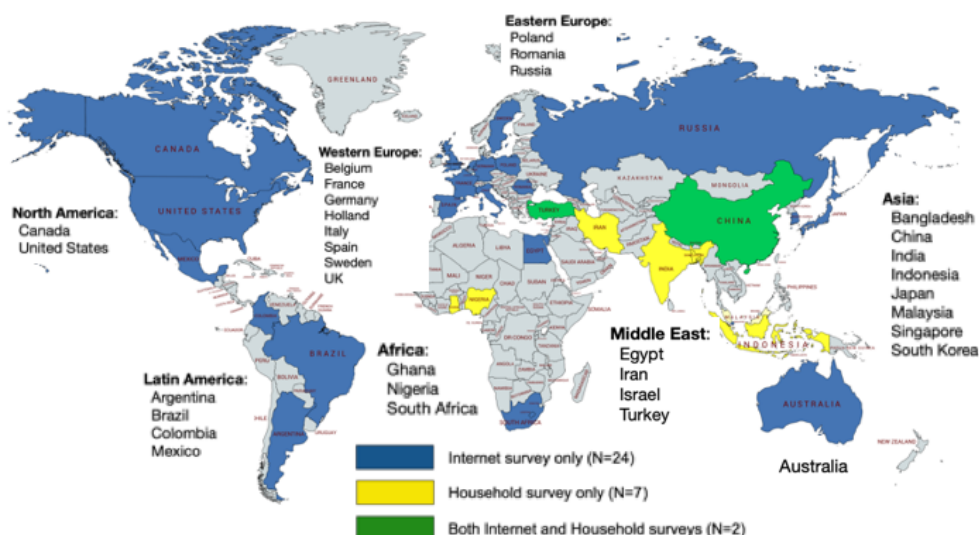


Data were collected by Internet survey (Qualtrics, Ltd.) in 26 countries where this was feasible. We conducted house-to-house personal interviews in 7 countries where this was not the case. We conducted surveys in two countries, China and Turkey. The predefined demographic parameters were 50% females and 50% males, and the age distribution was 40% for 18-39 years, 40% for 40-64 years, and 20% for 65+ years.

The data collection phase was completed in 2018 with a final database of 73,076 respondents: 36,148 women (49·47%) and 36,928 men (50·53%). We successfully achieved equal sex distribution and pre-planned age ranges with both surveying methods.

We established a Database Committee headed by Dr. Olafur Palsson, a Statistical Analysis Committee headed by Dr. Shrikant Bangdiwala at McMaster University, Canada, to do the initial analyses, and a Publications Committee headed by Dr. Ami Sperber. We vetted candidates for global study statisticians and established regional and local statistical analysis cores. We held a one-and-a-half-day Global Study Statistical Workshop in Barcelona, Spain, in October 2019. We now have 29 statisticians from around the world working with us on various analyses of datasets in progress.

We have a website where proposals for abstracts or papers related to the database could be submitted. All submissions undergo a review process (including the statistical analysis plan), such as editorial reviews in medical journals, to improve and approve the proposals prior to acceptance.

In March-May 2021, we conducted a successful 8-session CME course on the Global Study. The presentation of study results expanded to a general course on DGBI with multiple case presentations and discussions based on the Multidisciplinary Clinical Profile (MDCP) approach. The sessions were presented live and remain available online to all paying participants for a year.The first paper, summarizing the major findings, was published in Gastroenterology (Sperber AD, Bangdiwala SI, Drossman DA, Ghoshal UC, Simren M, Tack J, et al. Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study. Gastroenterology. 2021;160:99-114). This paper was rated as one of the most impactful papers of the year by AGA and as a "hot paper" by Web of Science. It now has over 1,100 citations (Web of Science) and is a leading resource for research in the field.

The following is the graphical abstract from that paper:



**Worldwide Prevalence of Functional GI Disorders**
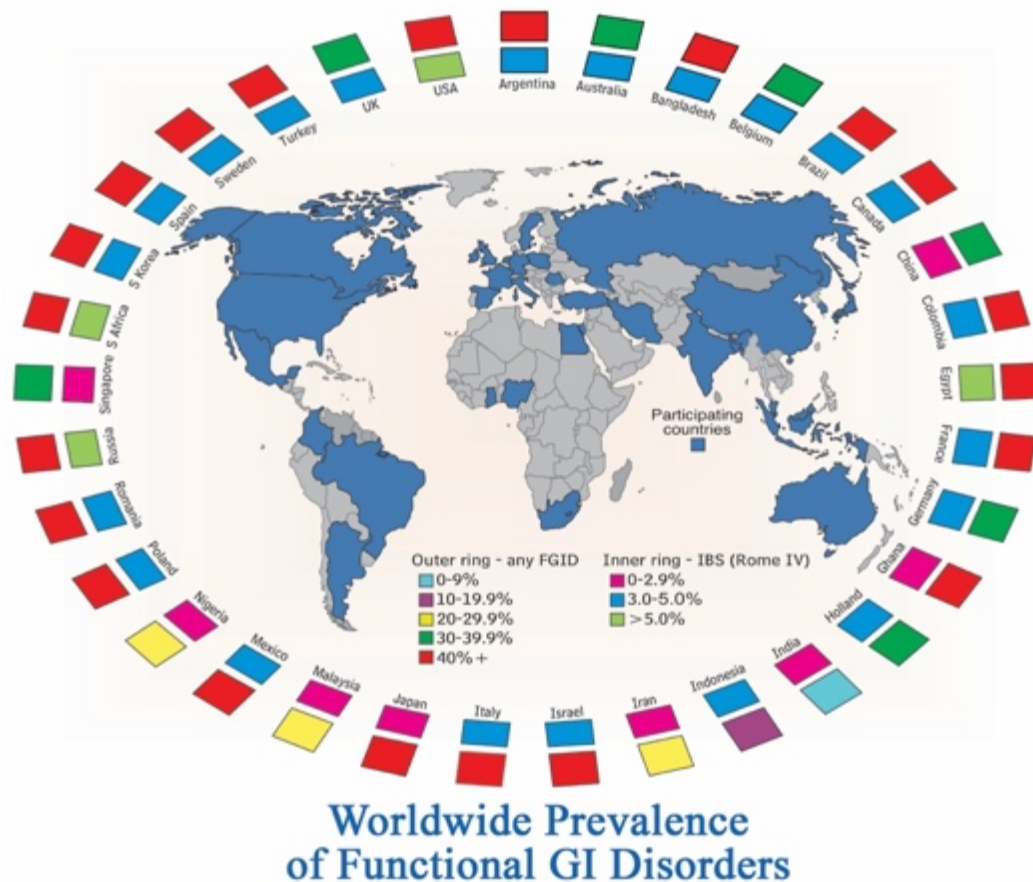
We have now published 43 papers from this global survey, 7 more are under review in different journals, and another 25 papers are in the data analyses or draft writing stage. In May 2023, a special edition of Neurogastroenterology and Motility was devoted to RFRES findings, with 15 global study papers. The citation for the Introduction paper, with full details on the global study, is:

Sperber, A. D. 2023. 'The Rome Foundation Global Epidemiology study: Conception, implementation, results, and future potential,' *Neurogastroenterol Motil*, 35: e14567.

