Rome Foundation Research Institute Annual Report

For year 2021

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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 through the development of 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

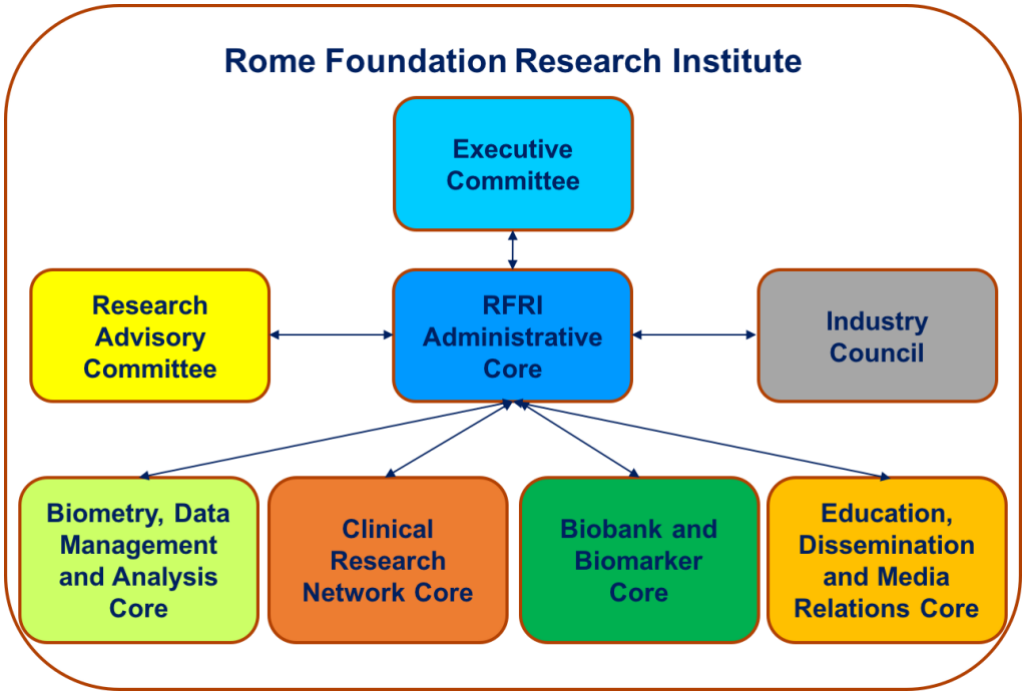
Aim. To increase the knowledge of the causes, identification, treatment and care of patients with DGBI.

Implementation. To establish an international academic research initiative with leading experts, in order 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 the development, administration and analysis of clinical research in DGBIs.
- Develop a portfolio of current and future study protocols and an accessible database of knowledge which 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 Executive Committee of RFRI and Board Member of RF), Douglas Drossman MD (RF President Emeritus and COO) and Jan Tack MD, PhD (RF President). 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) and Johannah Ruddy (Secretary/Treasurer) 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. The terms for the members are for five years and are renewable, with the replacement process staggered to allow for gradual change of leadership.

