Imperial College London

Clinical and Translational Research Studies in Gastroenterology: Motility and Functional Disorders

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Doctor of Science degree

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Statement regarding how the publications have contributed to knowledge:

Clinical and Translational Research Studies in Gastroenterology: Motility and Functional Disorders

The body of my work has advanced knowledge and learning in the areas of gastrointestinal, colonic and anorectal physiology, pathophysiology, pharmacology, pharmacogenetics, diagnosis and management of motility and functional gastrointestinal disorders. The work has impacted the diagnosis and management of disorders such as gastroparesis, chronic constipation, irritable bowel syndrome, functional dyspepsia, and carcinoid diarrhea. These publications are selected from around 800 articles published (625 original articles, >175 invited reviews or editorials in journals) over more than 35 years. They have been selected to show the sustained and consistent contribution I have made to the translational and clinical science research in gastroenterology. These original contributions have usually been made jointly with students I have supervised, or fellows and collaborators I have worked with. This work has been published in international journals and has been cited extensively by others. In many instances, this work has achieved a long-term impact and has led to further developments by others and citations over a long time.

According to Google Scholar, my published work has been cited over 65372 times, with 22400 in the last 5 years, and my current h-index is 133. In addition to articles pertaining to original research detailed under 9 different categories below, I have selected 20 articles cited >100 times (based on Thomson Web of Science) and these are single author reviews (as in the New England Journal of Medicine), national or international guidelines that have impacted the field significantly, or original research. All the selected papers are in English. As recommended in the instructions, I have identified 20 papers with some of the highest numbers of citations in the literature, and provided the Journal, Title of the article, full list of authors and number of times cited according to the Web of Science database. I have also added my role in the article, and this is verifiable by the name of the corresponding or senior author of each article, or by first authorship. This information appears in the table, and pdfs of the articles are attached in the same order.

20 Publications cited >100 times (based on Thomson Web of Science)

#	Journal	Title	Authors	# of times cited	Role of applicant
1	Gastroenterology 2006;130:1466-79	Functional gastroduodenal disorders	Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR, Stanghellini V	1062	Member of Rome III Criteria Committee
2	Gastroenterology 2002; 123: 2108-2131	AGA technical review on irritable bowel syndrome	Drossman DA, Camilleri M, Mayer, EA, Whitehead WE	911	Member of Appointed Committee
3	**N Engl J Med** 2003;349:1360-8	Chronic constipation	Lembo A, Camilleri M	422	Senior Author
4	Am J Gastroenterol 2013;108:18-37	Clinical guideline: Management of gastroparesis	Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L, American College of Gastroenterology	328	First and Senior Author
5	Am J Gastroenterol 2008;103:753-63	Consensus Recommendations for Gastric Emptying Scintigraphy: A Joint Report of the American Neurogastroenterology and Motility Society (ANMS) and the Society of Nuclear Medicine (SNM)	Abell TL, Camilleri M, Donohoe K, Hasler WL, Lin HC, Maurer AH, McCallum RW, Nowak T, Nusynowitz ML, Parkman HP, Shreve P, Szarka LA, Snape WJ Jr, Ziessman HA; ANMS and SNM	311	Member of ANMS Expert Committee
6	**N Engl J Med** 2008;358:2344-54	A placebo-controlled trial of prucalopride for severe chronic constipation	Camilleri M, Kerstens R, Rykx A, Vandeplassche L	306	First and Senior Author
7	Eur J Clin Invest 1984;14:420-7	Abnormal intestinal motility in diabetics with the gastroparesis syndrome	Camilleri M, Malagelada J-R	266	First Author