We have also presented over 50 abstracts at multiple scientific meetings, such as DDW and UEGW, including oral presentations, posters of distinction, and posters. Nine abstracts were submitted to DDW 2025. Eight PhD dissertations have been based on the Study database, some in full and others in part.

Analysis of data from the Rome Foundation Global Epidemiology Study is an ongoing process that should continue to provide essential findings for papers and support other future research. It already serves as a significant reference for the field of Gastroenterology in general and Neuro-Gastroenterology in particular.

## Rome V Epidemiology Support Committee

This committee is the liaison between the RFGES and the Rome V project. The committee is coordinating studies involving RFGES data mining to provide background data for the Rome V committees, particularly analyses related to clinical criteria for DGBI. The committee is comprised of Drs. Sperber, Palsson, and Bangdiwala. The following flow diagram shows the breadth of RFRI studies at the present. The sections below are keyed to the numbers in this diagram.
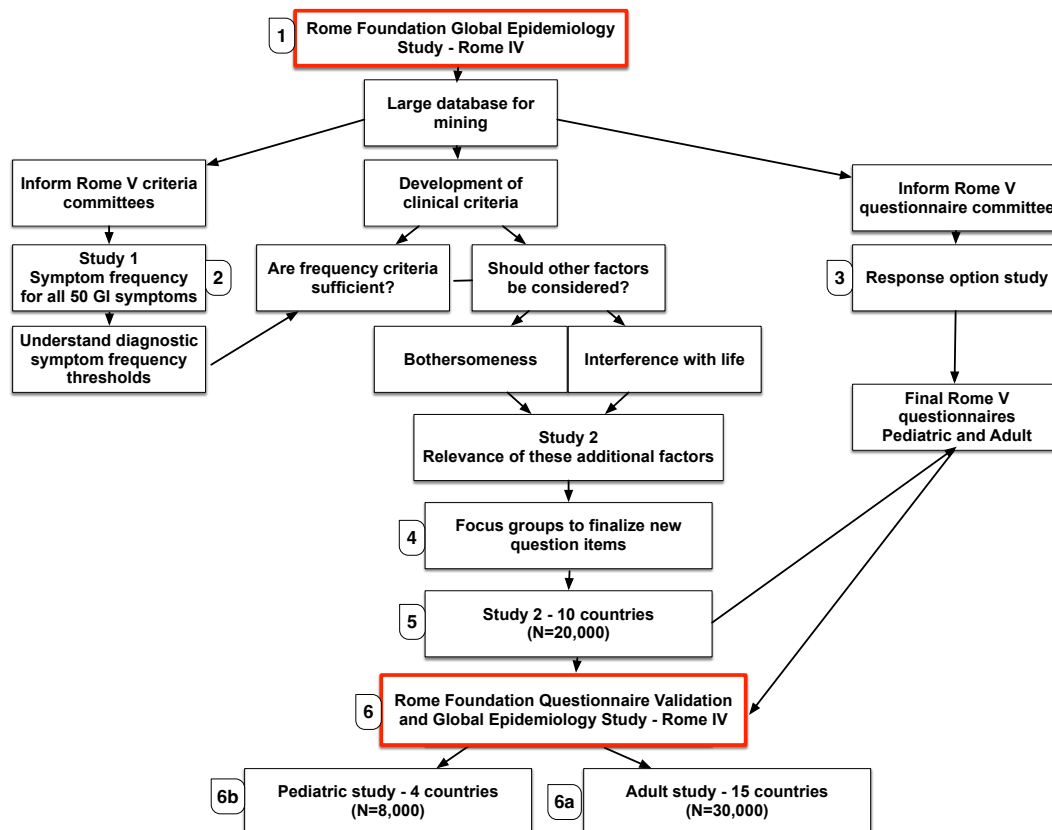
Box #2) **Symptom frequency threshold study**.

We conducted a global assessment and comparison of frequency thresholds for all 50 DGBI-related symptoms and diagnoses by country and geographic region by mining the RFGES database. The analyses have been completed, and the results have been circulated and explained to all relevant Rome V chapter committees.

Box #3) **Response option study**.

The Rome V Questionnaire Committee identified a problem with one of the main symptom frequency scales used in the Rome IV Diagnostic Questionniare for Adults, based on analysis of distributions of symptom frequencies in the RFGES dataset. It related to the response options representing uneven time intervals, and especially with 2-3 days a month and 2-3 days a week being problematic. To provide data to help solve that issue for the upcoming Rome V Diagnostic Questionnaire for Adults, we conducted a nationwide general population "Response scale options" survey with 2000 participants in the US that compared the performance of 3 different possible response scales for the same GI diagnostic questions. The results of the study provided clear evidence in favor of separating 2-3 days a month and 2-3 days a week, into separate 2 days and 3 days response options in the new Rome V questionnaire.

Boxes #4 and 5) **A closer look at clinical diagnostic criteria**.

In line with clinical expertise and the results of the Symptom Frequency study (Box #2) we assessed the effect of adding two additional factors to symptom frequency, i.e., a) the degree of bothersomeness of symptoms, and b) the extent to which they interefere with life (symptom impact). We began by conducting focus groups of IBS and FD patients in Australia and the US to assess these proposed new question items. This study confirmed the importance of addressing these factors in clinical practice beyond diagnosing based on symptom frequency alone. The results of the focus groups were published in a manuscript.

**Publication:** Coitinho, Y., Naude, C., Marchese, S. H., Evans, S., Barber, E., Parigi, E., Cheah, S., Palsson, O., Sperber, A. D., Tack, J., Drossman, D., Mikocka-Walus, A., & Taft, T. (2024). Symptom bothersomeness and life interference support Rome clinical criteria as clinically relevant indicators of DGBI. Neurogastroenterol Motil, e14936.

Folowing the focus groups we conducted a 10-country study on the addition of these factors to the frequency criteria. This study focused primarily on the two factors discussed above and how they affected the decision to consult or to not consult a doctor about the symptoms. The study assessed these relationships and their association with the need to seek healthcare for GI symptoms and other factors, such as anxiety, depression, somatization, et al., in individuals meeting diagnostic criteria for IBS and FD.

The study questionnaire was developed in English and translated into the languages of the participating countries, and we have completed data collection from approximately 2,000 adults in each of 10 countries by Internet survey  The participating countries are Argentina, Brazil, Canada, China, France, Germany, Japan, Mexico, Poland, Romania, and the US.

We are now analyzing the results and expect to make the key findings available to the Rome V chapter committees and the Rome V questionnaire committee by May 2025, Eventually these findings will be shared through publications in the GI literature.

Based on the above group of studies the Rome V Questionnaire Committee finalized the adult Rome V Diagnostic Questionnaire for testing in the Rome V Validation and Global Epidemiology study described below. In addition a supplemental questionnaire for that study was developed based on the suggestions of expert committees to revise and improve the supplemental questionnaire used in the RGES.