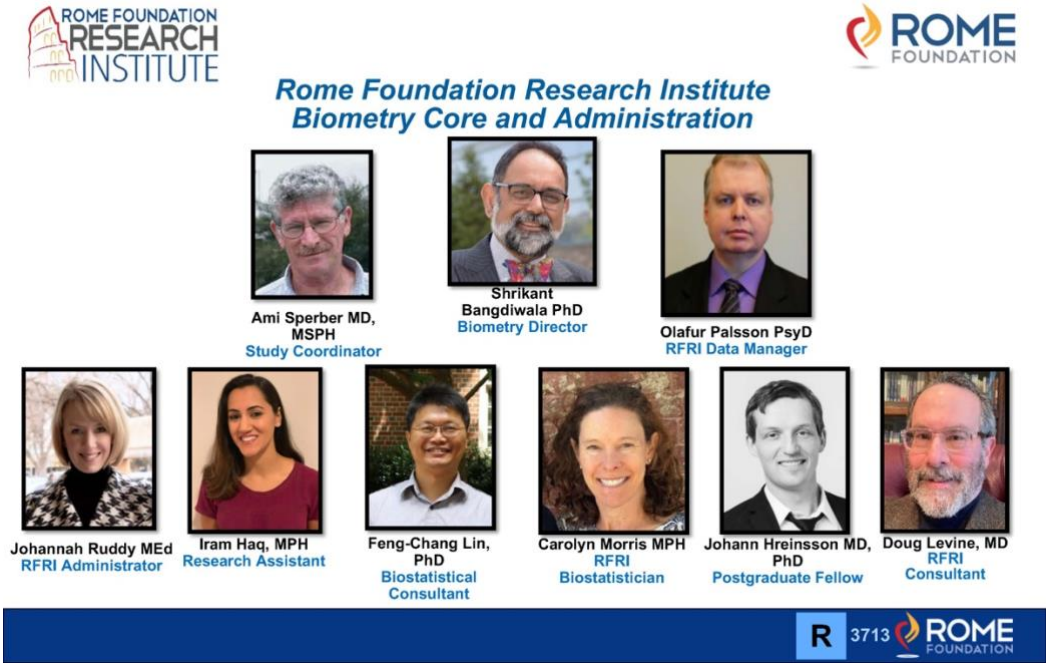
Administrative Core (AC). The AC is responsible for the oversight of the day-to-day activities of the RFRI relating to research administration and program implementation, training, education and dissemination of information, collaboration with sponsors and outside agencies, and quality control of all core programs. The AC consists of the three executive committee members, the Biometry Director (Shrikant Bangdiwala PhD), the Senior Study Coordinator (Ami Sperber MD, MSPH), the data manager of the RFRI (Olafur Palsson Psy.D.), an external industry consultant who advises on collaborations with commercial organizations in the Life Sciences (biopharmaceutical, device, and diagnostics companies) (Doug Levine, MD) and an RFRI administrator (Johannah Ruddy M.Ed., Executive Director of the RF). The AC is also advised 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 TAD is composed of RF Board members who have been selected based on their academic record of scientific achievement, 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 PhD, Brian Lacy, MD, Samuel Nurko MD, MPH, Max Schmulson MD, and Ami 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 is comprised of 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 Michael Shetzline, MD PhD, Christina Almansa MD, for Ironwood Pharmaceuticals, and Vijay Yajnik MD, and Mena Boules MD for 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/or ensuring the standards for high quality data management systems, quality assurance processes, and statistical analytic aspects for the RFRI. It works under the direction of the Executive Committee. Core members include Shrikant Bangdiwala Ph.D., the biometry director Olafur Palsson Psy.D. who is the data manager and coordinator of activities, Carolyn Morris PhD, biostatistician, Feng-Cheng Lin, biostatistical consultant, Ami Sperber MD MSPH, senior study coordinator, Johann Hreinsson MD, study administration, and Iram Haq, research

coordinator. This Core is actively involved with ongoing research proposals, as discussed below.



Clinical Research Network Core (Research Core). The Research Core is responsible for providing the infrastructure and maintaining the standards for clinical investigative studies involving epidemiological, clinical outcomes, and treatment studies. It is co-directed by Lin Chang MD and William Chey MD, and members include: Laurie Keefer PhD, Samuel Nurko MD, Ami Sperber MD, MSPH and Jan Tack MD, PhD. 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. The chair and the co-chair lead this committee, in close collaboration with the members of the Executive Committee and the Research Manager. 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 biobanking 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 during the coming years.

Education, Dissemination and Media Relations Core (Education Core). The Education Core serves primarily to assure quality control in disseminating research knowledge accumulated from the RFRI and support its translation into clinical practice. The Core members are Douglas Drossman MD (director), Johannah Ruddy (administrator and Executive Director of the RF), 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 publications printed and digital, will be scientifically based, unbiased, and non-commercial. The Core also monitors media, publications, and other communications from external sources (e.g., news bureaus, scientific organizations, industry) to ensure the information provided is accurate, scientifically based, and unbiased.

