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The role of pharmacogenetics in nonmalignant gastrointestinal diseases

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Abstract

Genetic variation influences the absorption and efflux of drugs in the intestine, the metabolism of drugs in the liver and the effects of these drugs on their target proteins. Indeed, variations in genes whose products have a role in the pathophysiology of nonmalignant gastrointestinal diseases, such as IBD, have been shown to affect the response of patients to therapy. This Review provides an overview of pharmacogenetics in the management of nonmalignant gastrointestinal diseases on the basis of data from clinical trials. Genetic variants that have the greatest effect on the management of patients with IBD involve the metabolism of thiopurines. Variation in drug metabolism by cytochrome P450 enzymes also requires attention so as to avoid drug interactions in patients receiving tricyclic antidepressants and PPIs. Few genotyping tests are currently used in the clinical management of patients with nonmalignant gastrointestinal diseases, owing to a lack of data from clinical trials showing their effectiveness in predicting nonresponse or adverse outcomes. However, pharmacogenetics could have a beneficial role in enabling pharmacotherapy for nonmalignant gastrointestinal diseases to be targeted to the individual patient.

Introduction

Pharmacokinetics refers to the study of the relationship between drug dose and drug concentration in plasma or tissue (often as a function of time). Pharmacokinetic variation among individuals reflects differences in drug absorption, distribution, metabolism and excretion—factors that modulate the availability of the drug or metabolite at therapeutic targets. Pharmacodynamics involves the study of the relationship between drug concentrations and drug effects, which can be measured through clinical end points or biomarkers. One type of biomarker that will be described in this article is colonic transit measured by scintigraphy.¹

Pharmacogenetics is the study of the contribution of variants in one or several genes to the response of patients to drugs. A fundamental concept in pharmacogenetics is that a particular drug response is influenced by a limited number of genes whose products include drug-metabolizing enzymes, receptors and transporters; the altered functions of these gene products contribute to the pathophysiology of disease.² By contrast, genome-wide studies explore outcomes of drug treatment based on the entire genome, and this discipline is termed pharmacogenomics.^{3,4}

Competing interests

The author declares no competing interests.

The proposed and anticipated benefit of pharmacogenetics is that it will lead to improved, 'personalized' care for individuals and so will maximize therapeutic responses while minimizing adverse effects and toxicity. For single-gene testing to be useful, variation in the response to a drug must largely reflect functional differences between the products of a gene that exist in a limited number of versions (known as alleles). Generally, each person has inherited two identical or dissimilar alleles; the functional activity of the gene product reflects the presence of two, one or no functional alleles (Box 1).²

Box 1

Principles of genetic variation

Genetic variants that affect <1% of the general population are referred to as mutations. In pharmacogenetics, the genetic variants are usually present in >1% of the population, and are called polymorphisms. Many genetic variants do not change the amino acid translated in the synthesized protein (called synonymous) or do not affect protein quantity, structure or function when compared with the original protein (nonfunctional). Polymorphisms are functional when they alter protein quantity or function, potentially resulting in therapeutic failure or unwanted drug adverse effects. In candidate genes, the genetic variants could plausibly explain a given phenotype, such as severity of disease or a response to drug (termed pharmacokinetics and pharmacodynamics, respectively).⁴

Principles of genetic variation

Variations in genes (and their encoded proteins) can alter the outcomes of drug-based therapy through two broad mechanisms. First, variations in germline genes affect drug processing and/or metabolism as these genes encode transporters, receptors or enzymes in the metabolic pathway of a drug. Second, variations in the germ-line or somatic genes that regulate metabolic pathways involved in the pathophysiology of gastrointestinal diseases also affect drug efficacy. These genetic variations might result from insertions or deletions, gene rearrangements, splice variants or copy number variants, or, more commonly, from substitutions of one or multiple nucleotides in the DNA (Box 1). Variations in somatic genes are germane to malignant diseases, rather than non-malignant gastrointestinal diseases, which constitute the focus of this Review.

Variants can also affect the protein-coding region of a gene, which leads to changes in the primary amino acid sequence and protein function, potentially affecting either the pharmacokinetics or pharmacodynamics of the drug. Variants in noncoding regions, which regulate the amount of mRNA transcribed and, thus, the amount of protein synthesized, might also have a considerable effect on drug function. The effect and clinical relevance of such metabolic alterations are greater when there is a narrow therapeutic index or a small difference between the amount of a drug required for an effective dose and that of a toxic dose, or when a single pathway is primarily involved in the elimination of the drug. Polymorphisms in the genes encoding drug-metabolizing enzymes can either modify functional groups (phase I reactions) or conjugate with endogenous substituents (phase II reactions).⁵

