Personalized management in functional gastrointestinal disorders based on genomics: hope at last or just feigned praise?

Xiao Jing (Iris) Wang and Michael Camilleri (iD)

Background

With the arrival of technology that has facilitated deoxyribonucleic acid (DNA) testing, there is an increasing push from both physicians and patients to practice precision medicine with the goal of maximizing therapeutic benefits and minimizing adverse events. The recently published Rome Foundation Working Team Report cites pharmacogenomic testing as a potential tool for optimizing neuromodulator use as primary or augmentation therapy.[1] The interest in precision medicine has also been increasing in medical[2–4] as well as lay media questioning its true utility.[5] In light of this interest, we seek to provide a review of the role of pharmacogenomics in the treatment of functional gastrointestinal (GI) diseases.

Precision medicine is based on identification of a patient's specific disease subtype, pathogenetic mechanism or pharmacokinetics, and utilizes targeted therapy to treat the disease without damage to healthy organs or tissue. Examples of this have been achieved in various cancers such as human epidermal growth factor receptor 2 (HER2)-positive breast cancers or Philadelphia chromosome positive leukemias. In these diseases, the medications, Herceptin® and imatinib, respectively, are targeted directly to the aberrant mechanism causing the disease, with minimal adverse consequences to normal tissue.

Despite this success, the application of precision medicine has not been widely implemented outside of the oncology sphere due to several challenges. In order to deliver precise therapy, there has to first be an identifiable target that is the root cause of the disease, and then therapy can be preferentially directed at that target. A second corollary is that the genetics-based intervention has to be consequential and cost effective. Both of these preconditions need to be met for genomics-based personalized management to take root in the practice of gastroenterology, particularly for functional GI diseases (FGID).

Pharmacogenomics evaluates genetic variation and how changes in the genetic code can lead to changes in drug effects *via* alterations in metabolism or by changes in therapeutic targets. The variability of the genetic code comes largely in the form of polymorphisms, defined as one or more variants of a particular DNA sequence, most commonly at a single base pair, termed a single nucleotide polymorphism. These can lead to disease, changes in drug response, or other changes in phenotypes. Larger polymorphisms can involve insertions or deletions of longer stretches of DNA, which can cause significant damage if the encoded protein is abnormal in structure, truncated, or not produced entirely. The clearest application of pharmacogenomics in FGID therapeutics relates to the central neuromodulators. Taking a leaf from the widespread application of cytochrome p450 (CYP) testing in psychiatry, gastroenterologists are testing CYP2D6, 2C19 and 3A4 in patients being considered for such agents.

Drug metabolism

Once administered, pharmacologic agents undergo several phases of metabolism to change their therapeutic activity and eventually facilitate excretion. Phase I metabolism generally increases hydrosolubility of molecules *via* enzymatic reactions. The CYP enzymes are responsible for about 75% of these reactions and catalyze oxidative reactions including hydroxylation, epoxidation, dealkylation, deamination, and dehalogenation.[6]

Correspondence to:
Michael Camilleri

Clinical Enteric Neuroscience Translational and Epidemiological Research (CENTER), Division of Gastroenterology, Mayo Clinic, Charlton Building, Room 8-110, 200 First St SW, Rochester, MN 55905, USA
camilleri.michael@mayo.edu

Xiao Jing (Iris) Wang, M.D.

Division of Gastroenterology, Mayo Clinic, Rochester, MN, USA

Polymorphisms in CYP enzymes can alter the functions of these enzymes, leading to different rates of drug metabolism and subsequent differences in drug tolerance among individuals, changing both therapeutic and toxicity thresholds. 'Ultrarapid metabolizers' have no drug response at normal doses (nonresponders); 'extensive metabolizers' have expected response to standard doses (normal); 'intermediate metabolizers' have slight increased response and increased toxicity to standard doses; 'poor metabolizers' have slow, to no, drug metabolism, leading to high drug levels at standard doses and higher risk for drug toxicity.

