Rome Foundation Research Institute Annual Report

For year 2023

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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

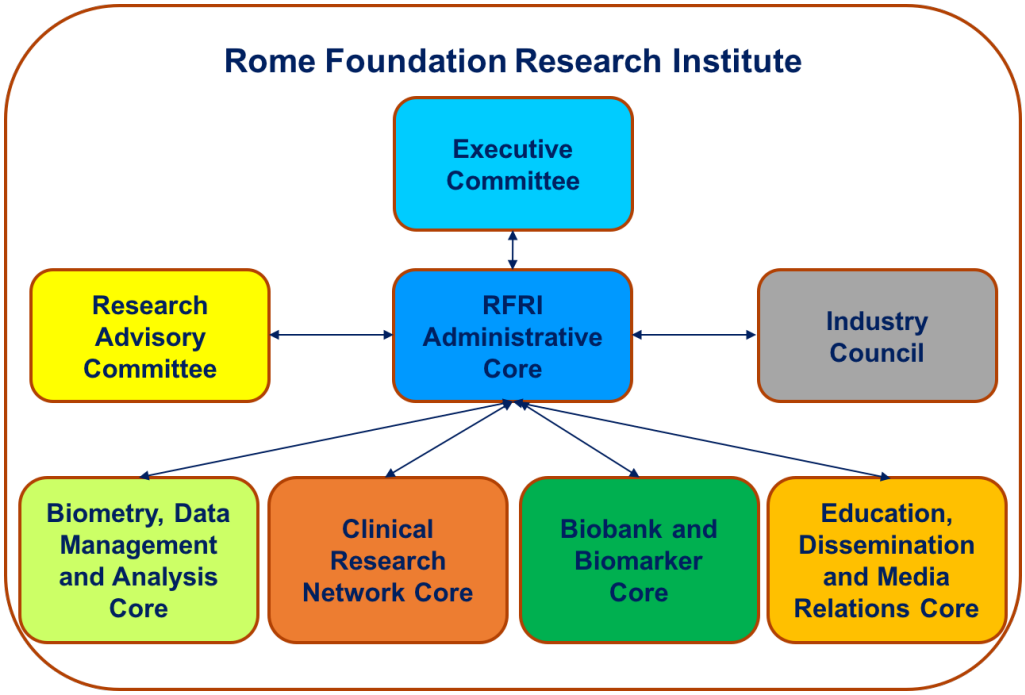
Aim. To increase the knowledge of the causes, identification, treatment and care of patients with DGBI.

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.



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.

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. The current IC members are Ironwood Pharmaceuticals and Takeda Pharmaceuticals. Additional industry members will be added as new sponsors come on board.

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

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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 Mark Schmitter (marketing 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 2023

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 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 additional clinical sites in Asia, Latin America, Europe, and the U.S. are currently preparing to start data collection with this system, including in Leuven in Belgium and the Mayo Clinic in Rochester in the U.S.

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 three sites in the Global Research Network are:

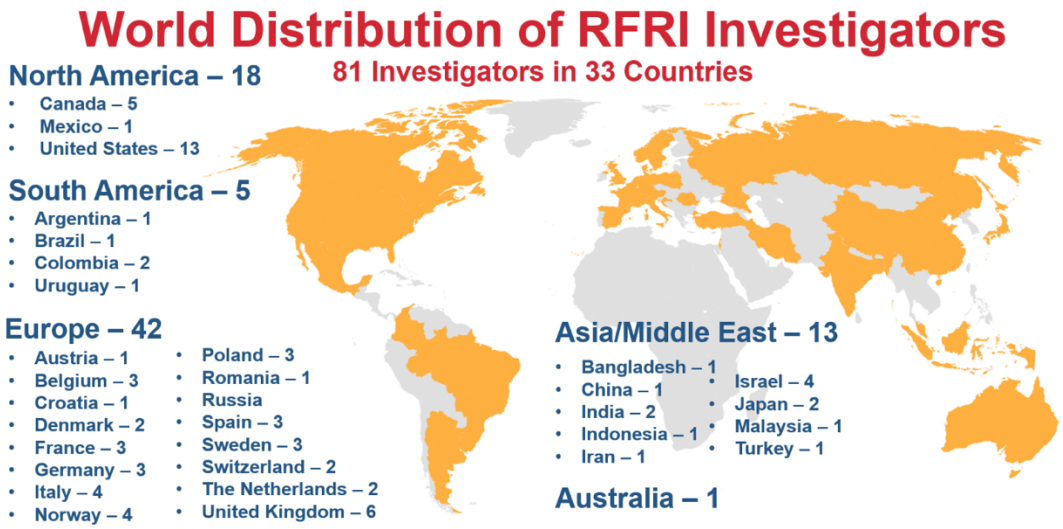
- University of Gothenburg, Sweden (PI: Magnus Simren, MD, PhD)
- KU Leuven, Belgium (PI: Jan Tack, MD, PhD)
- Mayo Clinic, Rochester, Minnesota, USA (PI: Madhu Grover MBBS)