Variations in protein-coding or noncoding regions of DNA can alter the regulation of gene expression, transcription of receptors, transporters or drug targets and so affect the pharmacodynamics of the drug. Such variants tend to be disease or drug specific and control drug–target responsiveness to fixed drug concentrations.^{6,7} This Review addresses the role of pharmacogenetics in nonmalignant diseases of the gastrointestinal tract, excluding liver disease. The effect of pharmacogenetics is often appraised on the basis of data from clinical

trials. In the field of neurogastroenterology (such as motility disorders and IBS), however, little data from clinical trials exist, and therefore, pharmacogenetic effects on pharmacodynamic end points are described here. Some of these pharmacodynamic end points are based on biomarkers, such as colonic transit by scintigraphy, which are considered to be highly predictive of clinical response.¹ For each example, the criteria developed by Naranjo *et al.*⁸ and modified by Gardiner and Begg⁹ have been used to assess the evidence to support implementation of pharmacogenetic testing in a clinical setting (Box 2 and Box 3).

Box 2

Algorithm for association of altered drug effects and genetic variation

Scoring: 2 points for strong effect and/or evidence, 1 point for weak effect and/or evidence, 0 for no effect and/or evidence

- The net change in concentrations of major active moieties is marked
- All active moieties have been considered
- Genotype accurately predicts desired effects
- A clear concentration–effect relationship for desired effect is present
- Genotype accurately predicts adverse effects
- A clear concentration–effect relationship for serious adverse effects is observed
- The drug has a low therapeutic index
- Autophenocopying occurs (2 for strong evidence/effect, 1 for weak, 0 for none)
- Pharmacoeconomic analysis is supportive
- Prospective studies demonstrate benefits of genotyping

Usefulness of prospective genotyping: range 0–18

Definite: 14–18; probable: 9–13; possible: 4–8; unlikely: 0–3

Permission obtained from Gardiner, S. J. & Begg, E. J. Pharmacogenetics, drug-metabolizing enzymes, and clinical practice. *Pharmacol. Rev.* 58, 521–590 (2006).

Box 3

Assessing clinical implementation of pharmacogenetics

- Does genotype accurately predict adverse effect and/or nonresponse in patients?
- Does genotyping offer clear advantages over phenotyping?
- Does the drug have a narrow ‘therapeutic window’?
- Is there an equivalent alternative drug available?
- Is the adverse effect or consequence of nonresponse serious?
- Does the adverse effect/nonresponse occur at an ‘appreciable’ frequency?
- Is the pharmacoeconomics analysis supportive (that is, cost of testing is less than not testing)?

- Do prospective studies which demonstrate benefits of genotyping exist?

Drug absorption

P-glycoprotein

P-glycoprotein is encoded by the *ABCB1* gene (more commonly called the *MDR1* gene). P-glycoprotein is an ATP-dependent pump involved in drug transport through biological membranes and is expressed at several sites (including the lower gastrointestinal tract and blood–brain barrier). P-glycoprotein acts as an efflux pump that prevents the accumulation of several, potentially toxic, xenobiotics, such as bacterial toxins, plant-derived antibiotics from the environment or administered drugs. Therefore, this pump stops these drugs from reaching compartments and cells that express P-glycoprotein, such as enterocytes, hepatocytes, renal proximal tubular cells and capillary endothelial cells. P-glycoprotein in the intestinal mucosal epithelium reduces the bioavailability of drugs used for gastrointestinal diseases, including ciclosporin and corticosteroids. Conversely, administration of ciclosporin (which is a P-glycoprotein inhibitor) increases absorption of several drugs, including statins, from the gastrointestinal tract and so increases their intestinal availability.¹⁰

The clinical significance of P-glycoprotein in non-malignant gastrointestinal diseases has been demonstrated.¹¹ *ABCB1* gene expression in peripheral blood lymphocytes and intestinal epithelial cells was associated with a poor response to corticosteroids in inflammatory diseases of the large intestine.¹¹ Furthermore, over-expression of *ABCB1* mRNA in peripheral blood mono-nuclear cells in patients with IBD seems to be induced by high doses of corticosteroids;¹² overexpression of *ABCB1* might then impair the efficacy of steroids in these patients.¹³

Single nucleotide polymorphisms (SNPs) in the *ABCB1* gene (*ABCB1*2677G>T/A and *ABCB1*3435C>T) were associated with a reduced response to azathioprine in 327 Spanish patients with Crohn's disease.¹⁴ Although the *ABCB1*2677TT genotype was associated with a good short-term remission rate in patients with steroid-resistant ulcerative colitis treated with tacrolimus,¹⁵ this genotype was also associated with a higher risk of ciclosporin failure in patients with this disease.¹⁶

Genetic characteristics that are associated with the response of patients to domperidone therapy include polymorphism rs9282564 (*ABCB1*61A>G), which was significantly associated with an effective dose of domperidone ($P = 0.0277$ by univariate analysis) in patients with gastroparesis.¹⁷ Indeed, patients with *ABCB1*61AG and *ABCB1*61AA genotypes required an average dose of 94.6 mg/day and 68.9 mg/day, respectively, for the drug to be effective.¹⁷ Nonsynonymous *ABCB1* variants and haplotypes with an allele frequency 2% transiently expressed in HEK293T cells had a decreased sensitivity to specific substrates, including ciclosporin, than the wild-type gene.¹⁸ Altered efflux and bioavailability of domperidone (if domperidone is handled similarly to ciclosporin) might explain why the *ABCB1*61AG genotype group required a dose 1.5 times greater than the *ABCB1*61AA genotype group.