8	Am J Physiol 1985;249:G580-5	Relation between antral motility and gastric emptying of solids and liquids in humans	Camilleri M, Malagelada J-R, Brown ML, Becker G, Zinsmeister AR	244	First Author
9	Neurogastroenterol Motil 2005;17:687-96	A randomized controlled trial of a probiotic combination VSL #3 and placebo in irritable bowel syndrome with bloating	Kim HJ, Roque MIV, Camilleri M, Stephens D, Burton DD, Baxter K, Thomforde G, Zinsmeister AR	242	Senior Author
10	Clin Gastroenterol Hepatol 2005;3:543-52	Prevalence and socioeconomic impact of upper gastrointestinal disorders in the United States: results of the US Upper Gastrointestinal Study	Camilleri M, Dubois D, Coulie B, Jones M, Kahrilas PJ, Rentz AM, Sonnenberg A, Stanghellini V, Stewart WF, Tack J, Talley NJ, Whitehead W, Revicki DA	240	First Author
11	Gastroenterology 2013;144:903-11.e3	A controlled trial of gluten-free diet in patients with irritable bowel syndrome-diarrhea: effects on bowel frequency and intestinal function	Vazquez-Roque MI, Camilleri M, Smyrk T, Murray JA, Marietta E, O'Neill J, Carlson P, Lamsam J, Janzow D, Eckert D, Burton D, Zinsmeister AR	233	Senior Author
12	Arch Intern Med 2001;161:1733-40	A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome	Camilleri M, Chey WY, Mayer EA, Northcutt AR, Heath A, Dukes GE, McSorley D, Mangel AM	210	First Author
13	Am J Physiol Gastrointest Liver Physiol 2012;303:G775-85	Irritable bowel syndrome: methods, mechanisms, and pathophysiology. The confluence of increased permeability, inflammation, and pain in irritable bowel syndrome	Camilleri M, Lasch K, Zhou W	189	First and Senior Author
14	**N Engl J Med** 2012;367:1626-35	Peripheral mechanisms in irritable bowel syndrome	Camilleri M	173	Sole Author
15	Gastroenterology 2007;133:761-8	Effect of 5 days linaclotide on transit and bowel function in females with constipation-predominant irritable bowel syndrome	Andresen V, Camilleri M, Busciglio I, Grudell A, Burton D, McKinzie S, Foxx-Orenstein A, Kurtz CB, Sharma V, Johnston JM, Currie MG, Zinsmeister AR	169	Senior Author
16	Gastroenterology 2004;127:1685-94	Contributions of gastric volumes and gastric emptying to meal size and post-meal symptoms in functional dyspepsia	Delgado-Aros S, Camilleri M, Cremonini F, Ferber I, Stephens D, Burton DD	167	Senior Author
17	**N Engl J Med** 2007;356:820-9	Diabetic gastroparesis	Camilleri M	166	Sole Author
18	Am J Physiol Gastrointest Liver Physiol	Effect of GLP-1 on gastric volume, emptying, maximum volume ingested,	Delgado-Aros S, Kim DY, Burton DD, Thomforde GM,	146	Senior Author

	2002;282:G424-31	and postprandial symptoms in humans	Stephens D, Brinkmann BH, Vella A, Camilleri M		
19	Clin Gastroenterol Hepatol 2008;6:772-81	Prospective study of motor, sensory, psychologic, and autonomic functions in patients with irritable bowel syndrome	Camilleri M, McKinzie S, Busciglio I, Low PA, Sweetser S, Burton D, Baxter K, Ryks M, Zinsmeister AR	145	First and Senior Author
20	**N Engl J Med** 1993;329:1073-8	Motor dysfunction of the small bowel and colon in patients with the carcinoid syndrome and diarrhea	von der Ohe MR, Camilleri M, Kvols LK, Thomforde GM	126	Senior Author

Selected papers have been grouped according to specific content in 9 areas of academic endeavor:

1. Identification of role of antral hypomotility and impaired gastric accommodation in gastroparesis and functional dyspepsia, and development of diagnostic and therapeutic strategies,
2. Identification of individual differences in quantitative studies of gastrointestinal functions, behavioral and psychological traits in overweight and obesity to propose individualizing or personalizing therapy directed at specific traits
3. Peripheral mechanisms involved in irritable bowel syndrome
4. Identifying the role of bile acids in the clinical phenotype and pathophysiology in patients with IBS- D and increased fecal bile acid excretion as well as laboratory diagnosis and international guidelines for management of bile acid diarrhea
5. Studies to identify potential genetic and expression mechanisms in patients with IBS-D and increased fecal bile acid excretion
6. The leaky gut or increased intestinal permeability
7. Using validated measurements of colonic transit to correctly predict by single center pharmacodynamics studies whether experimental medications in development for use in humans would prove efficacious or not in phase IIB and III clinical trials
8. Personalized Therapy: Pharmacogenetics and Actionable Biomarkers in Gastroenterology
9. Understanding the mechanism of carcinoid diarrhea

The following section will review the selected original publications, describing the significance by summarizing Historical background that frames the scientific problem, Central Findings, Influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology, and Specific role in the described work. Although there is some overlap, these areas represent ongoing efforts that have spanned 3-4 decades of clinical and translational research in my research career.

1. Identification of role of antral hypomotility and impaired gastric accommodation in gastroparesis and functional dyspepsia, and development of diagnostic and therapeutic strategies, as exemplified by

Camilleri M, Brown ML, Malagelada JR. Relationship between impaired gastric emptying and abnormal gastrointestinal motility. Gastroenterology 91:94 99,1986

Mearin F, Camilleri M, Malagelada J R: Pyloric dysfunction in diabetics with recurrent nausea and vomiting. Gastroenterology 90:1919 1925, 1986

Bouras EP, Delgado-Aros S, Camilleri M, et al. SPECT imaging of the stomach: comparison with barostat and effects of sex, age, body mass index, and fundoplication. Gut 51:781-786, 2002;

Bredenoord AJ, Chial HJ, Camilleri M, et al. Gastric accommodation and emptying in evaluation of patients with upper gastrointestinal symptoms. Clinical Gastroenterology and Hepatology 1:264-272, 2003

Camilleri M. Diabetic gastroparesis. N Engl J Med 356:820-829, 2007;

Camilleri M, et al. Gastroparesis. Nature Rev Dis Primers 1;4(1):41, 2018;;

Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L. Clinical Guideline: Management of gastroparesis. Am J Gastroenterol 108:18-37,2013;

Camilleri M, McCallum RW, Tack J, Spence SC, Gottesdiener K, Fiedorek FT. Efficacy and Safety of Relamorelin in Diabetics With Symptoms of Gastroparesis: A Randomized, Placebo-Controlled Study. Gastroenterology. 2017;153:1240-1250;

Park S-Y, Acosta A, Camilleri M, et al. Gastric motor dysfunction in patients with functional gastroduodenal symptoms. Am J Gastroenterol 112:1689-1699, 2017

Vijayvargiya P, Jameie-Oskooei S, Camilleri M, Chedid V, Erwin PJ, Murad MH. Association between delayed gastric emptying and upper gastrointestinal symptoms: a systematic review and meta-analysis. Gut. 2019;68:804-813;

Vijayvargiya P, Camilleri M, Chedid V, Mandawat A, Erwin PJ, Murad MH. Effects of Promotility Agents on Gastric Emptying and Symptoms: A Systematic Review and Meta-analysis. Gastroenterology. 2019;156:1650-1660.

Historical background that frames the scientific problem: The pathophysiology of symptoms and diagnostic modalities in patients with upper gastrointestinal symptoms such as nausea, postprandial fullness, bloating and pain/discomfort, as well as the rarer chronic vomiting are unclear and the subject of unmet clinical need.
Central finding(s): Studies over three decades demonstrated the role of antral hypomotility and pylorospasm in gastroparesis and identified the role of impaired gastric accommodation in patients with upper gastrointestinal symptoms. From a report on 1287 patients, it is clear that delayed gastric emptying and/or impaired gastric accommodation are present in ~70% of patients when they can be tested with validated noninvasive methods developed by the PI. These constitute opportunities for correction of the pathophysiology by pharmacodynamics approaches and assessment of the effects on patient reported outcomes. Recent work using systematic reviews and meta-analyses documented the relationship between delayed gastric emptying and symptoms, and correlation of responses to therapy for delayed gastric emptying. Proof of concept studies are ushering the introduction of novel approaches targeting serotonergic 5-HT_4, dopaminergic $D_{2/3}$, cannabinoid CB_2, and secretin receptors.
Influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology: These findings are being pursued in further studies in which specific pathophysiological mechanisms, such as accelerated gastric emptying and reduced satiety, are targeted by specific treatments to increase the effectiveness of obesity pharmacotherapy.
Specific role in the described work: Principal investigator (as research fellow in 1985-7; as staff PI in all subsequent work) involved in conceptual development, development and validation (including performance characteristics of gastric emptying and accommodation tests), studies of large patient cohorts, proof of concept through clinical trials, lead investigator in multicenter clinical trials such as with Relamorelin, lead author in consensus guidelines, and single author of New England Journal of Medicine review.

2. Identification of individual differences in quantitative studies of gastrointestinal functions, behavioural and psychological traits in overweight and obesity to propose individualizing or personalizing therapy directed at specific traits, as exemplified by:

Delgado-Aros S, Camilleri M, Cremonini F, et al. Contributions of gastric volumes and gastric emptying to meal size and post-meal symptoms in functional dyspepsia. Gastroenterology 2004; 127:1685-1694

Camilleri M. Integrated upper gastrointestinal response to food intake.Gastroenterology. 2006;131:640-658

Vazquez Roque MI, Camilleri M, Stephens DA, et al: Gastric sensorimotor functions and hormone profile in normal weight, overweight and obese people. Gastroenterology 131:1717-1724, 2006

Acosta A, Camilleri M, Shin A, et al. Quantitative gastrointestinal and psychological traits associated with obesity and response to weight-loss therapy. Gastroenterology 2015;148:537-546, e4

Halawi H, Khemani D, Eckert D, O'Neill J, Kadouh H, Grothe K, Clark MM, Burton DD, Vella A, Acosta A, Zinsmeister AR, Camilleri M. Effects of liraglutide on weight, satiation, and gastric functions in obesity: a randomised, placebo-controlled pilot trial. Lancet Gastroenterol Hepatol. 2017;2:890-899

Historical background that frames the scientific problem: The predictors of clinically relevant weight loss with obesity pharmacotherapy are unclear. As a result, pharmacotherapy for obesity is still a “hit-or-miss” affair. There was no consideration of the traits that contributed to obesity and the potential to individualize obesity therapy based on the gastrointestinal, behavioral and psychological traits.
Central finding(s): From a study of over 500 people of normal weight, overweight or obesity, principal component analysis identified latent dimensions that accounted for approximately 81% of the variation among overweight and obese subjects, including satiety or satiation (21%), gastric motility (14%), psychological factors (13%), and gastric sensorimotor factors (11%). In a study addressing the concept that the traits were “actionable” by specific targeting with medication, the weight loss in response to the combination of phentermine and topiramate was associated with calorie intake at a prior ad libitum buffet meal. A subsequent study showed that the degree of weight loss with the GLP-1 analog liraglutide after 5 and 16 weeks of treatment is positively correlated with the degree of prolongation of gastric emptying.

Influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology: These findings are being pursued in further studies in which specific pathophysiological mechanisms, such as accelerated gastric emptying and reduced satiety, are targeted by specific treatments to increase the effectiveness of obesity pharmacotherapy.
Specific role in the described work: Principal Investigator involved in conceptual development, development and validation (including performance characteristics of satiation, satiety, gastric emptying and accommodation tests) of studies of large patient cohorts, proof of concept through clinical trials.

3. **Peripheral mechanisms involved in irritable bowel syndrome**: Based on the novel insights from prospective studies of individual mechanisms of colonic transit, sensation, permeability, mucosal expression in hundreds of patients, these peripheral mechanisms were summarized and placed in perspective relative to central dysfunction, ushering a renaissance in IBS including understanding the role of female sex as a biological variable in UIBS, as published in *New England Journal of Medicine* and other reviews:

Camilleri M. Peripheral mechanisms in irritable bowel syndrome. N Engl J Med 2012;367:1626-1635

Camilleri M, Carlson P, Acosta A, Busciglio I. Colonic mucosal gene expression and genotype in irritable bowel syndrome patients with normal or elevated fecal bile acid excretion. Am J Physiol 2015;309:G10-20; Camilleri M, Oduyebo I, Halawi H. Chemical and molecular factors in irritable bowel syndrome: current knowledge, challenges, and unanswered questions. Am J Physiol. 2016;311(5):G777-G784

Camilleri M. Sex as a biological variable in irritable bowel syndrome. Neurogastroenterol Motil. 2020 Jan 13:e13802. doi: 10.1111/nmo.13802. [Epub ahead of print]

In addition, the role of colonic transit, permeability, and neurotransmitter mechanisms were demonstrated by single center, prospective original studies, or by leading (first or senior author) multicenter randomized controlled trials as in:

Camilleri M, McKinzie S, Busciglio I, Low PA, Sweetser S, Burton D, Baxter K, Ryks M, Zinsmeister AR. Prospective study of motor, sensory, psychologic, and autonomic functions in patients with irritable bowel syndrome. Clin Gastroenterol Hepatol. 2008;6: 772-81;

Rao AS, Camilleri M, Eckert DJ, Busciglio I, Burton DD, Ryks M, Wong BS, Lamsam J, Singh R, Zinsmeister AR. Urine sugars for in vivo gut permeability: validation and comparisons in irritable bowel syndrome-diarrhea and controls. Am J Physiol Gastrointest Liver Physiol. 2011;301: G919-28;

Camilleri M, Northcutt AR, Kong S, Dukes GE, McSorley D, Mangel AW. Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomised, placebo-controlled trial. Lancet. 2000;355:1035-40;

Camilleri M, Chey WY, Mayer EA, Northcutt AR, Heath A, Dukes GE, McSorley D, Mangel AM. A randomized controlled clinical trial of the serotonin type 3 receptor antagonist alosetron in women with diarrhea-predominant irritable bowel syndrome. Arch Intern Med. 2001;161: 1733-40.

Camilleri M, Kerstens R, Rykx A, Vandeplassche L. A placebo-controlled trial of prucalopride for severe chronic constipation. N Engl J Med. 2008;358: 2344-54;

Nakajima A, Seki M, Taniguchi S, Ohta A, Gillberg PG, Mattsson JP, Camilleri M. Safety and efficacy of elobixibat for chronic constipation: results from a randomised, double-blind, placebo-controlled, phase 3 trial and an open-label, single-arm, phase 3 trial. Lancet Gastroenterol Hepatol. 2018;3:537-547.

Historical background that frames the scientific problem: The prevailing dogmas against which this work was performed were that (a.) IBS was a constellation of symptoms whose diagnosis was based on symptoms without proven objective markers or diagnostic tests, and (b.) the prevailing problem was brain dysfunction leading to the symptoms.
Central finding(s): 33% of patients with IBS have abnormal colonic transit [48% of IBS-diarrhea (IBS-D) and 20% of IBS-constipation (IBS-C)]; 25% of patients with functional constipation or IBS-C have a rectal evacuation disorder; 25-40% of patients with functional diarrhea or IBS-D have diarrhea due to bile acids.
Influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology: These findings led to the development and application of diagnostic tests and specific therapy directed at the disorder of peripheral function (transit, bile acid diarrhea) in patients with functional gastrointestinal disorders that constitute 15% of the patient population seen in gastroenterology practice.
Specific role in the described work: Principal Investigator involved in conceptual development, development and validation (including performance characteristics of diagnostic tests that have since become clinical tests), studies of large patient cohorts, proof of concept through clinical trials.