Box 6) **Rome V "Validation" and Global Epidemiology Studies**

A new major 15-country epidemiology study of adult DGBI, and a 4-country study of pediatric DGBI is now being implemented. This effort has has three main components:

a) **Validation" study for the Rome V diagnostic questionnaires (adult and pediatric)**.

In this study, we are assessing the validity of the new Rome V diagnostic questionnaire in 15 countries around the world in North America, Latin America, Western Europe, Eastern Europe, the Middle East, and Asia).

Based on the results, the Rome V diagnostic questionnaire, the associated diagnostic scoring formulas, or even some of the Rome V diagnostic criteria may be revised prior to final publication.

Box 6a) **Adult Rome V Global DGBI Epidemiology Study**.

Unlike the RFGES, where data were collected starting in 2017, a year **after** the publication of the Rome IV diagnostic criteria , the entire new global study will be completed **in advance** of the publication of the criteria, as it is being used for the "validation" study in combination with the epidemiology study. Thus, we expect to have analyses of the global epidemiology of DGBI according to Rome V diagnostic criteria ready for publication shortly after the embargo lifts (after DDW, May 2026 on Rome V).

Box 6b) **Pediatric Multi-national Validation and Rome V DGBI Epidemiology Study**.

As part of the Rome V diagnostic questionnaire validation process, we completed the **first** multi-national study of the epidemiology of pediatric DGBIs. This study will provide initial validation for the newly developed Rome V pediatric upper and lower diagnostic questionnaires, as well as the Rome V infant questionnaire. Supplemental items regarding quality of life, access to healthcare, and psychosocial variables were included to provide relevant supplemental information on the children whose GI symptoms were reported, mirroring the methodology of the adult studies. The online survey was completed by mothers of children with DGBI in the United States, Mexico, China, and Italy (approximately 2,000 participants per country). These data will inform a subsequent clinical validation study of the Rome V pediatric criteria (for which we need the validated questionnaires) involving multiple clinics and using clinician diagnosis as the gold standard, as well as an anticipated more extensive pediatric global epidemiological study.

**Domino Trial**

*Efficacy of diet versus medication in primary care IBS*

The DOMINO trial (Diet Or Medication in Irritable bowel syNdrOme) was a randomized trial for newly diagnosed or treated patients with IBS in primary care to evaluate a dietary intervention's short-term efficacy and long-term health economic impact compared to pharmacotherapy with a musculotropic spasmolytic agent (otilonium bromide, OB). The Belgian Government funded this trial, which was pragmatic and aimed at optimizing primary care. It used questionnaires developed for the Rome IV Global Epidemiology

study in Belgium and served as an opportunity to collect biobank material from primary care IBS patients. Patients were randomized to treatment with OB 60 mg t.i.d., the traditional first-line medical therapy, or by a FODMAP lowering diet provided via a smartphone application. Patients were randomized to medication or the diet app, and those with an improvement of at least 50 points on IBS-Symptom Severity Scale (IBS-SSS) were considered responders. Before and after 8 weeks of treatment, patients completed questionnaires evaluating demographics, stool types, Rome IV criteria, IBS-SSS, anxiety (GAD), depression (PHQ9) and somatization (PHQ15).

The study randomized 459 patients (41±15 years, 76% female), recruited by 61 primary care practitioners. At baseline, 70% of these primary care-diagnosed IBS patients fulfilled the Rome IV criteria (Rome+). Although this was optional, 95% of the subjects provided biobanking samples for genetics, serum, and stool analysis for microbiota and biochemical parameters. Based on the IBS-SSS, 41 and 39% of patients had moderate or severe IBS, respectively. Stool pattern subtype distribution was IBS-D 27%, IBS-C 23%, IBS-M 38% and IBS-U 12%.

The responder rate after 8 weeks, defined as an improvement of at least 50 points on the IBS-SSS, was significantly higher with diet compared with otilonium bromide (71% versus 61%), p=0.03) and the difference was more pronounced in the Rome+ subgroup (77% versus 62%, p=0.004). Patients allocated to the diet app were 94% treatment adherent compared with 73% in the medication arm (p<0.001). The significantly higher response rate with diet was already observed after 4 weeks (62% versus 51%), p=0.02) and a high symptom response persisted during follow-up. Predictors of response were female gender (OR=2.08, p=0.04) for the diet and a higher somatization score (PHQ15; OR=1.10, p=0.02) for otilonium bromide. It was concluded that a FODMAP-lowering diet application was superior to a spasmolytic agent in improving IBS symptoms. A FODMAP-lowering diet should be considered the first-line treatment for IBS in primary care.

**Publication:** The primary outcome manuscript was published in *Gut*. (Diet or medication in primary care patients with IBS: the DOMINO study - a randomized trial supported by the Belgian Health Care Knowledge Centre and the Rome Foundation Research Institute. Carbone F, Van den Houte K, Besard L, Tack C, Arts J, Caenepeel P, Piessevaux H, Vandenberghe A, Matthys C, Biesiekierski J, Capiau L, Ceulemans S, Gernay O, Jones L, Maes S, Peetermans C, Raat W, Stubbe J, Van Boxstael R, Vandeput O, Van Steenbergen S, Van Oudenhove L, Vanuytsel T, Jones M, Tack J; DOMINO Study Collaborators; Domino Study Collaborators. Gut. 2022 Nov;71(11):2226-2232.)

### *Genetic determinants of response to diet or medication in primary care IBS*

In addition, we analyzed the genetic samples for predictors of response to either treatment. Significant association with a response to OB was detected for polymorphisms

in 3 genes: SLC6A4, TRPA1 and CACNA1C. Polymorphisms from two genes were associated with a response to dietary intervention: IL5RA and CCR3. Expression data from publicly available databases support an impact of the polymorphisms in SLC6A4 and in CCR3 on protein expression in the gastrointestinal tract. The predictive role of the polymorphism in the serotonin transporter gene SLC6A4 is in line with the antispasmodic properties of otilonium bromide. The association of a genetic polymorphism in CCR3 with response to dietary treatment suggests that (altered) eosinophil function plays a role in diet-related symptom generation in IBS. These genetic associations need to be studied in future larger cohorts.

**Publication**: Genetic analyses of treatment response in primary care IBS, a pilot study. Balsiger LM, Van den Houte K, Zheng T, Toth J, Besard L, Franke A, D'Amato M, Tack J, Carbone F. Gut. 2023 Sep;72(9):1803-1804.

*Role of carbohydrate maldigestion in the response to diet versus medication in primary care IBS*

The role of genetic alterations in carbohydrate digestive enzymes in predicting the response to the diet wals also studied. Patients with variants leading to decreased enzymatic efficacy were more likely to benefit from the diet intervention.

**Publication**: Functional Variation in Human CAZyme Genes in Relation to the Efficacy of a Carbohydrate-Restricted Diet in IBS Patients. Zamfir-Taranu A, Löscher BS, Carbone F, Hoter A, Esteban Blanco C, Bozzarelli I, Torices L, Routhiaux K, Van den Houte K, Bonfiglio F, Mayr G, Corsetti M, Naim HY, Franke A, Tack J, D'Amato M. Clin Gastroenterol Hepatol. 2024 Oct 14:S1542-3565.