In summary, P-glycoprotein genotyping is generally not applied in clinical practice because the genotype has not been shown to accurately predict an adverse effect and/or nonresponse to drugs that are affected by genetic variations in *ABCB1*.

Drug metabolism

Phase I metabolism

Cytochrome P450 (CYP) enzymes are responsible for the metabolism of endogenous and exogenous compounds in the human body. Among the 18 identified human CYP families, CYP2 is the most diverse and is associated primarily with phase I metabolism (including oxidation, dehydrogenation and esterification) of a large number of exogenous compounds.¹⁹ Indeed, the CYP2 family includes a variety of drug-metabolizing enzymes encoded by polymorphic genes. Molecular variations in the genes encoding CYP2D6, CYP2C19 and CYP2C9 have the greatest clinical impact.²⁰ Furthermore, when samples from Finnish, Indian, American and diverse African populations were analyzed at four *CYP2C9*, two *CYP2C19*, and 12 *CYP2D6* loci, those variants that conferred altered enzyme activity were found to occur in all geographic regions, reaching extremely high frequencies in certain populations (Figure 1).²¹ A distinct geographic pattern of variation of the genes studied was observed, suggesting that population substructure can strongly affect the variation in pharmacogenetic loci.²¹ The cause of the marked inter-racial variation in CYP drug metabolizer phenotypes is incompletely understood; an intriguing hypothesis is that worldwide differences in diet or xenobiotics in the environment contribute to the development of variation.^{22,23}

CYP2D6—CYP2D6 participates in the hepatic metabolism and elimination of more than 100 drugs.² CYP2D6 metabolism can be classified as ultra-rapid, extensive, intermediate or poor, according to the number of functional alleles (>3–0). Poor metabolizers constitute ~1% among Asian populations and 5–10% among white populations.²⁴ Gene multiplication might result in three or more functional *CYP2D6* alleles, and some ethnic groups have >10 functional alleles.²⁵ Multiple copies of the *CYP2D6* gene are relatively infrequent among Northern Europeans, whereas in East African populations the frequency of multiple copies of the gene can be as high as 29%.^{21,25,26} Functional alleles include *CYP2D6**1, *CYP2D6**2, *CYP2D6**9, *CYP2D6**10 and *CYP2D6**17. The most common nonfunctional alleles are *CYP2D6**3, *CYP2D6**4, *CYP2D6**5 and *CYP2D6**6.²

CYP2D6 metabolism affects tricyclic antidepressants and selective serotonin-reuptake inhibitors, which are extensively used to treat functional gastrointestinal disorders and visceral hypersensitivity.²⁷ CYP2D6 genotyping and phenotyping are not routinely performed in gastroenterological practice, on the assumption that escalating the dosage of drugs on the basis of measured blood levels or inadequacy of clinical response is relatively safe. Nevertheless, given the multitude of drugs metabolized by CYP2D6, as well as the number of drugs that inhibit or activate it, gastroenterologists should be aware of possible drug interactions. No consensus has been reached in the psychiatry literature regarding the routine use of *CYP2D6* testing for prescribing antidepressants.²⁸

Codeine analgesia results from *O*-demethylation of 10% of the administered dose by CYP2D6 to produce morphine.²⁹ Normally, approximately 90% of codeine is inactivated by CYP3A4, either through *N*-demethylation to norcodeine or by undergoing glucuronidation.³⁰ The 10% of white people who are poor metabolizers might not therefore achieve analgesia at standard doses. Although not described in the context of gastrointestinal practice, the presence of multiple functional alleles of *CYP2D6* (in approximately 10% of white people, and potentially more people of East African origin) might lead to ultra-rapid metabolism, resulting in potentially fatal respiratory depression,³⁰ as proposed for the lactation-related death of an infant.^{31,32}

CYP2C19—The *CYP2C19* gene contains several polymorphisms that result in poor metabolism of multiple drugs (such as PPIs), including: *CYP2C19*681G>A on exon 5

(*CYP2C19**2);³³ *CYP2C19*636G>A on exon 4 (*CYP2C19**3);³⁴ *CYP2C19*A>G in the initiation codon (*CYP2C19**4)³⁵ and *CYP2C19*1297C>T on exon 9 (*CYP2C19**5).³⁶