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 Michigan, USA (PI: William Chey, MD);
- University of California Los Angeles, USA (PI: Lin Chang, MD);
- Queen's University School of Medicine, Canada (PI: Steve Vanner, MD, MSc)
- 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 several sites anticipated to be fully operational in the research network during 2024, the network will be able to start offering unique research opportunities of interest to sponsors and industry based on the coordinated data collection. We expect the number of sites in the RFRI Global Research Network will grow over the next few years. DGBI investigators worldwide have joined the 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

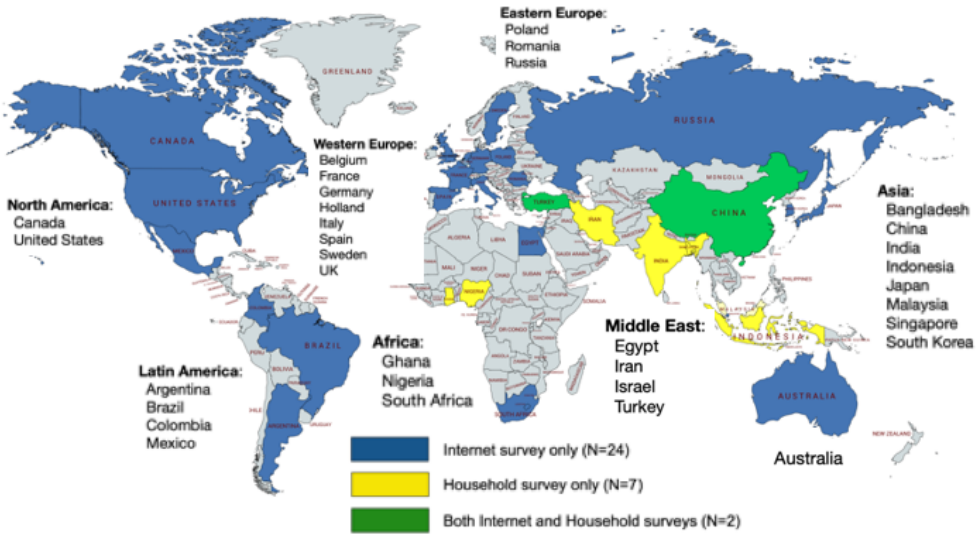


Engagement with Industry Consultant. We are pleased to have Doug Levine, MD, continue as our external industry consultant. His assistance to the Executive Committee through advisement on pharmaceutical industry perspectives, practices, and engagement of external investigators to inform RFRI approaches for establishing research collaborations and sponsorships is invaluable. Through his support of collaborative projects, review of research proposal drafts, budgets, and contracts, internal planning documents related to RFRI infrastructure, and funding support strategies, we are well-positioned for the coming years.

Rome Foundation Global Epidemiology Study (RFGES), Data Analysis and Publication Status. 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 FGID 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.