Part Two: Activities of the RFRI for 2021

Introduction. Over the past two years, the RFRI developed and consolidated the infrastructure with further refinement of the biometry and biobank cores, creating a database of investigators, and developing 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 include the Rome Foundation Global Epidemiology Study data analysis, completion of the Domino clinical trial and implementation of the ROBOT studies, a contract with Danone Pharmaceuticals to study gals and abdominal bloating, 2021-2022, and consultations concerning prospective projects with two pharmaceutical companies.

Finally, we are most pleased to have Ironwood Pharmaceuticals under the directorship of Mike Shetzline MD and Cristina Almansa, MD as a full diamond sponsor and Vijay

Yajnik MD and Mena Boules MD of 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 secure Internet-based data collection system has just been completed. 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 will begin recruiting patients from the ROBOT project at the Gothenburg and Leuven sites in Summer 2022.

The use of the RFRI-IP online data collection system will quickly create an unprecedented large 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 will be instantly scored and available in the clinical encounters, and thus clinically useful to doctors and patients at each participating site.

All patient data collection using the RFRI-IP will be strictly de-identified and HIPAA and GDPR compliant. To minimize costs and demands on staff at the clinical research sites, data collection will be 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 will be by patients at home prior to clinic visits or via computer tablets in the waiting rooms. The assessment will be fully mobile-device compatible so patients can use their mobile phones to complete the assessments if preferred. Staff-assisted entry and paper questionnaires will only be used in exceptional circumstances if needed.

The patient phenotyping assessment will consist of an initial 25-30 min. patient-completed questionnaire, and a shorter assessment (5-10 min.) in return clinic visits, primarily designed to update information on clinical status in the database. These patient-completed assessments will be supplemented with a limited set of 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, will include 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) will be 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 and bio-samples on large numbers of DGBI patients. It 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 first sites in the network will include some of the world's top DGBI centers.

The first two sites in the Global Research Network will systematically collect data with the RFRI Investigator Platform in the first half of 2022 and will pilot test the platform. These sites are:

- University of Gothenburg, Sweden (PI: Magnus Simren, MD, PhD)
- KU Leuven, Belgium (PI: Jan Tack, MD, PhD)

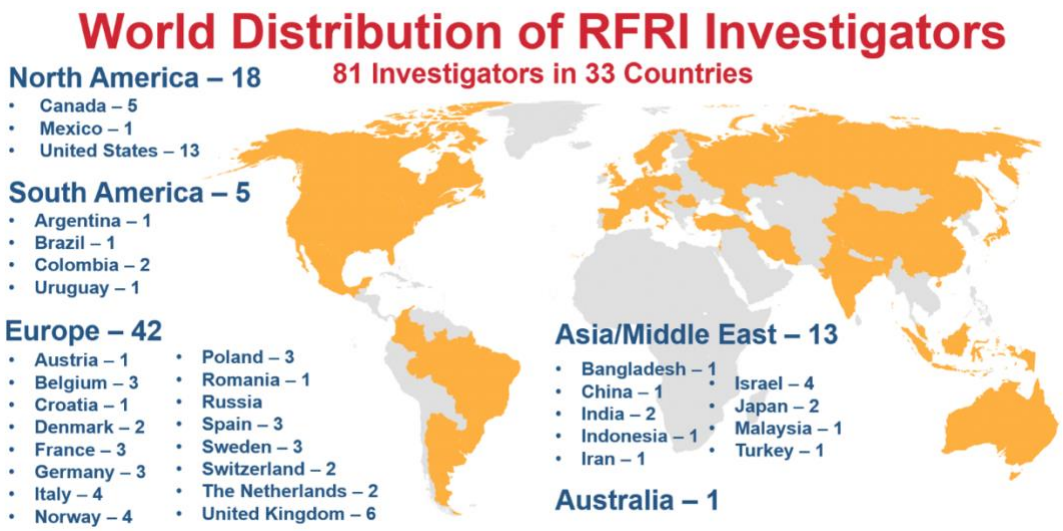
Several other sites will join the Global Research Network within the next year and start collecting data via the RFRI-IP into the uniform central database. Early additional sites in the network are likely to include the following:

- University of California Los Angeles, USA (PI: Lin Chang, MD);
- University of Michigan, USA (PI: William Chey, MD);
- Queen's University School of Medicine, Canada (PI: Steve Vanner, MD, MSc)
- Harvard Medical School, USA (PI: Anthony Lembo, MD)

- Universidad Nacional Autónoma de México (UNAM), Mexico (PI: Max Schmulson, MD)
- University of Bologna, Italy (PI: Giovanni Barbara, MD)

We expect that the number of sites in the RFRI Global Research Network will grow over the next few years. DGBI investigators world-wide have shown in joining 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



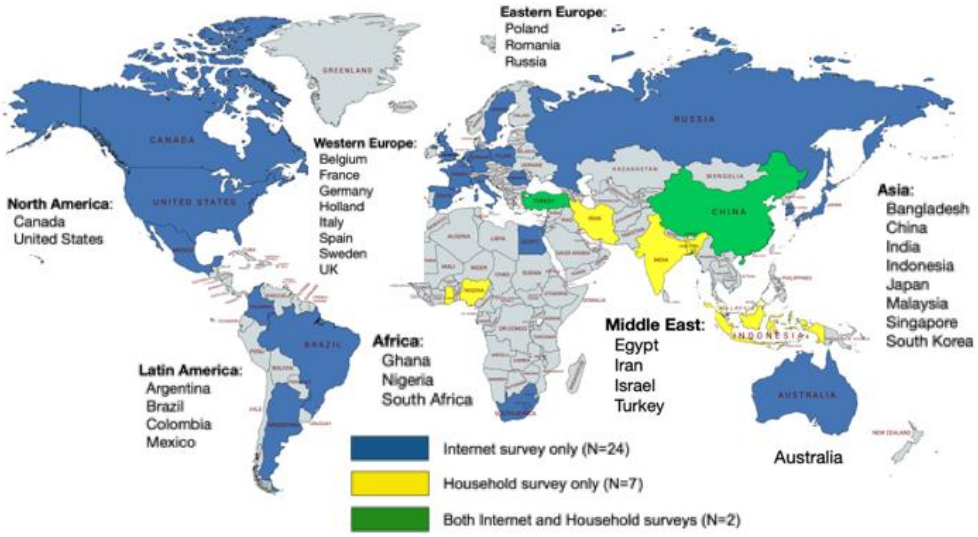
Engagement with Industry Consultant. We are pleased to have Doug Levine MD continue as our external industry consultant. His assistance to the Executive Committee-through advisement on pharmaceutical industry perspectives, practices, and engagement of external investigators to inform RFRI approaches for establishing research collaborations and sponsorships is invaluable. Through his support of the 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 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 global study are 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

are 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) to 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. In two countries, China and Turkey, we conducted both surveys. The predefined demographic parameters were 50% females and 50% males, and age distribution of 40% for 18-39 years, 40% for 40-64 years, and 20% for 65+ years.