An in-depth analysis of the impact of the dietary intervention on IBS subtypes and individual symptoms was recently finalized.

**Publication**: DOMINO trial post hoc analysis: evaluation of the diet effects on symptoms in IBS subtypes. Di Rosa C, Van den Houte K, Altomare A, Guarino MPL, Besard L, Arts J, Caenepeel P, Piessevaux H, Vandenberghe A, Matthys C, Biesiekierski JR, Capiau L, Ceulemans S, Gernay O, Jones L, Maes S, Peetermans C, Raat W, Stubbe J, Van Boxstael R, Vandeput O, Van Steenbergen S, Van Oudenhove L, Vanuytsel T, Jones M, Tack J, Carbone F. Therap Adv Gastroenterol. 2024 Jul 30;17:17562848241255296

*Health economic impact of dietary therapy for primary care IBS*: An additional publication from the DOMINO trial hase been submitted:

**Submitted**: Inflammatory biomarkers in newly diagnosed primary care Irritable Bowel Syndrome: a subanalysis of the DOMINO trial. Tack C, Van den Houte K, Gehesquière B, Raes J, Tack J. and Carbone F. Submitted for publication 2025.

## ROBOT Project

RFRI finalized the planning of the **RO**me Foundation **BiO**marker and phenotyping projec**T** (ROBOT), to support the launch of this multinational project in 2021. The launch of this project was delayed due to the pandemic and focused on other projects, but in 2022, the project was approved by the ethical review board in Gothenburg, Sweden, and the recruitment of subjects started in the fall of 2022. In 2023 the project was IRB approved after a single IRB application procedure in the US. Mayo Clinic in Rochester, MN is the first activated US site and has been followed by UCLA, University of Michigan, University of Texas -Austin and Stony Brook University in 2024. . In addition, the project has been launched in Asia in 2024, with University of Singapore being the first Asian site, and with several sites following shortly . The IRB applications are planned / underway in several Euroepan countries, including France, UK, Mexico, Belgium, and Israel. In addition, expansion to other sites around the globe is planned, and active discussions with other sites about their participation are ongoing. With the finalization of the RFRI-IP, and SOPs for data collection and storage, the expansion of this project globally can now proceed rapidly as the interest in participation is high.

The aim of ROBOT is to develop a state-of-the-art biobank and database of patients with DGBI, supported by an international network of top international research sites. Patients in the database will be characterized to include clinical phenotype and associated demographic, medical history, psychosocial and lifestyle factors will be established, fecal, blood, and urine samples will be collected and stored in a standardized fashion, and select sites, biopsies from the upper and/or lower GI tract will be collected depending on the predominant symptom profile. The collection of bio-samples and data will enable the evaluation of different biomarkers in large groups of well-characterized individuals in different parts of the world. We will then assess their validity as diagnostic and /or predictive tools. A centralized electronic database will enable the development of profiles of available clinical phenotypes and biosamples at any time to assess the feasibility of new studies. Hence, the ROBOT includes data from the RFRI-IP with detailed patient phenotypic characterization, biosamples, and physiological data.

ROBOT will involve leading global DGBI research sites. In the first phase of ROBOT each center will recruit ≥100 patients who fulfill Rome IV diagnostic criteria for at least one DGBI. The project has started in 2022. We aim to have a 50:50 split between predominantly upper, i.e. esophageal and gastroduodenal, and lower, i.e. bowel and anorectal DGBI. This will be to be separately negotiated with each site, depending on

their expertise and research focus. Eligible sites will ideally also include 20-30 healthy controls without current GI symptoms. All patients will complete questionnaires and provide information for the RFRI clinical phenotyping tool (see below). In most patients, blood, fecal, and urine samples will also be collected, as well as GI biopsies in sites where this is possible. The samples will be stored at the individual sites in a local biobank. In select centers, a small number of patients will also undergo physiologic testing. Thus, based on site capabilities, patient characterization / data collection in ROBOT will vary and yield different levels of integrated information from individual sites:

1.    RFRI clinical phenotyping tool alone

2.    RFRI clinical phenotyping tool and collection of bio-samples.

3.    RFRI clinical phenotyping tool, collection of bio-samples, and performance of physiologic testing.

Each investigator will "own" the samples from their patients and be listed as an author in publications/projects where their samples are used. After discussions with participating investigators, a study management committee will make decisions about the prioritization of proposals for sample analyses from individual investigators and/or external collaborators, e.g., RFRI sponsors / academic collaborators. Specifically, if approved, samples will be shipped to analytical centers from the local biobanks; after the analyses are completed, the remainder of the samples will be shipped back to the local biobanks at the sites for continued storage.

The program in Gothenburg began in 2022, and the first US site (Mayo Clinic) has started recruiting in 2023. Additional 4 US sites have been activated in 2024. All US sites will be under a single IRB umbrella, facilitating faster implementation and a path towards participant recruitment. This also enables standardization of the protocol across sites, reduces IRB-associated workload for study teams at each site, and facilitates faster implementation of the changes to the protocol, as well as procurement of future funding from federal agencies and industry partners. The program has now also been launched in Asia, where the interest to join the program is large. Additionally, other sites in Asia, Latin America, and Europe will follow over 2025-26.

**RFRI- a survey of bloating and other gas-related symptoms, sponsored by Danone Nutricia Research**

This study was a secure Internet population survey of 5,978 adults in the United States, Mexico, and the United Kingdom, conducted to evaluate bloating, distention, and other gas-related symptoms and a wide range of potentially related factors. The study was designed collaboratively by the RFRI and Danone and sponsored by Danone.

The study aimed to a) assess the population prevalence of bloating, distention and other gas-related symptoms and their associations with demographics, other symptom characteristics, diet, DGBI, quality of life impairment, and healthcare utilization; b) assess the population prevalence of Rome IV Functional Abdominal Bloating/Distention and to what extent bloating-only, distention-only and mixed subgroups exist within that diagnosis; and c) assess the impact of bloating, distention and combination of both on QoL and healthcare utilization. A subset of 1437 participants completed a 25-minute online VioScreen follow-up survey about their diet over the past 3 months.

This is the first study to examine the current and chronic presence of bloating/distention and numerous potential associated factors in the same population-based sample. It is yielding a comprehensive picture of the scope of these symptoms. The findings show that in a 24-hour period, almost all people in the three-nation survey sample experienced some gas-related symptoms, ranging from 39% for bloating to 81% for flatulence. A more significant number of gas-related symptoms was associated with poorer physical and mental QoL, higher scores on life stress, anxiety, depression, and non-GI body symptom scores, and increased healthcare utilization. The average number of gas-related symptoms was markedly higher in Mexico than in the U.S. and the U.K. The study also revealed a great excess of gas-related symptoms in individuals with gastroduodenal and bowel DGBI. The study has resulted in five scientific abstracts presented at UEG Week and DDW, and the first paper is under review for publication. Additional analyses of this dataset are ongoing and planned, and further diet sub-study analyses that Danone Nutricia Research will likely conduct..