Notably, if the medication administered is in the form of a prodrug which requires metabolism for activation, then the impact of polymorphisms is opposite that of above. Ultrarapid metabolizers will have increased drug levels given increased levels of activation whereas poor metabolizers will have low to no levels of active drug.[7] It is estimated in population studies that ultrarapid and poor metabolizers each constitute 8% of the population.[8] As these subgroups have the greatest risk of aberrant drug behavior, it follows that pharmacogenomics are likely to be clinically relevant in less than 20% of the population. Generally, intermediate metabolizers may require dose adjustment if optimal response is not achieved with the recommended dose, but one does not expect negative clinical consequences.

Several of the CYP enzymes responsible for phase I metabolism are important in drug metabolism in FGIDs.

CYP2D6 and the central neuromodulators

The CYP2D6 enzyme has more than 100 genetic variations, with both functional and non-functional alleles. CYP2D6 is responsible for metabolism of antidepressants including tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), both of which are frequently used for management of pain modulation in treatment of FGIDs.[9] The number of functional CYP2D6 genes has been shown to be correlated with the metabolism of nortriptyline, a TCA.[1] How this translates to therapeutic response in FGID treatment needs to be studied further, but suggests that choice of therapy for improvement of pain control in these patients could be tailored to maximize drug efficacy depending on an individual patient's pharmacogenomics.

CYP2C19 and proton-pump inhibitors and H_2 receptor antagonists

For the treatment of functional dyspepsia, current guidelines recommend a trial of acid suppression,[10] and both proton-pump inhibitors (PPIs) and H_2 receptor antagonists have been shown as superior to placebo.[11] The majority of PPIs, as well as cimetidine, are inactivated by the CYP2C19 enzymes, and polymorphisms of CYP2C19 lead to variable efficacy of this class of medication. In this case, poor metabolizer variants lead to decreased degradation rates and increased drug levels. The frequency of this genetic variation varies by ethnicity and is higher in Asian populations (15–20% of Japanese) compared with Whites (2–6%). Patients with functional dyspepsia who are homozygous for this variant, CYP2C19, have been shown having dyspepsia resolution with shorter mean durations of treatment.[12] This has also been supported with lower failure rates with on-demand pantoprazole therapy after esophagitis treatment for patients who are poor metabolizers.[13] Conversely, patients who are ultrarapid metabolizers have poor response to the majority of PPIs and to trial with the PPI, rabeprazole, which is metabolized through the CYP3A4 enzymes, and may produce a more robust therapeutic response.

CYP3A4

In addition to metabolism of rabeprazole, CYP3A4 is responsible for the metabolism of a vast array of drugs, including immunosuppressants, chemotherapeutics, and antifungal and antimicrobial agents. Included in this extensive list are the prokinetic agents, cisapride [a 5-hydroxytriptamine $(HT)_4$ receptor agonist] and erythromycin (a motilin agonist), both of which are used rarely off label in the treatment of gastroparesis and functional dyspepsia. Polymorphisms leading to poor metabolizer states, as well as inhibitors of CYP3A4, can cause increased drug levels. When used together with CYP3A4 inhibitors, these drugs have been associated with *torsade de pointes* and cardiac arrhythmias.[7] Lists of CYP3A4 inducers and inhibitors are provided elsewhere.[7]

CYP3A4 is responsible for metabolism of the short-acting benzodiazepine, alprazolam, and, in

conjunction with other CYP enzymes, it also metabolizes alosetron, a $5HT_3$ receptor antagonist used in the treatment of diarrhea-predominant inflammatory bowel disease. Coadministration of these medications, which may be clinically indicated in this patient group, may lead to competitive inhibition of the enzyme and increased drug levels of one or both medications. Whereas, an open-label, randomized, crossover study in healthy volunteers did not show change in pharmacokinetics of alprazolam with coadministration of alosetron;[14] this has not been tested in patients with FGID or in patients who are CYP3A4 poor metabolizers, in whom the drug effects may be augmented.