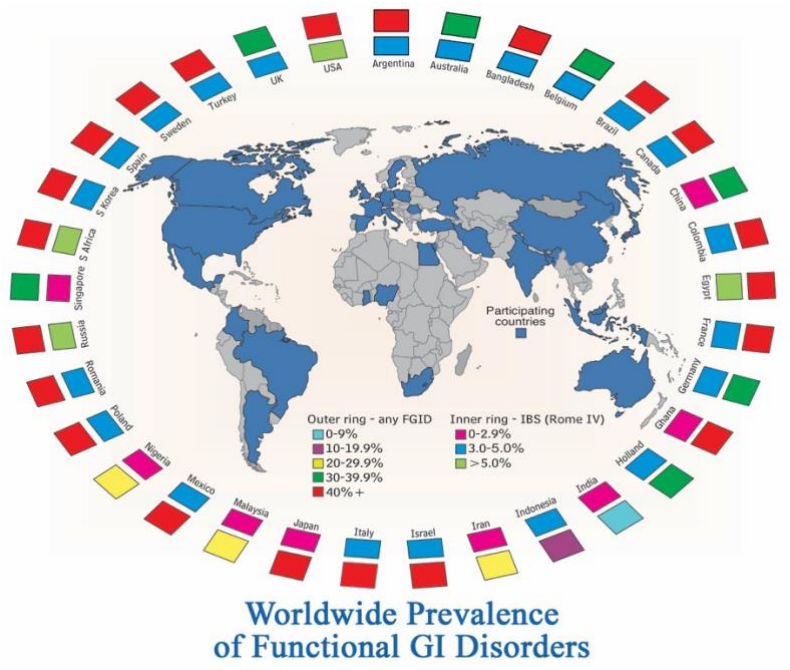
The data collection phase was completed in 2018 with a final database of 73,076 respondents: 36,148 women (49·47%) and 36,928 men (50·53%). We successfully achieved equal sex distribution and pre-planned age ranges with both surveying methods.

We established a Database Committee, a Statistical Analysis Committee headed by Dr. Shrikant Bangdiwala at McMasters, Canada, to do the initial analyses, and a Publications Committee. We vetted candidates for global study statisticians and established regional and local statistical analysis cores. We held a one and one-half day Global Study Statistical Workshop in Barcelona, Spain in October 2019. About 40 participants attended who would serve as data analysts for regional and local

manuscripts and investigators who intend to be lead authors of manuscripts from the study.

We have a website to submit proposals for abstracts or papers for studies related to the database. All submissions undergo a review process (including the statistical analysis plan) like editorial reviews in medical journals, but to improve and approve the proposals, not reject them.

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). The following is the graphical abstract from that paper:



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.

Since the initial paper, we have published four other articles, and another one is under review in a top-tier journal. The four published papers are:

1) Sperber AD, Freud T, Aziz, I. et al. (2021). Greater overlap of Rome IV disorders of gut-brain interactions leads to increased disease severity and poorer quality of life. *Clin Gastroenterol Hepatol* https://doi.org/10.1016/j.cgh.2021.05.042.

2) Josefsson A, Hreinsson JP, Simrén M, Tack J, Bangdiwala SI, Sperber AD, Palsson OS, Törnblom H. (2022) Global prevalence and impact of Rumination syndrome. Gastroenterol 2021 162: 731-742. doi: 10.1053/j.gastro11.008

3) Sperber AD, Freud T, Abu-Freha N, Shibli F, Brun R, Bangdiwala, SI, Palsson OS, Dickman R. (2022) The Epidemiology of Disorders of Gut-Brain Interaction in Israel: Results from the Rome Foundation Global Epidemiology Study. Neurogastroenterol Motil. doi: 10.1111/nmo.14323.

4) Colomier E, Melchior C, Algera, JP, Hreinsson JP, Störsrud S, Törnblom H, Van Oudenhove L, Palsson OS, Bangdiwala SI, Sperber AD, Tack J, Simrén S. (2022) Global prevalence and burden of meal-related abdominal pain. BMC-Medicine 20:71. doi.org/10.1186/s12916-022-02259-7.

Twenty other studies have been approved and are in varying data analysis and manuscript preparation stages.

We are receiving more proposals for study regularly. The Rome Foundation Research Institute (RFRI) will now coordinate studies related to the global study database, including global study data mining, to provide background data for the Rome V committees. Drs. Sperber, Palsson, and Bangdiwala will lead this work.

We have presented abstracts at multiple scientific meetings including DDW and UEGW, starting in 2020 and will be presenting 6 posters at DDW 2022:

1) Gastroparesis-like symptoms - Abstract # 3695758 on May 21
2) Diet and DGBI - Abstract # 3693820 (e-poster)
3) Burden of Pain in DGBI - Abstract # 3691932 on May 23
4) Psychological factors in DGBI - Abstract 3696085 on May 23
5) Factor analysis - Abstract # 3698357 on May 23
6) DGBI Romania - Abstract # 3692626 on May 24

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 in Gastroenterology in general and Neuro-Gastroenterology in particular.