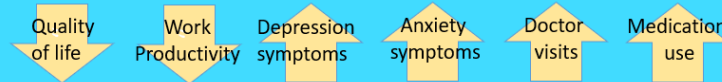**Study of sub-diagnostic GI symptoms in the general population, sponsored by Danone Nutricia Research**

We completed an analysis of the 26-country RFGES Internet survey dataset to assess the global prevalence and associated characteristics of people who have frequent GI symptoms in spite of not meeting Rome IV criteria for any DGBI diagnosis and having no history of organic GI disease. The findings revealed that one in four adults have such sub-diagnostic GI symptoms and that they are associated with substantial adverse impacts on quality of life and reduced psychological well-being, as well as an increase in need for healthcare. This adverse impact is greater if people have multiple sub-diagnostic symptoms or if the symptoms have become chronic (i.e., occurring for at least 6 months). An abstract from the study was presented at UEG Week 2022, and a paper describing the main findings has just been published: Palsson OS, Tack J, Drossman DA, et al. Worldwide population prevalence and impact of sub-diagnostic gastrointestinal symptoms. Aliment Pharmacol Ther. 2024;59(7):852-864. doi:10.1111/apt.17894. The graphical abstract of the paper below outlines the key findings of this analysis project.
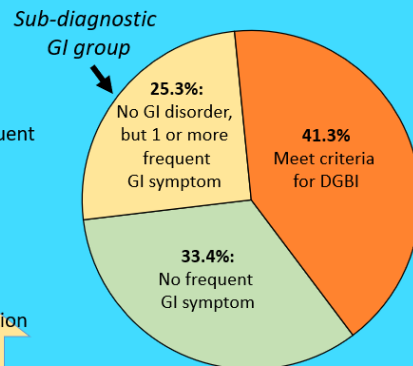
A population-based Internet survey from 26 countries was used to examine the prevalence of having gastrointestinal (GI) symptoms frequent enough to meet diagnostic thresholds for Disorders of Gut-Brain Interaction (DGBI), without fulfilling Rome IV DGBI criteria. Data were analyzed from 50,033 people.

**Prevalence in the global study sample:**

*Sub-diagnostic GI group*

*Key findings:*
- ¼ of adults have no organic GI disorder or DGBI, but nonetheless have frequent GI symptoms and can be characterized as a sub-diagnostic GI group.
- Such sub-diagnostic GI individuals are similarly prevalent in different world regions, and among males and females.
- Compared to people with no frequent GI symptoms, sub-diagnostic GI individuals exhibit poorer functioning and wellbeing, including:

**25.3%:** No GI disorder, but 1 or more frequent GI symptom

**41.3%** Meet criteria for DGBI

**33.4%:** No frequent GI symptom

Quality of life ↓ | Work Productivity ↓ | Depression symptoms ↑ | Anxiety symptoms ↑ | Doctor visits ↑ | Medication use ↑

AP&T

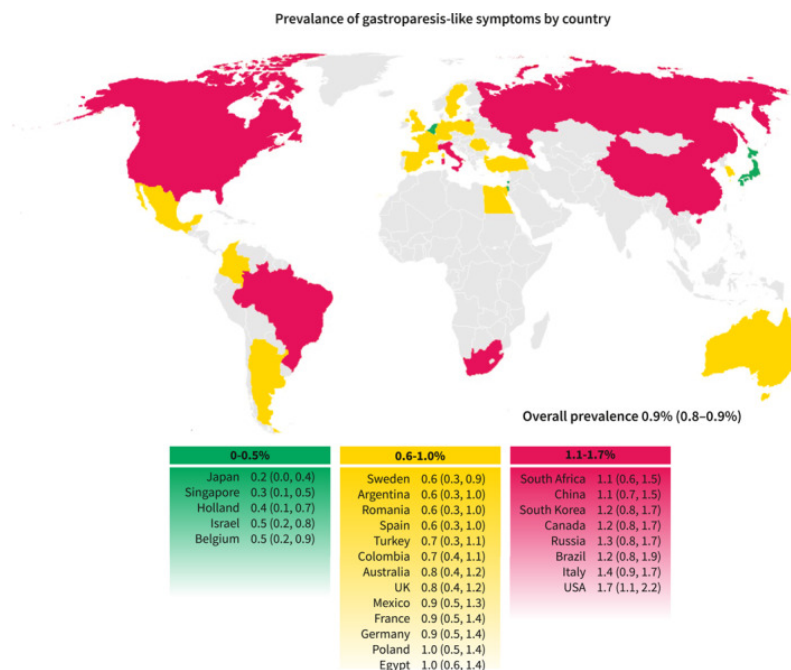## Gastroparesis, Functional Dyspepsia and Cyclic Nausea Vomiting Syndrome.

Gastroparesis is a condition characterized by epigastric symptoms and significantly delayed gastric emptying rate in absence of any mechanical obstruction. Gastroparesis is a well-known complication of diabetes, especially type 1 diabetes, and may also occur following upper gastrointestinal tract surgery, but in the largest subgroup no underlying cause is identified and these patients are referred to as having idiopathic gastroparesis. The epidemiology of gastroparesis in primary care is not fully elucidated, as this would require procedures such as gastric emptying tests to make a firm diagnosis. Moreover, clinical or hospital records do not provide accurate information as gastric emptying test usage varies widely across countries and, moreover, poorly validated and poor-quality testing is not infrequently used in less specialized clinical practice.

*Analysis of the prevalence of gastroparesis-like symptoms in the Rome Foundation Global epidemiology study*

The results of the Rome Foundation Global Epidemiology Study will provide the opportunity to compare our results by identifying a suggestive symptom-pattern and subsequently to determine the prevalence of gastroparesis. Recently, the UEG and European Society for Neurogastroenterology and motility consensus defined Gastroparesis as a condition characterized by delayed gastric emptying in the absence of mechanical obstruction, with a symptom pattern of nausea and/or vomiting and overlapping postprandial distress syndrome. In the online survey part of the Rome Foundation Global Epidemiology Study, 54,127 respondents from 26 countries completed the questionnaires. We selected subjects with gastroparesis-like symptoms (nausea and/or vomiting ≥1 day/week and simultaneous postprandial distress syndrome symptoms). Patients reporting organic gastrointestinal disease, or fulfilling criteria for self-