Targeting biomarkers of gastrointestinal diseases

Within gastroenterology, clinicians attempting precision medicine have pursued multiple avenues, including development of enhanced imaging techniques and biomarkers to guide endoscopic biopsies,[15] isolation of gene abnormalities in fatty liver disease to develop targeted treatment,[16] and employment of pharmacogenomics to optimize drug selection and dosage.

Thiopurines in inflammatory bowel diseases: pharmacogenetics or pharmacokinetics?

Perhaps the most common application of pharmacogenomics in the practice of gastroenterology is the testing of the thiopurine S-methyltransferase (TMPT) gene prior to utilization of thiopurines such as azathioprine for immunosuppression in inflammatory bowel disease or autoimmune hepatitis. In Western populations, the main pathway in thiopurine metabolism is based on TPMT, but other pathways of metabolism have been shown in recent studies to also impact the therapeutic and toxicity index of the thiopurines. In Asian populations, nudix hydrolase or *NUDT15* gene variants have been shown to impact thiopurine toxicity,[17] and inosine triphosphate pyrophosphohydrolase [*ITPA]* gene impacts drug efficacy.[18] ITPA gene variants have also been shown to correlate positively with azathioprine response in Spanish and South American populations. Deficiencies have been associated with nonmyelosuppression adverse effects, such as nausea, pancreatitis, and skin rashes.[19]

With conventional thiopurine doses, homozygous *TPMT*-deficient patients (~1 in 178 to 1 in 3736 individuals with two nonfunctional *TPMT* alleles) experience severe myelosuppression; on the other hand, 30–60% of individuals who are heterozygotes (~3–14% of the population) show moderate toxicity, and homozygous wildtype individuals (~86–97% of the population) show lower active thioguanine nucleotides (and therefore potentially lower efficacy) and less myelosuppression.[20] However, given that normal red blood cell TPMT levels did not prevent the development of leukopenia in patients treated with thiopurines,[21] it is still controversial whether genetic testing or enzyme measurements are preferable for predicting efficacy or toxicity of thiopurines in inflammatory bowel disease.[22] Based on the costs of phenotype (drug level pharmacokinetics) testing and genotype testing over a decade ago, it was estimated that the former were more cost effective and had a greater likelihood of pre-empting leukopenia.[23] In fact, one could argue that a hematology check is indicated after the first month of treatment with a thiopurine anyway, and the risk of severe myelotoxicity is estimated at 1 in 176 to 1 in 3736. Therefore, a case could be made for forgoing genetic testing and only estimating red cell drug levels to optimize treatment dosage if the patient is not achieving optimal response based on standard dosing.

Pathways, targets and treatments in FGID

There are, as yet, no established 'druggable' mechanisms or pathways in FGID. While the majority of FGID is multifactorial, there are a few examples where genetic polymorphisms of certain receptor or protein targets have been implicated in the alteration of disease surrogates or biomarkers, such as GI transit. The prime example to date is SERT, a serotonin-transporter protein.

SERT is a sodium-dependent serotonin transporter central to fine tuning of 5HT neurotransmission in the brain, but is also a key regulator of endogenous and exogenous serotonin effects on the GI tract. SERT is located on the presynaptic neuron and acts to reuptake and clear 5HT from the synaptic cleft, limiting serotonergic activation of the postsynaptic $5HT_3$ and $5HT_4$ receptors.