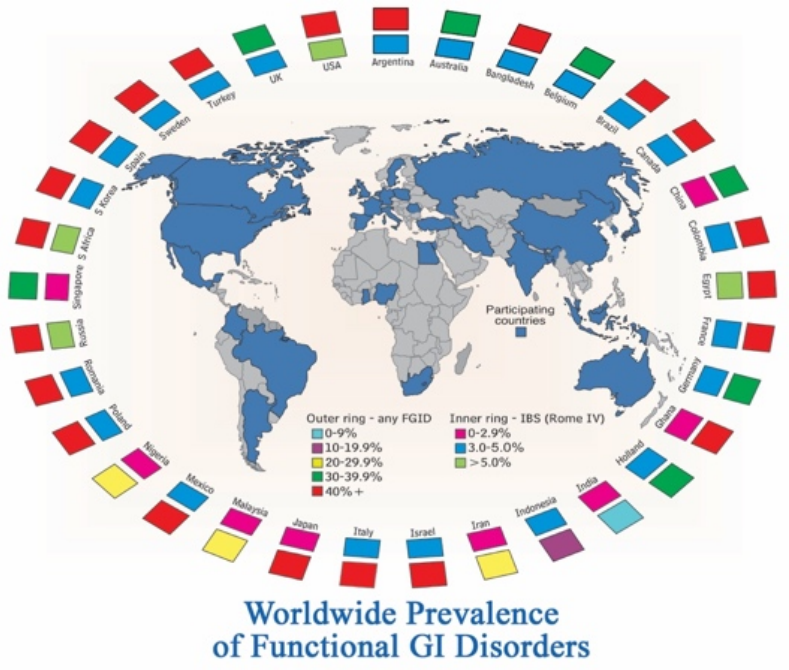
We established a Database Committee headed by Dr. Olafur Palsson, a Statistical Analysis Committee headed by Dr. Shrikant Bangdiwala at McMaster University, Canada, to do the initial analyses, and a Publications Committee headed by Dr. Ami Sperber. We vetted candidates for global study statisticians 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 28 statisticians from around the world working with us on various analyses of datasets in progress.

We have a website where you can submit proposals for abstracts or papers for studies related to the database. 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 close to 900 citations and is a leading resource for research in the field.

The following is the graphical abstract from that paper:



We have now published 31 papers from this global survey, 9 more of which are under review in different journals, and another 31 papers are in the data analyses or draft writing stage. In May 2023, an entire 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 47 abstracts at multiple scientific meetings, such as DDW and UEGW, including oral presentations, posters of distinction, and posters. Seven abstracts will be presented at DDW 2024, including one oral presentation, one poster of distinction, and 5 other posters.

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 two main current projects are:

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

b) A new 10-country study on factors associated with the bothersomeness of symptoms, their impact on quality of life, and the decision to consult a doctor about the symptoms. The rationale for this project is that we need to move from purely frequency-based diagnostic criteria to criteria that more accurately reflect clinical practice. Some DGBI patients have infrequent (sub-diagnostic threshold) GI symptoms, but the negative effect of those symptoms is strong. In contrast, other patients have frequent symptoms but are less bothered by them. The study assesses 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 finalized after we completed focus groups in Australia and the US to assess the proposed questions, after which the English questionnaire was translated into the languages of the participating countries, and the survey of 2,000 adults in each of 10 countries is being conducted by Internet by the RFRI. Data collection has been successfully completed in Argentina, Canada, China, France, Germany, Japan, Mexico, Poland, Romania, and the US, but is still pending in Brazil.

We are now analyzing the results in the 9 countries surveyed so far and expect to make the key findings available to the Rome V chapter committees, the Rome V questionnaire committee, and through publications in the GI literature in the next year or two.

A second study will survey 5 gastroenterologists in each of the 10 participating countries to gain an understanding of doctors' perspectives on how symptoms of IBS, FD, and IBS+FD affect their patients and which factors are the most central to the clinical effects of symptoms. We hope to complete this study by the end of 2024.

Rome V "Validation" and Global Epidemiology Study

A new major epidemiology study is now in the late preparation stage. It will have three main components:

a) "Validation" study for the Rome V diagnostic questionnaire.

In preparation for the release of the Rome IV Adult Diagnostic Questionnaire, the questionnaire committee conducted a validation study in the U.S. only. While the results contributed to finalizing the diagnostic criteria and scoring, they were criticized for "ethnocentrism" in that frequency data from the U.S. were only used as a reference for setting diagnostic symptom thresholds for the worldwide population.

In this study, we will assess the validity of the new Rome V diagnostic questionnaire in 16 countries around the world (2 in North America, 3 in Latin America, 5 in Western Europe, 2 in Eastern Europe, 1 in the Middle East, and 3 in 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 publication.

b) “Rome V Global DGBI Epidemiology Study”.

A supplemental questionnaire will be completed by survey respondents together with the Rome V diagnostic questionnaire in the new global study, as was done in the RFGES. The previous supplemental questionnaire has been upgraded based on input from expert advisory committees that suggested revisions to the RFGES supplemental questionnaire, as well as based on experience from the conduct of the RFGES.