22

induced vomiting, cyclic vomiting or cannabinoid hyperemesis syndrome were excluded. We found that the global prevalence of gastroparesis-like symptoms was 0.9% overall and 1.3% among diabetic individuals. Subjects with gastroparesis-like symptoms had significantly lower body mass index, QoL, more non-gastrointestinal somatic complaints, symptoms of anxiety and depression, higher medication usage and doctor visits in the overall and diabetic population, compared to subjects without these symptoms. The data show that gastroparesis-like symptoms are common worldwide and more common in diabetic patients. The symptom complex is associated with multiple aspects of illness and an increased healthcare consumption.
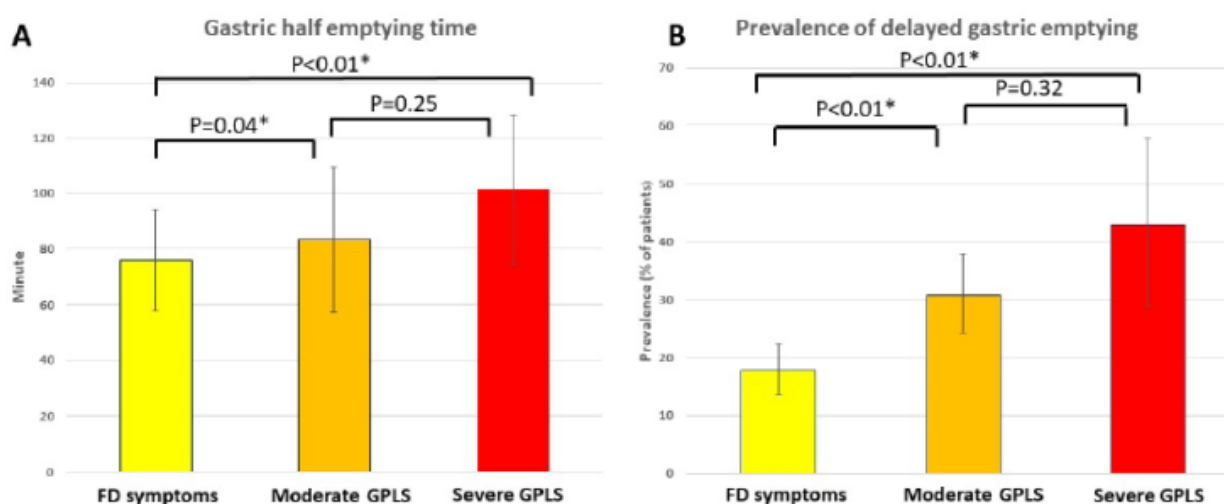


Prevalance of gastroparesis-like symptoms by country

Overall prevalence 0.9% (0.8–0.9%)

| 0-0.5% | 0.6-1.0% | 1.1-1.7% |
|---|---|---|
| Japan 0.2 (0.0, 0.4) | Sweden 0.6 (0.3, 0.9) | South Africa 1.1 (0.6, 1.5) |
| Singapore 0.3 (0.1, 0.5) | Argentina 0.6 (0.3, 1.0) | China 1.1 (0.7, 1.5) |
| Holland 0.4 (0.1, 0.7) | Romania 0.6 (0.3, 1.0) | South Korea 1.2 (0.8, 1.7) |
| Israel 0.5 (0.2, 0.8) | Spain 0.6 (0.3, 1.0) | Canada 1.2 (0.8, 1.7) |
| Belgium 0.5 (0.2, 0.9) | Turkey 0.7 (0.3, 1.1) | Russia 1.3 (0.8, 1.7) |
| | Colombia 0.7 (0.4, 1.1) | Brazil 1.2 (0.8, 1.9) |
| | Australia 0.8 (0.4, 1.2) | Italy 1.4 (0.9, 1.7) |
| | UK 0.8 (0.4, 1.2) | USA 1.7 (1.1, 2.2) |
| | Mexico 0.9 (0.5, 1.3) | |
| | France 0.9 (0.5, 1.4) | |
| | Germany 0.9 (0.5, 1.4) | |
| | Poland 1.0 (0.5, 1.4) | |
| | Egypt 1.0 (0.6, 1.4) | |

The epidemiological analysis has been published in *UEG Journal*: Worldwide prevalence and burden of gastroparesis-like symptoms as defined by the United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) consensus on gastroparesis. Huang IH, Schol J, Khatun R, Carbone F, Van den Houte K, Colomier E, Balsiger LM, Törnblom H, Vanuytsel T, Sundelin E, Simrén M, Palsson OS, Bangdiwala SI, Sperber AD, Tack J. United European Gastroenterol J. 2022 Oct;10(8):888-897.

*Analysis of the association of gastroparesis-like symptoms and delayed gastric emptying at different levels of care*

In a next phase, the link between gastroparesis-like symptoms and delayed gastric emptying will be studied in two cohorts: a group of subjects with upper gastrointestinal symptoms recruited from primary care and a group of subjects with upper gastrointestinal symptoms and negative endoscopy recruited from specialist care, to undergo gastric emptying testing and symptom assessment. For the former group, recruitment is still

23

ongoing. In specialist care, in 637 patients from Leuven University Hospital, gastroparesis-like symptoms were associated with a significantly higher likelihood of having delayed emptying compared to patients with only dyspeptic symptoms: 33.2% versus 17.6%, p<0.01. Patients with gastroparesis-like symptoms had a significantly lower body mass index (19.9 (15.7-23.1) vs 21.2 (18.2-24.8), p<0.01). The rate of delayed emptying was higher in those with severe gastroparesis-like symptoms compared to those with moderate symptoms (42.9 vs. 30.7%). In addition, a cohort of patients in the Belgian diabetic association is invited to undergo gastric emptying testing and symptom assessment. This will generate data on association between gastroparesis-like symptoms and delayed gastric emptying in this specific disease cohort.



The association of the gastroparesis-like symptom pattern with gastric emptying rate was published in *Alimentary Pharmacology and Therapeutics*: Prevalence of delayed gastric emptying in patients with gastroparesis-like symptoms. Huang I, Schol J, Carbone F, Chen YJ, Van den Houte K, Balsiger LM, Broeders BB, Vanuytsel T and Tack J. Aliment Pharmacol Ther 2023 in press.

*International consensus on gastroparesis definition*

The definition, clinical characteristics, and existence as a clinical entity of gastroparesis is currently facing many challenges and controversies. Despite considerable industry efforts, there is a lack of approved therapy for gastroparesis. A recent paper from the NIH/NIDDK gastroparesis clinical research consortium suggests that functional dyspepsia and idiopathic gastroparesis are indistinguishable entities that are on the same spectrum. There is a clear need to identify the level of consensus on gastroparesis and its different aspects at an international level. Moreover, functional dyspepsia is relevant to the Rome Foundation as it is one of the most prevalent disorders of gut-brain interaction.

To initiate this process, the Rome Foundation has contacted all international motility societies, asking about their interest in such a consensus and asking them to identify 2 participants. A favorable response was obtained from all societies. After a kick-off meeting at Digestive Disease Week 2022, the consortium agreed on a large set of voting statements. For each statement, a literature survey was conducted to support three voting rounds. A consensus manuscript was finalized by the end of 2023 and is now under review in a leading journal in the international peer-reviewed literature.

*Publication:* Rome Foundation and International Neurogastroenterology and Motility Societies consensus on Idiopathic Gastroparesis. Schol J, Huang IH, Carbone F, Bustos Fernandez LM, Gourcerol G, Ho V, Kohn G, Lacy BE, Lopez Colombo A, Miwa H, Moshiree B, Nguyen L, O'Grady G, Siah KTH, Stanghellini V, Tack J. Lancet Gastroenterol Hepatol . 2025 Jan;10(1):68-81.