4. Identifying the role of bile acids in the clinical phenotype and pathophysiology in patients with IBS- D and increased fecal bile acid excretion as well as laboratory diagnosis and international guidelines for management of bile acid diarrhea:

Wong BS, Camilleri M, et al. Increased bile acid biosynthesis is associated with irritable bowel syndrome with diarrhea. Clin Gastroenterol Hepatol 2012;10:1009-15, e3

Shin A, Camilleri M, et al. Bowel functions, fecal unconjugated primary and secondary bile acids, and colonic transit in patients with irritable bowel syndrome. Clin Gastroenterol Hepatol 2013;11: 1270-75

Camilleri M, et al. Effect of increased bile acid synthesis or fecal excretion in irritable bowel syndrome-diarrhea. Am J Gastroenterol 2014;109: 1621-30;

Valentin N, Camilleri M, et al. Biomarkers for bile acid diarrhea in lower functional gastrointestinal disorders with diarrhea: a systematic review and meta-analysis. Gut 2016; 65:1951-1959;

Vijayvargiya P, Camilleri M, Burton D, Busciglio I, Lueke A, Donato LJ. Bile and fat excretion are biomarkers of clinically significant diarrhoea and constipation in irritable bowel syndrome. Aliment Pharmacol Ther. 2019;49: 744-758;

Vijayvargiya P, Camilleri M, Chedid V, Carlson P, Busciglio I, Burton D, Donato LJ. Analysis of Fecal Primary Bile Acids Detects Increased Stool Weight and Colonic Transit in Patients With Chronic Functional Diarrhea. Clin Gastroenterol Hepatol. 2019;17: 922-929;

Vijayvargiya P, Camilleri M. Current Practice in the Diagnosis of Bile Acid Diarrhea. Gastroenterology. 2019;156:1233-1238;

Sadowski DC, Camilleri M, Chey WD, Leontiadis GI, Marshall JK, Shaffer EA, Tse F, Walters JRF. Canadian Association of Gastroenterology Clinical Practice Guideline on the Management of Bile Acid Diarrhea. Clin Gastroenterol Hepatol. 2020;18: 24-41

Historical background that frames the scientific problem: The prevalence of bile acid diarrhea in patients with IBS-D as well as the clinical manifestations and physiological disturbances in colonic transit and permeability, fecal bile acids and hepatic bile acid synthesis in this disorder are unclear. As a result, the standard of care in the United States was a trial of cholestyramine without definitive diagnosis, and without clear mechanistic endpoints.

Central finding(s): A systematic review and meta-analysis showed that ~28% of patients with IBS-D have evidence of bile acid malabsorption or increased hepatic bile acid synthesis. From a prospective study of 64 patients, IBS-D patients with fecal BA >2.34 mM per 48 h had significantly greater body mass index, fecal fat, percent chenodeoxycholic acid (CDCA) in feces, and intestinal permeability, and increased colonic transit. Those IBS-D patients with increased hepatic bile acid synthesis (serum 7α C4 >47.1 ng/ml) had increased total fecal BA excretion, borderline increased colonic permeability, and association with genes involved in feedback regulation of bile acid synthesis (*KLB* and *FGFR4*).

Influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology: Fecal bile acid excretion and serum C4 measurement were established as diagnostic tests for bile acid diarrhea and are now offered as clinical or research tests. Identifying bile acid diarrhea and specifically treating it has changed the paradigm for management of patients with IBS-D.

Specific role in the described work: Principal Investigator involved in conceptual development, development and validation (including performance characteristics of transit, and bile acid tests), proof of concept through clinical trials.

5. **Studies to identify potential genetic and expression mechanisms in patients with IBS-D and increased fecal bile acid excretion** as exemplified by

Camilleri M, Klee EW, Shin A, Carlson P, Li Y, Grover M, Zinsmeister AR. Irritable bowel syndrome-diarrhea: characterization of genotype by exome sequencing, and phenotypes of bile acid synthesis and colonic transit. Am J Physiol 2014;306:G13-26

Camilleri M, Carlson P, Acosta A, Busciglio I, Nair AA, Gibbons SJ, Farrugia G, Klee EW. RNA sequencing shows transcriptomic changes in rectosigmoid mucosa in patients with irritable bowel syndrome-diarrhea: a pilot case-control study. Am J Physiol 2014;306: G1089-98

Camilleri M, Shin A, Busciglio I, Carlson P, Acosta A, Bharucha AE, Burton D, Lamsam J, Lueke A, Donato LJ, Zinsmeister AR. Genetic variation in GPBAR1 predisposes to quantitative changes in colonic transit and bile acid excretion. Am J Physiol 2014;307: G508-16

Camilleri M, Carlson P, Acosta A, Busciglio I. Colonic mucosal gene expression and genotype in irritable bowel syndrome patients with normal or elevated fecal bile acid excretion. Am J Physiol 2015;309:G10-20;

Camilleri M, Carlson P, Valentin N, Acosta A, O'Neill J, Eckert D, Dyer R, Na J, Klee EW, Murray JA. Pilot study of small bowel mucosal gene expression in patients with irritable bowel syndrome with diarrhea. Am J Physiol 2016;311:G365-76

Historical background that frames the scientific problem: The genetic mechanisms and mucosal expression in association with bile acid diarrhea in patients with IBS-D are unclear.