Unlike the RFGES, where data were collected starting in 2017, a year after the publication of the Rome IV questionnaire, the entire new global study will be completed in advance of the publication of the diagnostic questionnaire, as it is being used for the “validation” study in combination with the epidemiology study. Thus, we expect to have analyses ready for publication as soon as the embargo lifts on Rome V.

c) Pediatric Multi-national Validation and Rome V DGBI Epidemiology Study.

As part of the Rome V diagnostic questionnaire validation process, we will complete 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 will be included to mirror the methodology of the adult studies. The online survey will be completed by mothers of children with DGBIs in the United States, Mexico, China, and Italy (2,000 participants per country). Data from the initial study will guide 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 a more extensive pediatric global epidemiological study.

Domino Trial

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.

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.)

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.

Houte K, Zheng T, Toth J, Besard L, Franke A, D'Amato M, Tack J, Carbone F. Gut. 2022 Sep 23:gutjnl-2022-328430.)

A number of additional upcoming publications from the DOMINO trial have been finalized:

a) 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 2024.

b) DOMINO trial post – hoc analysis: evaluation of the diet effects on symptoms in IBS subtypes. Di Rosa C.,Van den Houte K., Besard L., Arts J., Caenepeel P., Piessevaux H., Vandenberghe A., Matthys C., Biesiekierski J.R., 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. and Carbone F. Submitted for publication 2024.

c) Functional variation in human Carbohydrate-Active enZYmes (hCAZymes) influences the efficacy of a FODMAP-reducing diet in IBS patients. Taranu AZ, Löscher BS, Carbone F, Hoter A, Esteban Blanco C, Bozzarelli I, Torices L, Routhiaux K, Van den Houte K, Mayr G, Corsetti M, Naim HY, Franke A, Tack J and D'Amato M. Submitted for publication 2024.

A number of additional upcoming publications from the DOMINO trial are being finalized:

d) A Cost-Consequence Analysis based on the randomized controlled DOMINO trial: dietary intervention dominant over pharmacotherapy for newly diagnosed or newly treated irritable bowel syndrome in primary care. In preparation for publication 2024.

Analysis of the role of gut microbiota composition: Gut microbiota composition in newly diagnosed primary care irritable bowel syndrome: a sub-analysis of the DOMINO trial.

e) Characteristics and impact of IBS in newly diagnosed patients from primary care.

f) A separate paper on the otilonium bromide arm: Symptom response and determinants of outcome in a large cohort of primary care IBS patients treated with otilonium bromide.

ROBOT Project

RFRI finalized the planning of the **RO**me Foundation **B**i**O**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 already enrolled ~15 patients. Shortly, the University of Michigan will be activated as the second US site. The IRB applications are planned / underway in several Asian 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 recruited ~15 patients, 10 of who have deposited stool/blood samples along with the questionnaire completion. Additional 5 US sites are planned to be 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. Additionally, other sites in Asia, Latin America, and Europe will follow over 2024-25.