The promoter region of the SERT coding sequence (SERT-P) contains a polymorphic

region with a long and short variant. The long variant, *5-HTTLPR*LL,* allows normal promoter-mediated transcription and production of the transporter protein. One copy of the short variant allele (*5-HTTLPR*LS*) is enough to cause decreased SERT transcription[24] and, subsequently, to cause increased serotonin activation of the postsynaptic neuron, which then leads to accelerated colonic transit.[25]

The pharmacogenomic implication of this genetic variation was demonstrated in the responsiveness of patients with irritable bowel syndrome (IBS) to the $5HT_3$ antagonist, alosetron, used in the treatment of diarrhea-predominant IBS (IBS-D), as well as to the $5HT_4$ agonist, tegaserod, used in the treatment of constipation-predominant IBS (IBS-C). In patients with *5-HTTLPR*LL*, there is a relatively decreased amount of residual serotonin in the synaptic cleft due to optimal synthesis of SERT and reuptake into the presynaptic neuron. As expected, studies have shown enhanced colon transit in response to alosetron (increased efficacy of $5HT_3$ receptor antagonism),[26] and decreased patient response to tegaserod in comparison to those with the LS variant.[27] Thus, depending on the allelic make up of *5-HTTLPR*, there are different levels of transcription of the SERT protein, and patients with IBS may require targeted adjustments of their medication dose to optimize therapeutic effect.

Clinical implementation of pharmacogenomics in gastroenterology

Implementation of pharmacogenetics has been most widely available in oncology where gene testing for oncogenic aberrancies allows for targeting of chemotherapy. *TMPT* testing in gastroenterology is widely available and utilized to guide the dosage of azathioprine. Currently, there are approximately 1236 US Food and Drug Administration (FDA)-approved drugs whose targets have known functional genetic variants that may influence drug dosing, efficacy, and toxicity. Pharmacogenomic testing is commercially available for all of the CYP enzymes discussed above. However, while there was general agreement in the genotyping results across different companies conducting the tests, there were differences in the predicted phenotype from those test results and, therefore, recommendations issued from such tests are currently not standardized and testing from distinct companies should not

be used interchangeably.[28] Studies of the FDA-approved medications estimate that approximately 7% of the 1236 FDA-approved drugs and 18% of prescriptions in the United States may be affected by genes for which pharmacogenomic testing is available.[29] While the clinical impact of these variants requires further evaluation, the prevalence of these genetic variants and our experience with variable responses to medication therapy suggest great potential for improved efficacy by matching the medication dose to the type of enzyme metabolism in the individual patient.

In FGIDs, while studies suggest that genetic polymorphisms in immunomodulatory and neuromodulatory proteins contribute to the pathogenesis of the disease,[30] the presence of these polymorphisms has not been associated with a difference in treatment response. For example, in functional dyspepsia, homozygosity for a G-protein beta-3 (GNB3) subunit gene polymorphism (825C) was shown to be associated with unexplained upper GI symptoms.[31] However, while homozygosity of this polymorphism in patients with nonsteroidal anti-inflammatory drug (NSAID)-induced GI complaints was associated with higher baseline symptom load compared with heterozygous patients, the presence of the polymorphism did not predict therapeutic response to treatment with PPIs.[32] Similarly, neither the presence of GNB3 835C nor 5HTTLPR influenced the response to therapy in functional dyspepsia patients treated with tricyclic or SSRI antidepressants.[33] In deciding whether to use these central modulators such as tricyclic or SSRI antidepressants, which are also often used for pain control in IBS, physicians in psychiatry have benefited from pharmacogenomic testing to maximize benefit and minimize toxicity. However, studies using pharmacogenomic profile testing to guide the selection of dosing of these medications for GI disorders are lacking.[1]

These data suggest that, while there is a large potential for the use of pharmacogenomics in the treatment of FGIDs, the practical application of these data to a therapeutic plan still requires further study.