## Analysis of the epidemiology of cyclic nausea vomiting syndrome and other vomiting disorders

Cyclic vomiting syndrome (CVS) is a disorder of gut–brain interaction characterized by severe episodic emesis, separated by periods of relative wellness. Many associated symptoms, such as gastrointestinal, autonomic, and behavioral, are observed in patients with CVS. Prior to the Rome Foundation Global Epidemiology Study, epidemiologic studies on CVS have been limited, and the overlap with/ differentiation of CVS from other nausea and vomiting disorders is a hot topic.

The Rome Foundation Global Epidemiology Study database was used to analyze the prevalence of CVS worldwide, define the association between CVS and other nausea and vomiting disorders and medical conditions, and test the association between CVS and prescription pain medicine or cannabinoid intake. In addition, the impact of CVS on quality of life, health care consumption, and the association with psychological distress (somatization, anxiety, and depression) were analyzed. The manuscript has been submitted for publication.

*Publication:* Worldwide Prevalence and Description of Cyclic Vomiting Syndrome According to the Results of the Rome Foundation Global Epidemiology Study. Authors: Izagirre A, Sarasqueta C, Flores-Arriaga J, Aso MC, Pérez M, Tack J, Huang IH, Sperber AD, Palsson OS, Bangdiwala SI, D'Amato M, Lanas A, Lobo B, Alonso-Cotoner C, Santos J and Bujanda L. J Gastroenterol. 2024 Sep 25. doi: 10.14309/ajg.0000000000003105*.*

**Characterization of Lower Abdominal Pain and Associated Factors in the Global Adult Population.**

This study is a collaborative set of analyses by RFRI and Sanofi Pharmaceuticals designed to advance understanding of abdominal pain in the adult global population, using RFGES study data from 54,127 individuals surveyed nationwide in the general populations of 26 countries. The presence of abdominal pain is based on self-report of pain of any frequency in the past 3 months anywhere in the abdomen, using responses to a question from the Rome IV diagnostic questionnaire. The specific aims of the study are to (1) gain insights into the occurrence of abdominal pain (i.e., overall prevalence and demographic distribution), (2) identify characteristics of individuals who have abdominal pain, and (3) assess the impact of abdominal pain on quality of life, productivity and psychological wellbeing. The analyses have been completed and a paper is presently in preparation.

**Studies on changes in DGBI population prevalence after the COVID-19 pandemic.**

The RFRI has conducted two separate population studies to investigate the change in the prevalence of DGBI in national populations. Both studies were multi-national surveys that used comparable methodology and had equivalent national samples to the Rome Foundation's RFGES, and utilized the RFGES data for pre-pandemic comparison prevalence comparisons. The two studies provide clear and consistent evidence that DGBI rates have increased markedly in the world adult population following the COVID-19 pandemic.

One of these studies was a two-nation survey of a total of 4050 adults in the U.S. and U.K. (approximately 2000 people in each country), led by Dr. Imran Aziz. The overall prevalence of having any (one or more) Rome IV DGBI was significantly increased from the pre- (RFGES data) to post- pandemic timepoint (38.3% vs. 42.6%, p<0.0001), both in the combined two-country samples and in each country separately, and this increase was found in both females (44.4% vs. 48.3%; p=0.02) and males (32.2% vs. 36.9%; p=0.002). The post-pandemic DGBI increase was statistically significant for esophageal, gastroduodenal and bowel DGBI, but not anorectal DGBI. Functional dyspepsia increased from 8.3% to 11.9% (p<0.0001) and irritable bowel syndrome from 4.7% to 6.0% (p=0.006). In the post-pandemic survey, higher DGBI prevalence was significantly associated with history of test-confirmed COVID, having been moderately or severely ill during COVID infection, currently having lingering symptoms from past COVID infection, and having never been vaccinated for COVID. People with a DGBI were twice as likely as non-DGBI to have long COVID (22.1% vs. 11.1%; p<0.0001). DGBI people with long COVID had poorer physical and mental QOL scores and higher anxiety and depression scores than others with DGBI. A paper on these findings has been submitted for publication, and the study is being presented in a poster at DDW 2025.

The other study was a sub-study within the 10-country clinical critieria survey conducted by the RFRI in 2023-2024, which focused on IBS and functional dyspepsia and included the Rome IV diagnostic questions for those disorders, as well as questions about history of COVID-19 infection and illness. The countries surveyed were Brazil, Canada, China, Germany, Japan, Mexico, Poland, Romania, Spain, and the United States, and the total sample size was 19,704 participants (about 2000 in each country). People in this post-pandemic 10-country sample had higher prevalence of both Rome IV IBS (8.2% vs. 3.8%; $p<0.0001$) and FD (13.3 vs. 7.3%; $p<0.0001$) compared to the combined pre-COVID RFGES sample for the same countries. The post- vs. pre-pandemic prevalence rates of FD and IBS were numerically higher in all countries, and in all age and sex subgroups. People who reported having had test-confirmed COVID had higher IBS (9.9% vs. 7.0%; $p<0.0001$) and FD (15.4% vs. 11.8%; $p<0.0001$) prevalence than those without a COVID test-positive history. Those who were moderately or very ill during COVID infection had higher prevalence of IBS (12.6% vs. 7.1%; $p<0.0001$) and FD (18.4 vs. 12.3%; $p<0.0001$) compared to those with mild or no symptoms. People with current lingering symptoms from past COVID infection ("long COVID") had higher IBS (16.8% vs. 7.8%; $p<0.0001$] and FD (22.9% vs. 12.6%; $p<0.0001$) prevalence than fully recovered individuals. People who had not been vaccinated for COVID had higher prevalence of FD (14.4% vs. 13.3%; $p<0.0001$) but not IBS [8.4% vs. 8.1%; $p=0.04$]) compared to the vaccinated. A paper on the findings of this study is being prepared for publication, and the preliminary results were presented as a poster at UEG Week 2024.

**Education Core: Rome-DrossmanCare Communications Program Analyses.**

**Evaluation of Communication Skill Training Programs**. Over the last several years, the Rome Foundation, in collaboration with the Center for Education and Practice of Biopsychosocial Care (DrossmanCare), has conducted several workshops, symposia, and train-the-trainer sessions PRE-COVID to help clinicians improve their communication skills. The RFRI took on the responsibility of studying the value of these programs. Thus, we embedded online questionnaires in all programs to obtain feedback. These data are available to Rome Foundation and RFRI sponsors on request.

Our objective is to empower key opinion leaders in Neurogastroenterology, educating them to become proficient educators and facilitators for fellow providers and trainees. To gauge the effectiveness of our 1 ½ day train-the-trainer (TTT) programs, focused on imparting communication skills, video utilization, role-playing exercises, and small group facilitation techniques, we are currently undertaking a prospective study involving gastroenterology and gastropsychology practitioners. The study aims to assess the impact of these programs on participants. Figure 1 encapsulates the aggregated responses gathered upon the completion of five such training initiatives.