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

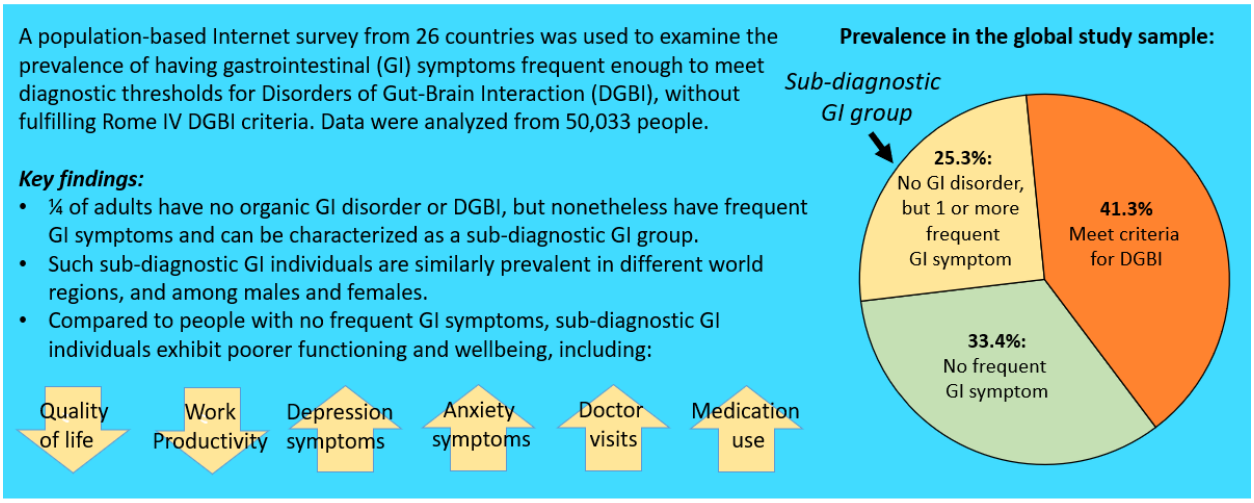
This study was a secure Internet population survey of 5,978 adults in the United States, Mexico, and the United Kingdom, conducted to evaluate bloating, distention, and other gas-related symptoms and a wide range of potentially related factors. The study was designed collaboratively by the RFRI and Danone 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 three scientific abstracts presented at UEG Week and DDW, and the first paper is being submitted for publication. Additional analyses of this dataset are ongoing and planned, including cluster analysis of individuals with bloating and distention, to be presented at DDW 2024, 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.



Palsson, et al. *Aliment. Pharmacol. Ther. 2024;*59(7), 852–864.
https://doi.org/10.1111/apt.17894

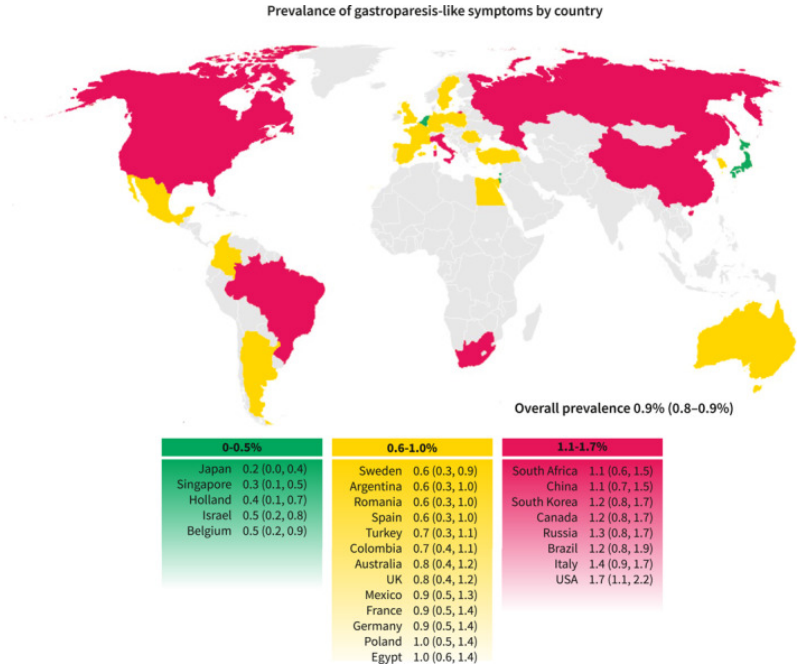
Gastroparesis, Functional Dyspepsia and Cyclic Nausea Vomiting Syndrome.

Gastroparesis is a condition characterized by epigastric symptoms and a significantly delayed gastric emptying rate in the 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. Still, 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. 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 determining 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-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.