Central finding(s): *GPBAR1* is associated with colonic transit; mucosal ion transport mRNA (for several genes [*GUCA2B, PDZD3*] and PDZD3 protein) are upregulated and barrier protein mRNA (*RBP-2, FN-1*) down-regulated in IBS-D compared with healthy controls. Exome DNA sequencing identified additional variants in *KLB* and *FGFR4* associated with bile acids or colonic transit in IBS-D.

Influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology: These findings provide the rationale for the application to renew DK92179 and have opened a new line of investigation to decipher the basic mechanism responsible for IBS-D. The data also reinforce the concept that peripheral mechanisms are key factors in the pathophysiology of IBS-D.

Specific role in the described work: Principal Investigator involved in conceptual development, conduct of the studies, work with bioinformatics and statistical geneticists to decipher potential mechanisms in IBS-D; studies partly supported by NIH RO1-DK92179.

6. The leaky gut or increased intestinal permeability

The role of increased intestinal permeability is identified in patients with inflammatory bowel disease, gut allergies, and also in patients with IBS-diarrhea. The contributions of this research program have focused on the latter, IBS-D, gluten intolerance without celiac disease, and environmental enteropathy in stunted children in tropical countries in Africa and South America, as exemplified by:

Rao AS, Camilleri M, Eckert DJ, Busciglio I, Burton DD, Ryks M, Wong BS, Lamsam J, Singh R, Zinsmeister AR. Urine sugars for in vivo gut permeability: validation and comparisons in irritable bowel syndrome-diarrhea and controls. Am J Physiol 301:G919-G928, 2011

Camilleri M, Lasch K, Zhou W. Irritable bowel syndrome: methods, mechanisms, and pathophysiology. The confluence of increased permeability, inflammation, and pain in irritable bowel syndrome. Am J Physiol 303:G775-G785, 2012

Vazquez-Roque MI, Camilleri M, Smyrk T, Murray JA, O'Neill J, Carlson P, Lamsam J, Eckert D, Burton D, Ryks M, Rhoten D, Zinsmeister AR. Association of HLA-DQ gene with bowel transit, barrier function and inflammation in irritable bowel syndrome with diarrhea. Am J Physiol 303:G1262-G1269, 2012

Camilleri M, Madsen K, Spiller R, Van Meerveld BG, Verne GN. Intestinal barrier function in health and gastrointestinal disease. Neurogastroenterol Motil 24:503-512, 2012

Vazquez-Roque MI, Camilleri M, Smyrk T, Murray J, Marietta E, O'Neill J, Carlson P, Lamsam J, Janzow D, Eckert D, Burton D, Zinsmeister AR. A controlled trial of gluten-free diet in irritable bowel syndrome-diarrhea: effect on bowel frequency and intestinal functions. Gastroenterology 144:903-911, e3, 2013

Acosta A, Camilleri M, Shin A, Linker Nord S, O'Neill J, Gray AV, Lueke AJ, Donato LJ, Burton DD, Szarka LA, Zinsmeister AR, Golden PL, Fodor A. Effects of rifaximin on transit, permeability, fecal microbiome, and organic acid excretion in irritable bowel syndrome. Clin Transl Gastroenterol 7:e173, 2016

Faubion WA, Camilleri M, Murray JA, Kelly P, Amadi B, Kosek MN, Enders F, Larson J, Boe G, Dyer R, Singh R. Improving the detection of environmental enteric dysfunction: a lactulose, rhamnose assay of intestinal permeability in children aged under 5 years exposed to poor sanitation and hygiene. BMJ Glob Health 1:e000066, 2016

However, there have also been claims that altered gut permeability may be playing a role in diverse diseases including neurodegenerative diseases, eosinophilic esophagitis, as well as nutritional supplements. These required in depth analysis of the published literature as well as the development of more rigorous tests (including optimization of the times of urine collection) to measure intestinal permeability in humans in vivo.

Camilleri M, Lyle BJ, Madsen KL, Sonnenburg J, Verbeke K, Wu GD. Role for diet in normal gut barrier function: developing guidance within the framework of food-labeling regulations. Am J Physiol Gastrointest Liver Physiol. 2019;317: G17-G39;

Camilleri M. Leaky gut: mechanisms, measurement and clinical implications in humans. Gut. 2019;68:1516-26

Katzka DA, Geno DM, Blair HE, Lamsam JL, Alexander JA, Camilleri M. Small intestinal permeability in patients with eosinophilic oesophagitis during active phase and remission. Gut 64:538-543, 2015

Camilleri M, Nadeau A, Lamsam J, Linker-Nord S, Ryks M, Burton D, Sweetser S, Zinsmeister AR, Singh R. Understanding measurements of intestinal permeability in healthy humans with urine lactulose and mannitol excretion. Neurogastroenterol Motil 22:e15-26, 2010

Grover M, Camilleri M, Hines J, Burton D, Ryks M, Wadhwa A, Sundt W, Dyer R, Singh RJ. ^{13}C mannitol as a novel biomarker for measurement of intestinal permeability. Neurogastroenterol Motil 28:1114-1119, 2016

Historical background that frames the scientific problem: Many disease states or complications are attributed to "leaky gut" but it is unclear whether this can be specifically reversed except in conditions associated with severe intestinal inflammation or immune activation, such as Crohn's disease or celiac disease.