Figure 1. Overall assessment and learning of facilitation skills in Train the Trainer Programs



**DrossmanCare - Rome Foundation Train the Trainers Course**
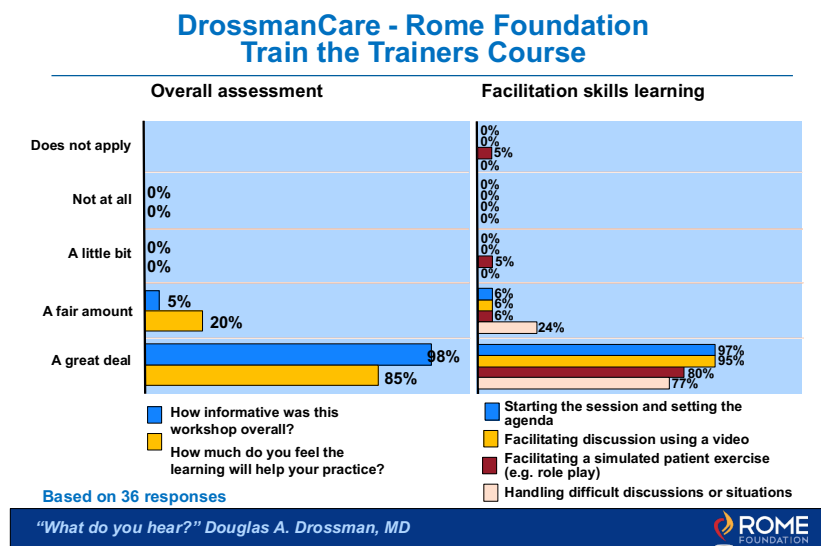
Currently, we are engaged in a qualitative analysis to assess the enduring impact of our Train-the-Trainer (TTT) programs on participants' knowledge, skills, and teaching behaviors, with a specific focus on outcomes at least one year post-training. In Figure 2, we present an overview of participants' self-reported ratings pertaining to the development of facilitation skills, offering insights into the sustained influence of the TTT experience on their professional capabilities in this domain.

Figure 2. Responses related to facilitation skills developed over one year past TTT participation.



**> 1Year Post Train the Trainer Post Course Evaluation Facilitation Training**
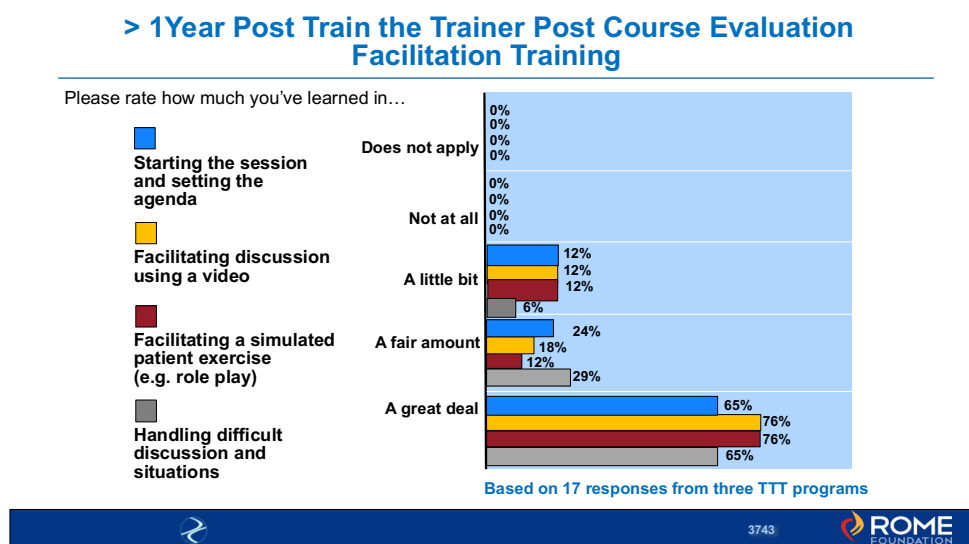
**Survey to Identify Key Elements in the Physician-Patient Relationship that Contribute to Patient Satisfaction and Development of a Short Form PPR Scale for Research and Clinical Care**. We surveyed 173 patients seeking health care from GI faculty members who underwent a communication workshop at Johns Hopkins Medical Center. We sought to determine the value of clinician training concerning patient satisfaction. The key questionnaires included two validated questionnaires developed by Dr. Drossman: the *Satisfaction with Care Scale (SAT-37) and the Patient-Provider Relationship Scale – Patient Version (PPRS-Patient)*. These questionnaires, in addition to demographic factors, patient symptoms, and psychological scores, were administered to the patients to accomplish four objectives: 1) identify the critical factors in the patient-provider relationship that predict overall satisfaction with care, 2) perform exploratory factor analysis to identify specific clinical factors in the patient-provider relationship, 3) perform multivariate analyses to determine the robustness of these factors in predicting overall satisfaction, and 4) develop a short version of the physician-patient relationship scale that predicts satisfaction with the care to be used as a clinical and research tool to assess physician performance in the clinical setting (PPRS Patient Version Short Form). Figure 4 shows the correlations of the items in the Physician-Patient Relationship Scale with overall clinical satisfaction (SAT-37).

**Figure 4. Correlations or patient PPRS items with Overall Satisfaction (SAT-37)**

This study is published: Drossman DA, Palsson O, Stein E, Ruddy J, O'Broin Lennon AM. What elements in the physician-patient relationship (PPR) contribute to patient satisfaction: Development of a short form PPRS-Patient Version (PPRS-Patient SF) Questionnaire.  Neurogastroenterol Motil 2022;34:e14191.
https://doi.org/10.1111/nmo.14191

**Consultations with Industry.** Over the past several years, the RFRI has consulted with industry relating to surveys and related studies in DGBI.

- **Transparency and Rose Pharmaceuticals**. This study evaluated the efficacy and safety of the GLP-1 analogue ROSE- 010 in reducing moderate to severe acute abdominal pain in IBS.
- **Alnylam Pharmaceuticals**. The RFRI discussed the development of a proposal to evaluate the prevalence of porphyria with Alnylam.  We developed a proposal that was used in their studies.
- **Arena Pharmaceuticals**. RFRI consulted to develop a detailed proposal for Arena to access the database of the Rome Foundation's Global Epidemiology Study of Functional Gastrointestinal Disorders. The goal was to evaluate the phenotypic features of patients with chronic abdominal pain.
- **Sanofi Pharmaceutical.** We are consulting with Sanofi to evaluate the characteristics of individuals having abdominal pain in the Global Epidemiology Database.

**Conclusion**

In 2024, the RFRI advanced to become a global leader in DGBI research. With the support of Ironwood Pharmaceuticals and Takeda Pharmaceuticals, we established an efficient infrastructure consisting of an Executive Committee, academic and industry advisory boards, and five cores.

We consulted with four pharmaceutical companies on their programs, designed and implemented our epidemiological studies and clinical trials, completed the Domino study, and progressed with the ROBOT program. with a central IRB, established the ability to collect bio-samples, established a global network of investigation sites, and are beginning to analyze and publish the results.

The RFRI continues several international studies and builds a global research network to expand our research capability. We expect that these activities will continue to grow over the next year and fulfill our mission: To improve patients' lives with DGBI through ground-breaking research.