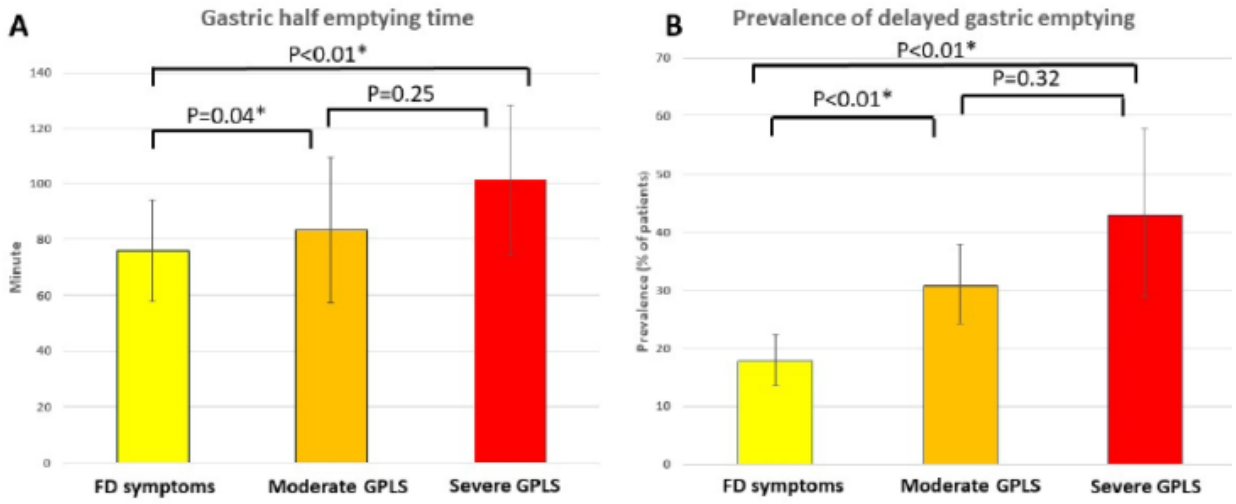


The epidemiological analysis has been published in *UEG Journal*: Worldwide prevalence and burden of gastroparesis-like symptoms as defined by the United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) consensus on gastroparesis. Huang IH, Schol J, Khatun 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 the 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 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. Submitted for publication 2024.

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.

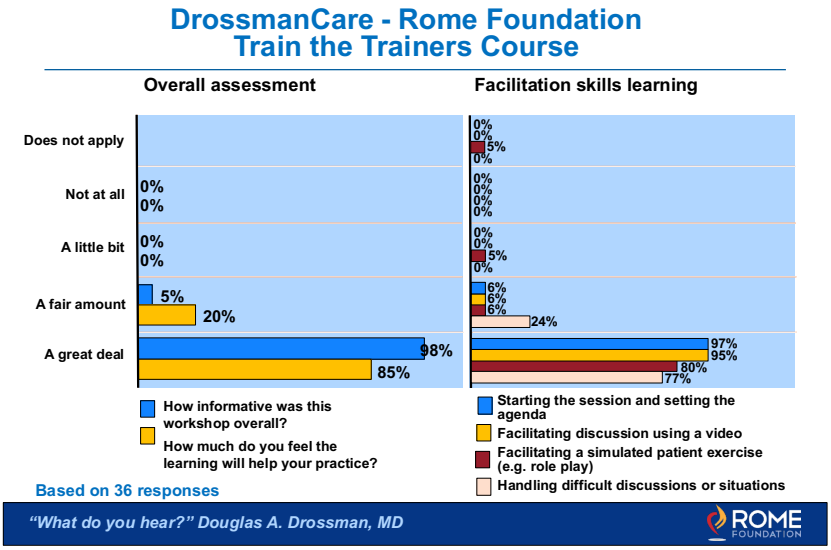
Manuscript: Worldwide Prevalence and Description of Cyclic Vomiting Syndrome According to the Results of the Rome Foundation Global Epidemiology Study. Authors: Izagirre A, Sarasqueta C, Flores-Arriaga J, Aso MC, Pérez M, Tack J, Huang IH, Sperber AD, Palsson OS, Bangdiwala SI, D'Amato M, Lanas A, Lobo B, Alonso-Cotoner C, Santos J and Bujanda L. Submitted for publication 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.