Central finding(s): Measurements of probe molecules ingested orally and excreted in urine should focus on 0-2h for small intestinal permeability and 8-24h for colonic permeability. In patients with IBS-D without celiac disease, gluten free diet is associated with lower small intestinal permeability than gluten containing diet and this is associated with reduced diarrhea. The measurement of mucosal permeability in vitro may not reflect barrier function measured *in vivo*, because of the lack of mechanisms that impact barrier function in vivo that are not replicated in *in vitro* studies of the biopsied mucosa e.g. loss of surface mucus, unstirred water layer and submucosal neural control of permeability.

Influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology: These studies have led to new standards that the FDA will require for claims of benefits on barrier function by nutrients; similarly, new methods are being validated for optimizing in vivo measurements of intestinal barrier function.

Specific role in the described work: Principal Investigator involved in conceptual development, studies of patient cohorts to demonstrate the pathophysiology of IBS-diarrhea, and the effect of gluten withdrawal in non-celiac patients with IBS-D. In addition, I was the leader of FDA- and ILSI-commissioned appraisal of the methodology and development of improved measurements and generating normal data, which is ongoing research work.

7. Using validated measurements of colonic transit to correctly predict by single center pharmacodynamics studies whether experimental medications in development for use in humans would prove efficacious or not in phase IIB and III clinical trials as summarized in

Camilleri M. Review Article: Biomarkers and personalized therapy in lower functional gastrointestinal disorders. Aliment Pharmacol Ther 2015;42:818-828).

In addition, these pharmacodynamics studies provided the rationale for discussing novel pharmacological agents for functional gastrointestinal disorders:

Camilleri M. Toward an effective peripheral visceral analgesic: responding to the national opioid crisis. Am J Physiol Gastrointest Liver Physiol. 2018;314: G637-G646.

Camilleri M. What's in the pipeline for lower functional gastrointestinal disorders in the next 5 years? Am J Physiol Gastrointest Liver Physiol. 2019;317: G640-G650

Historical background that frames the scientific problem: The prevailing approach to prove efficacy of experimental medications started with demonstration of activity and dose-response in experimental animals, demonstrating safety and approximate dose-response based on extrapolations from animal studies and toxicity in phase I human studies. There was no valid biomarker that correctly identified the optimal dose to be tested in phase IIB and III trials; this led to many failed drug development programs and high costs from failed drug development programs, as well as inappropriate potentially dangerous exposure of humans to ineffective therapies.

Central finding(s): Scintigraphic colonic transit measurement (noninvasive imaging method) developed for clinical diagnostic purposes provided measurements/endpoints that correctly demonstrated whether the experimental therapy would prove efficacious in phase IIB and III trials.

Influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology: These findings led to the eventual proof of efficacy and approval for marketing of several drugs used in functional GI disorders including alosetron, tegaserod, prucalopride, lubiprostone, and linaclotide. It also contributed to "no go" decisions on other medications for the same indications such as pexacerafont, solabegron, and talnetant.

Specific role in the described work: Principal Investigator involved in conceptual development of method and studies of patient cohorts to demonstrate the effects of experimental medications, chiefly on colonic transit.

8. Personalized Therapy: Pharmacogenetics and Actionable Biomarkers in Gastroenterology

Educational articles have introduced clinicians to the relevance of pharmacogenetics:

Camilleri M. Pharmacogenomics and functional gastrointestinal disorders. Pharmacogenomics. 2005 ;6: 491-501

Camilleri M. The role of pharmacogenetics in nonmalignant gastrointestinal diseases. Nat Rev Gastroenterol Hepatol. 2012;9: 173-84

Halawi H, Camilleri M. Pharmacogenetics and the treatment of functional gastrointestinal disorders. Pharmacogenomics. 2017;18:1085-1094.

Camilleri M. Implications of Pharmacogenomics to the Management of IBS. Clin Gastroenterol Hepatol. 2019;17:584-594

Multiple single center randomized controlled trials have explored the effect of genetic polymorphisms in target receptors or mechanisms of diverse pharmacological agents: serotonergic, cannabinoid, bile acid receptors.

Camilleri M, Atanasova E, Carlson PJ, Ahmad U, Kim HJ, Viramontes BE, McKinzie S, Urrutia R. Serotonin-transporter polymorphism pharmacogenetics in diarrhea-predominant irritable bowel syndrome. Gastroenterology. 2002 Aug;123(2):425-32.