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. 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. Before and after 8 weeks of treatment, patients completed questionnaires evaluating demographics, stool types, Rome IV criteria, IBS-Symptom Severity (IBS-SSS), anxiety (GAD), depression (PHQ9) and somatization (PHQ15).

The study ended in the Summer of 2020, with 470 patients enrolled and 95% of the subjects providing biobanking samples for genetics, serum, and stool analysis for microbiota and biochemical parameters. Patients were randomized to medication or the diet app, and those with an improvement of at least 50 points on IBS-SSS were considered as a responder. The following paragraphs summarize abstracts regarding this study, which were submitted to FNM 2020 and to DDW 2020 and 2021. The primary outcome data were a plenary presentation at the 2021 DDW.

At baseline, 71% of these primary care-diagnosed IBS patients fulfilled the Rome IV criteria (Rome+). The following IBS-SSS distribution was found: 4, 16, 41, 39 % for normal, mild, moderate, and severe IBS-SSS respectively. Patients were characterized according to the stool pattern: diarrhea (27%), constipation (23%), mixed stool type (38%) and normal (12%).

453 primary care IBS patients (41±15 years, 76% female, 71% Rome+) were randomized to either OB (n=231) or diet app (n=227). The responder rate in the diet group (71%) was significantly higher compared to OB (61%) after 8 weeks of treatment (p=.03) and this was more pronounced in Rome+ (77% vs. 62%, p=.005). The diet group maintained a significantly higher responder rate during follow-up (6 months: diet: 74%; OB: 58%, p<.001). Mean IBS-SSS improved significantly over time in both groups (OB: 267±100 vs 170±109 (p<.001); diet: 267±96 vs 188±109 (p<.001)), but with significantly larger improvement in the diet arm compared to OB (p=.02). Both with OB and diet, significant improvement was observed for IBS-QoL (OB=-7.34 (p<.001) vs diet=-8.07 (p<.001)) and levels of anxiety (OB=-0.99 (p<.001) vs diet=-1.19 (p<.001)), depression (OB=-1.09 (p<.001) vs diet=-1.36 (p<.001)) and somatization (OB=-1.31 (p<.001) vs diet=-1.80 (p<.001)), but without significant difference between treatment groups (p>.05). Female gender (OR=, p=.04) was a response predictor for diet-treated patients whereas higher somatization (OR=, p=.002) was a predictor of OB treatment response.

The revised version of the primary outcome manuscript is currently under review in Gut, and a decision is likely to be made over the next weeks.

In addition, we analyzed the genetic samples for predictors of response to either treatment. Below is a summary of the abstract, which will be an oral presentation at DDW 2022.

459 patients with physician-diagnosed IBS were randomized to receive a FODMAP lowering diet through a smartphone app (n=227) or a treatment with the antispasmodic agent otilonium bromide (n= 232). Improvement of 50 points in the IBS Symptom Severity Score (IBS-SSS) after 8 weeks of treatment was considered a responder. Whole genome single nucleotide polymorphism (SNP) Global Screening Arrays from Illumina were used to obtain genotype data from every patient. A selection of 6 and 7 candidate genes respectively for the diet and medication arms was tested for association with treatment response in a logistic regression model using plink2. IBS-SSS was significantly improved for both groups after 8 weeks of treatment (p<0.001). In the diet group 71% (95% CI: 65-77) of patients were responders, which was significantly higher than the 61% (95% CI: 54-68) responder rate in the medication arm (p=0.03).

SNPs from three genes (SLC6A4, TRPA1, CACNA1C) were associated with a response to medication and from two genes (IL5RA and CCR3) with response to dietary intervention respectively. Two of these SNPs are linked to expression quantitative loci (eQTL): Allele rs2020934G in the serotonin reuptake transporter gene SLC6A4 was associated with higher OB response rate ($p=9,05x10^{-5}$) and increased mRNA expression in aorta, breast, esophagus and adipose tissues. Allele rs7617872A from the C-C Motif Chemokine Receptor 3 gene CCR3 was associated with increased response to dietary intervention ($p=2,17x10^{-6}$) and increased expression of CCR3 in whole blood.