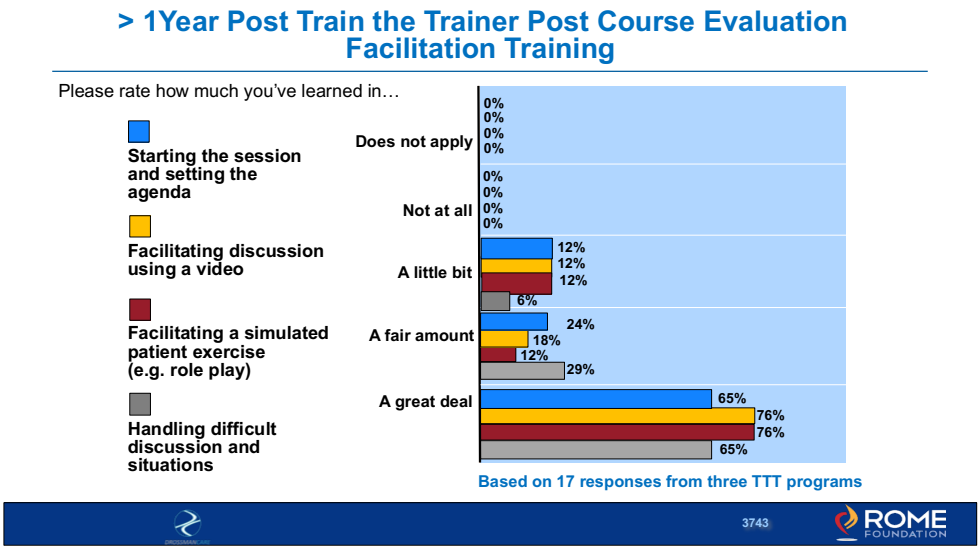
Our objective is to empower key opinion leaders in Neurogastroenterology, educating them to become proficient educators and facilitators for fellow providers and trainees. To gauge the effectiveness of our 1 ½ day train-the-trainer (TTT) programs, focused on imparting communication skills, video utilization, 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



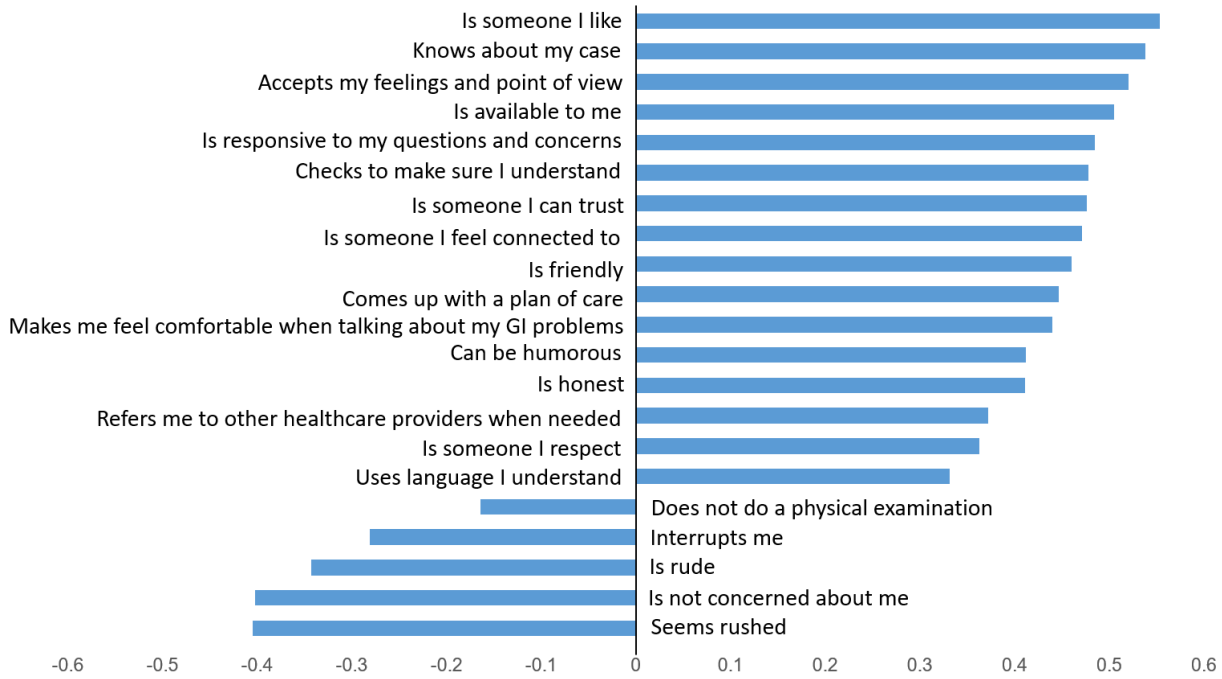
Currently, we are engaged in a qualitative analysis to assess the enduring impact of our Train-the-Trainer (TTT) programs on participants' knowledge, skills, and teaching behaviors, with a specific focus on outcomes at least one year post-training. In Figure 2, we present an overview of participants' 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.



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 2023, 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.