Camilleri M, Busciglio I, Carlson P, McKinzie S, Burton D, Baxter K, Ryks M, Zinsmeister AR. Pharmacogenetics of low dose clonidine in irritable bowel syndrome. Neurogastroenterol Motil. 2009;21:399-410

Rao AS, Wong BS, Camilleri M, Odunsi-Shiyanbade ST, McKinzie S, Ryks M, Burton D, Carlson P, Lamsam J, Singh R, Zinsmeister AR. Chenodeoxycholate in females with irritable bowel syndrome-constipation: a pharmacodynamic and pharmacogenetic analysis. Gastroenterology. 2010 Nov;139(5):1549-58

Wong BS, Camilleri M, Busciglio I, Carlson P, Szarka LA, Burton D, Zinsmeister AR. Pharmacogenetic trial of a cannabinoid agonist shows reduced fasting colonic motility in patients with non-constipated irritable bowel syndrome. Gastroenterology. 2011;141:1638-47

Wong BS, Camilleri M, Carlson PJ, Odunsi-Shiyanbade S, McKinzie S, Busciglio I, Burton D, Zinsmeister AR. Pharmacogenetics of the effects of colesevelam on colonic transit in irritable bowel syndrome with diarrhea. Dig Dis Sci. 2012;57: 1222-6.

Wong BS, Camilleri M, Eckert D, Carlson P, Ryks M, Burton D, Zinsmeister AR. Randomized pharmacodynamic and pharmacogenetic trial of dronabinol effects on colon transit in irritable bowel syndrome-diarrhea. Neurogastroenterol Motil. 2012;24: 358-e169.

In addition, there is increased attention to the importance of specifically diagnosing the mechanism of disease, with validated biomarkers and targeting treatment to the underling mechanism rather than focusing on symptom or symptom complexes. This is summarized in:

Camilleri M. Review Article: Biomarkers and personalized therapy in lower functional gastrointestinal disorders. Aliment Pharmacol Ther 42:818-828, 2015

Historical background that frames the scientific problem: The role of genetic mechanisms in modifying effects of pharmacological agents in functional gastrointestinal disorders is generally not considered.
Central finding(s): The most important observation among the medications studied is the impressive effect of a polymorphism in *5-HTTLPR*, the gene controlling the re-uptake (and inactivation) of serotonin, modifies the effect of the 5-HT_3 antagonist, alosetron, on colonic transit in patients with IBS-diarrhea. This results in a different interaction between the amount of ligand (serotonin) and the serotonergic receptors.
Influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology: These findings provide the rationale for modifying the medication selected (that is use of an laternative), or the dose of the medication alosetron if there is a known, relevant genetic polymorphism. Similar observations have been observed in the use of the non-selective cannabinoid (CB) agonist dronabinol and genetic variation in the CB1 receptor gene and the gene for the enzyme that degrades endogenous cannabinoids, such as fatty acid amide hydrolase (FAAH).
Specific role in the described work: Principal Investigator involved in conceptual development, conduct of the studies, work with statisticians to understand inter-individual differences in responses to medications in IBS.

9. Understanding the mechanism of carcinoid diarrhea (*von der Ohe M, Camilleri M, Kvols LK, Thomforde GM. Motor dysfunction of the small bowel and colon in patients with the carcinoid syndrome and diarrhea. N Engl J Med 1993;329:1073-1078*) **and pharmacological as well as hepatic embolization for control of diarrhea** as exemplified by

Maton PN, Camilleri M, Griffin G, Allison DJ, Hodgson HJ, Chadwick VS. Role of hepatic arterial embolisation in the carcinoid syndrome. Br Med J (Clin Res Ed).1983; 287(6397):932-5;

von der Ohe MR, Camilleri M, Kvols LK. A 5HT$_3$ antagonist corrects the postprandial colonic hypertonic response in carcinoid diarrhea. Gastroenterology. 1994;106: 1184-9;

Saslow SB, Scolapio JS, Camilleri M, Forstrom LA, Thomforde GM, Burton DD, Rubin J, Pitot HC, Zinsmeister AR. Medium-term effects of a new 5HT3 antagonist, alosetron, in patients with carcinoid diarrhoea. Gut.1998;42: 628-34

Historical background that frames the scientific problem: The prevailing theory was that carcinoid diarrhea was an intestinal secretory disorder for which the main therapy was cancer chemotherapy or non-specific inhibition of secretion with opioid agonists or somatostatin analogs.

Central finding(s): Patients with carcinoid diarrhea had extremely rapid colonic transit, colonic hypertonicity and hypercontractility postprandially, and these pathophysiological mechanisms could be extensively inhibited by administration of 5-HT$_3$ antagonists. While at Hammersmith Hospital, London, UK, multi-disciplinary was developed including hepatic arterial embolization as well as pharmacological agents to reduce the mass of carcinoid tumor and the levels of serotonin produced that cause the carcinoid diarrhea.

Influence of the finding(s) on the progress of science or the application of those finding(s) to health or technology: These findings led to the use of 5-HT$_3$ antagonists for relief of diarrhea in patients with carcinoid tumors.

Specific role in the described work: Principal Investigator involved in conceptual development, studies of patient cohorts to demonstrate the pathophysiology of colonic dysmotility and proof of concept that 5-HT$_3$ antagonist reverses the disorders of motor function.