This allows us to conclude that, in a group of primary care IBS patients, symptomatic response to a pharmacological or dietary intervention was associated with SNPs inviting further genetic studies in this direction. The SNP associated with medication response is linked to peripheral expression of a serotonin reuptake transporter- the mechanistic link to treatment with otilonium bromide remains elusive. The SNP associated with response to diet maps to a gene coding for a chemotactic receptor mainly expressed on eosinophils, suggesting a possible role for eosinophil chemotaxis in the symptomatic response to reduced FODMAP intake.

Future publications will include: a) the role of gut microbiota composition in response to either treatment arm, b) the baseline characteristics of primary care IBS patients, c) a health economic impact analysis of the study, and d) an analysis of the link between symptoms and treatment response on one hand and stool or blood markers (calprotectin, elastase, secretory immunoglobulin A, beta-defensin, C-reactive protein) on the other hand.

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. The plan was to launch this project in 2021 at a small number of sites. However, due to the Pandemic

and conflicting projects, the start of the study has been postponed to 2022. The Ethical review board now approves the project in Gothenburg, Sweden. The recruitment of subjects will start in the spring of 2022, followed by launch in Leuven, Belgium during the summer of 2022. After this initial launch in a few highly specialized clinical research units, we plan to expand this project to more sites.

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 in 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 for use as diagnostic and /or predictive tools. A centralized electronic database will enable development of profiles of available clinical phenotypes and biosamples at any time to assess the feasibility of new studies.

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. This will begin in May, 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. Each site will ideally also include 20-50 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 and 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 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 will begin in May and the one in Leuven in June, 2022. There will be a few more centers beginning in the fall 2022. .

RFRI- Bloating Survey, sponsored by Danone Nutricia Research

This study was a secure multinational 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.

The survey contents included demographics, Rome IV diagnostic questionnaire modules for gastroduodenal disorders and functional bowel disorders, questions about bloating and distention rated separately for the previous 3 months, the Intestinal Gas Questionnaire, questions about association of bloating/distension to meals, the PHQ-12 non-GI physical symptom questionnaire, selected medical and health history, questions about medications used regularly, and questions about anxiety and depression symptoms, stress, sleep, exercise, diet, quality of life, height and weight, and healthcare utilization. A subset of 1437 participants also completed a 25-minute online VioScreen follow-up survey about their total diet over the past 3 months.

This is the first study to examine both 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 and their impact in the population and reveals the relative prevalence and overlap of bloating vs. distention. The study has resulted in three scientific abstracts presented at UEG Week and DDW, with more to follow, and the first paper on the findings is currently in preparation.