Conclusion

The ideal goal of precision medicine is to provide individualized treatment to each patient, with optimized therapeutic effect and minimum

adverse effects. Pharmacogenomics is a subset of precision medicine that studies genetic variations in metabolism enzymes or drug targets and their impact on drug efficacy and toxicity. The clinical utility of pharmacogenomics in FGID faces similar challenges to that of precision medicine as a whole. The pathophysiology of FGID is likely a complex interaction of genetic and environmental influences, making it difficult to identify a clear target for diagnosis or treatment. Currently, the application of pharmacogenomics in FGID centers around genetic variations of the CYP450 system and several other genes influential in the development of specific FGID and are candidates for further pharmacogenomic analysis. Pharmacogenomic testing is now commercially available, and the prevalence of genetic variants related to drug action suggests a potential for significant clinical utility, but this will require further study. At this stage, we cannot conclusively determine whether the field fosters hope associated with the considerable hype, or is just deserving of feigned praise.

Conflict of interest statement
The authors declare that there is no conflict of interest.

ORCID iD
Michael Camilleri (iD) https://orcid.org/0000-0001-6472-7514

References
1. Drossman DA, Tack J, Ford AC, *et al*. Neuromodulators for functional gastrointestinal disorders (disorders of gut-brain interaction): a Rome foundation working team report. *Gastroenterology* 2018; 154: 1140–1171.e1141.

2. Ramaswami R, Bayer R and Galea S. Precision medicine from a public health perspective. *Annu Rev Public Health* 2018; 39: 153–168.

3. Chowkwanyun M, Bayer R and Galea S. "Precision" public health - between novelty and hype. *N Engl J Med* 2018; 379: 1398–1400.

4. Khoury MJ and Galea S. Will precision medicine improve population health? *JAMA* 2016; 316: 1357–1358.

5. Szabo L. Are we being misled about precision medicine? *The New York Times* 2018, https://www.nytimes.com/2018/09/11/opinion/cancer-genetic-testing-precision-medicine.html (last accessed 27 December 2018).

6. Mittal BT, Tulsyan S, Kumar S, *et al*. Cytochrome P450 in cancer susceptibility and treatment *Adv Clin Chem* 2015; 71:77–139.

7. Camilleri M. Implications of pharmacogenomics to the management of IBS. *Clin Gastroenterol Hepatol* 2018. [Epub ahead of print].

8. Bielinski SJ, Olson JE, Pathak J, *et al*. Preemptive genotyping for personalized medicine: design of the right drug, right dose, right time-using genomic data to individualize treatment protocol. *Mayo Clin Proc* 2014; 89: 25–33.

9. Dalen P, Dahl ML, Bernal Ruiz ML, *et al*. 10-Hydroxylation of nortriptyline in white persons with 0, 1, 2, 3, and 13 functional CYP2D6 genes. *Clin Pharmacol Ther* 1998; 63: 444–452.

10. Talley NJ, Goodsall T and Potter M. Functional dyspepsia. *Aust Prescr* 2017; 40: 209–213.

11. Zala AV, Walker MM and Talley NJ. Emerging drugs for functional dyspepsia. *Expert Opin Emerg Drugs* 2015; 20: 221–233.

12. Kim M and Kong E. Genetic polymorphisms of cytochrome P450 2C19 in functional dyspeptic patients treated with cimetidine. *Korean J Physiol Pharmacol* 2012; 16: 339–342.

13. Sheu BS, Cheng HC, Yeh YC, *et al*. CYP2C19 genotypes determine the efficacy of on-demand therapy of pantoprazole for reflux esophagitis as Los-Angeles grades C and D. *J Gastroenterol Hepatol* 2012; 27: 104–109.

14. D'Souza DL, Levasseur LM, Nezamis J, *et al*. Effect of alosetron on the pharmacokinetics of alprazolam. *J Clin Pharmacol* 2001; 41: 452–454.

15. Sturm MB and Wang TD. Endoscopic imaging techniques: beyond narrow band. *Am J Gastroenterol* 2018; 113: 1103–1107.

16. Wang JZ, Cao HX, Chen JN, *et al*. PNPLA3 rs738409 underlies treatment response in nonalcoholic fatty liver disease. *World J Clin Cases* 2018; 6: 167–175.