Study of Sub-Threshold Patients-Sponsored by Danone Nutricia Research

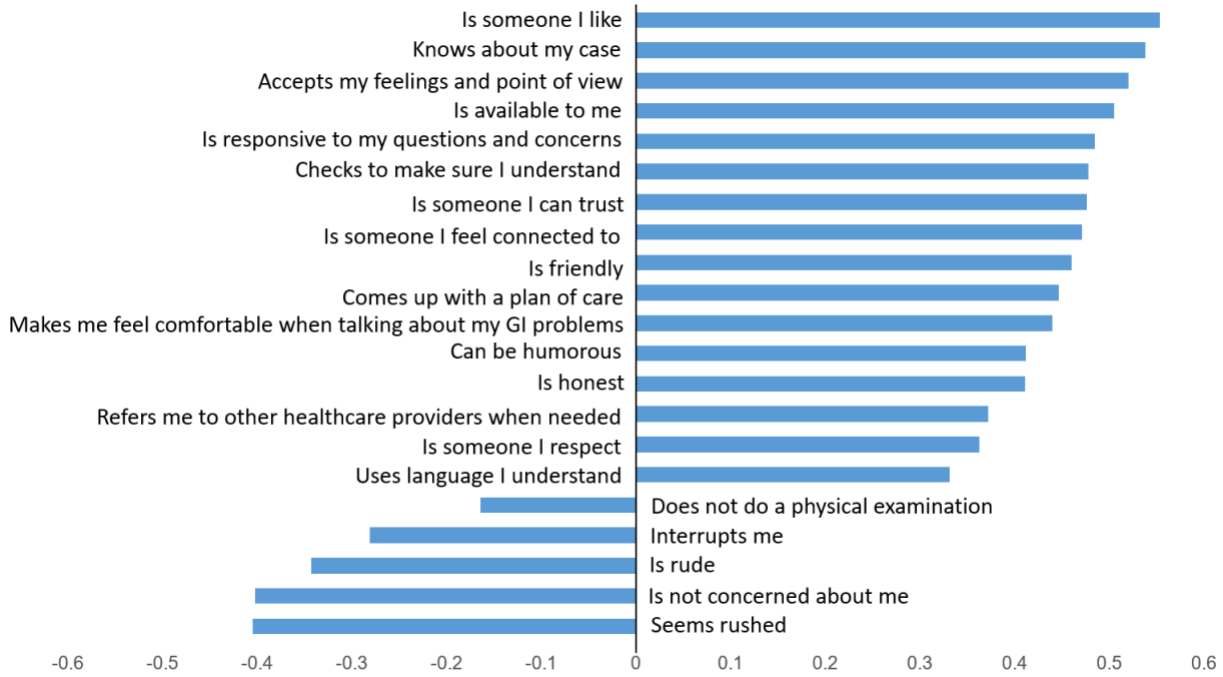
In addition, we are finalizing the Global Study data to characterize the global prevalence of people in 26 countries who are classified as having sub-threshold GI symptoms (bothersome but not meeting Rome IV Criteria for diagnosis). We plan to evaluate the associated impact on quality of life (QoL), healthcare utilization, and psychological wellbeing. We will also compare these individuals to people with DGBI and non-GI individuals in terms of sociodemographic, dietary, lifestyle, medication use, psychosocial & clinical variables. The results should prove to be quite interesting to see the burden of symptoms in people with GI distress who have yet to receive a diagnosis.

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) conducted several workshops, and symposia and train the trainer sessions PRE-COVID to help clinicians improve their communication skills. The RFRI took on the responsibility to study 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.

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 consulted with industry relating to surveys and related studies in the area of DGBI.

- **Transparency and Rose Pharmaceuticals**. Drs. Drossman, Chang and Chey consulted on the protocol of a Phase IIb study evaluating the efficacy and safety of the GLP-1 analogue ROSE- 010 in reducing moderate to severe acute abdominal pain in IBS.
- **Alnylam Pharmaceuticals**. Upon the company's request, Dr. Drossman initiated a study proposal further modified by Drs. Tack, Simren, Palsson and Bangdiwala to identify hepatic type porphyria (primarily AIP) at multiple sites globally. Dr. Doug Levine served as an external industry consultant to the Executive Committee. The company approved the initial proposal. Subsequently a full day meeting with the above consultants was held in June of 2019 to finalize the proposal which was submitted to the company. Unfortunately, a change of senior leadership and a shift in research priorities led the company to withdraw the study application

- **Arena Pharmaceuticals**. RFRI consulted to develop a detailed proposal for Arena to access the Rome Foundation's Global Epidemiology Study of Functional Gastrointestinal Disorders database. The goal was to evaluate the phenotypic features of patients with chronic abdominal pain
- **Sanofi Pharmaceutical.** We are presently consulting with Sanofi to evaluate the characteristics of individuals having abdominal pain in the Global Epidemiology Database

Conclusion

For 2021, 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 initiated the ROBOT program, established the ability to collect bio-samples, 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 believe that these activities will continue to grow over the next year and fulfill our mission: To improve the lives of patients with DGBI through ground-breaking research.