17. Wang HH, He Y, Wang HX, *et al*. Comparison of TPMT and NUDT15 polymorphisms in Chinese patients with inflammatory bowel disease. *World J Gastroenterol* 2018; 24: 941–948.

18. Tsuchiya A, Aomori T, Sakamoto M, *et al*. Effect of genetic polymorphisms of azathioprine-metabolizing enzymes on response to rheumatoid arthritis treatment. *Pharmazie* 2017; 72: 22–28.

19. Zabala-Fernandez W, Barreiro-de Acosta M, Echarri A, *et al*. A pharmacogenetics study of TPMT and ITPA genes detects a relationship with side effects and clinical response in patients with inflammatory bowel disease receiving azathioprine. *J Gastrointestin Liver Dis* 2011; 20: 247–253.

20. Relling MV, Gardner EE, Sandborn WJ, *et al*. Clinical pharmacogenetics implementation consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing. *Clin Pharmacol Ther* 2011; 89: 387–391.

21. Chisick L, Oleschuk C and Bernstein CN. The utility of thiopurine methyltransferase enzyme testing in inflammatory bowel disease. *Can J Gastroenterol* 2013; 27: 39–43.

22. Winter JW, Gaffney D, Shapiro D, *et al*. Assessment of thiopurine methyltransferase enzyme activity is superior to genotype in predicting myelosuppression following azathioprine therapy in patients with inflammatory bowel disease. *Aliment Pharmacol Therap* 2007; 25: 1069–1077.

23. Priest VL, Begg EJ, Gardiner SJ, *et al*. Pharmacoeconomic analyses of azathioprine, methotrexate and prospective pharmacogenetic testing for the management of inflammatory bowel disease. *Pharmacoeconomics* 2006; 24: 767–781.

24. Lesch KP, Bengel D, Heils A, *et al*. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science* 1996; 274: 1527–1531.

25. Camilleri M. The role of pharmacogenetics in nonmalignant gastrointestinal diseases. *Nat Rev Gastroenterol Hepatol* 2012; 9: 173–184.

26. Camilleri M, Atanasova E, Carlson PJ, *et al*. Serotonin-transporter polymorphism pharmacogenetics in diarrhea-predominant irritable bowel syndrome. *Gastroenterology* 2002; 123: 425–432.

27. Li Y, Nie Y, Xie J, *et al*. The association of serotonin transporter genetic polymorphisms and irritable bowel syndrome and its influence on tegaserod treatment in Chinese patients. *Dig Dis Sci* 2007; 52: 2942–2949.

28. Bousman CA and Dunlop BW. Genotype, phenotype, and medication recommendation agreement among commercial pharmacogenetic-based decision support tools. *Pharmacogenomics J* 2018; 18: 613–622.

29. Rautio J, Kumpulainen H, Heimbach T, *et al*. Prodrugs: design and clinical applications. *Nat Rev Drug Discov* 2008; 7: 255–270.

30. Adam B, Liebregts T and Holtmann G. Mechanisms of disease: genetics of functional gastrointestinal disorders–searching the genes that matter. *Nat Clin Pract Gastroenterol Hepatol* 2007; 4: 102–110.

31. Holtmann G, Siffert W, Haag S, *et al*. G-protein beta 3 subunit 825 CC genotype is associated with unexplained (functional) dyspepsia. *Gastroenterology* 2004; 126: 971–979.

32. Holtmann G, van Rensburg C, Schwan T, *et al*. Improvement of non-steroidal anti-inflammatory drug-induced gastrointestinal symptoms during proton pump inhibitor treatment: are G-protein beta3 subunit genotype, Helicobacter pylori status, and environmental factors response modifiers? *Digestion* 2011; 84: 289–298.

33. Saito YA, Locke GR, Almazar AE, *et al*. Polymorphisms of 5-HTT LPR and GNbeta3 825C>T and response to antidepressant treatment in functional dyspepsia: a study from the functional dyspepsia treatment trial. *Am J Gastroenterol* 2017; 112: 903–909.