Ethnic differences have been observed with respect to *CYP2C19**2 and *CYP2C19**3 alleles and genotype frequency. The frequency of poor metabolizers (homozygous for variant alleles) is 13–23% in Asian populations and 2–5% in white populations.³⁷ Poor metabolizers have decreased microsomal hydroxylation in the liver and demonstrate area under the curve (AUC) values that are 5–12 times higher than extensive metabolizers.³⁸ Those people who are heterozygous for the variant alleles demonstrate AUC values that are 2–4 times higher than extensive metabolizers (homozygous for nonvariant alleles)—consistent with a gene-dose effect. Enhanced pharmacokinetics translates into better pharmacodynamics, with median 24 h intragastric pH values reflecting the metabolizer status: highest pH (and PPI effect) in poor metabolizers, intermediate in heterozygotes, and lowest in extensive metabolizers.³⁸ Enhanced pharmacodynamics results in improved healing rates of esophagitis. Indeed, the endoscopic cure rate for esophagitis at 8 weeks for poor metabolizers, heterozygotes and extensive metabolizers was 85–100%, 68–95%, and 46–77%, respectively.^{39,40} In patients infected with *Helicobacter pylori*, the wild-type genotype for *CYP2C19* correlates with a poorer response (20% lower cure rate) to combination therapy with a PPI and two antibiotics, as found in two meta-analyses of 12 and 8 studies respectively.^{41,42}

Despite the advent of a commercially available micro-array-based genotyping test for CYP enzymes,⁴³ the low prevalence of *CYP2C19* polymorphisms in white populations makes genotyping of little clinical significance in the treatment of reflux esophagitis or peptic ulceration. Moreover, the practical implication for 1 in 5 Chinese people or patients with variant *CYP2C19* alleles is that standard doses of PPIs might be excessive. For example, in a midwestern US study in patients with reflux esophagitis, variant alleles of *CYP2C19* were associated with significantly lower odds of gastric acid breakthrough during PPI therapy.⁴⁴

The recurrence of GERD symptoms in Japanese *CYP2C19* homozygous extensive PPI metabolizers was substantially greater (38.5%) than heterozygous extensive (10.9%) or poor (5.6%) metabolizers.⁴⁵ In contrast to other PPIs, the metabolism of rabeprazole is less dependent on *CYP2C19*, as it is also metabolized by *CYP3A4* and degraded by nonenzymatic pathways.^{46,47}

The relevance of *CYP2C19* and PPIs in clinical practice has achieved greater importance because PPIs can reduce the antiplatelet activity of clopidogrel (a drug used to avoid the development of thromboses in intracoronary stents). PPIs are used extensively, for conditions such as reflux esophagitis, in patients on long-term clopidogrel treatment. *CYP2C19* inhibition prevents the generation of the active clopidogrel metabolite,⁴⁸ which is required to selectively block ADP-dependent platelet activation and aggregation. The FDA and European Medicines Agency discourage PPI use in patients treated with clopidogrel, based on observational studies that have demonstrated an increased risk of cardiovascular death, hospital readmission for myocardial infarction or acute coronary syndrome and nonfatal stroke.⁴⁹ However, these results were not observed in randomized controlled trials (RCTs).^{50,51} Moreover, the potential deleterious effect of coadministered PPI on outcomes with clopidogrel has also been questioned, because a study in which patients from two RCTs were genotyped showed that clopidogrel had a consistent effect (as compared with placebo), irrespective of *CYP2C19* loss-of-function carrier status.⁵² Conversely, a gain-of-function genetic variation in *CYP2C19* (mainly the *CYP2C19**17 allele) led to increased risk of bleeding, which could be manifested in gastrointestinal hemorrhage.⁵³

Although the controversy surrounding the use of clopidogrel in the field of cardiovascular medicine is not completely resolved,⁵⁴ gastroenterologists should be aware of the recommendations from the regulatory agencies for patients taking clopidogrel. Gastroenterologists and cardiologists should consider prescribing alternative medications, such as rabeprazole (which has less dependence on CYP2C19) or an H₂-receptor antagonist for reflux disease, and gastroenterologists should work with the patient's cardiologist to provide a different platelet inhibitor, such as aspirin, or other ADP antagonists, such as prasugrel (the majority of which is activated by CYP3A4 and CYP2B6), and ticagrelor (the majority of which is biotransformed by CYP3A4 or CYP3A5).⁵⁵

CYP3A4—CYP3A4 is the main CYP enzyme expressed in the liver, but it is also expressed in intestinal enterocytes. An estimated 60% of drugs are cleared by this CYP enzyme.² In adults, the CYP3A4 and CYP3A5 isozymes are the only CYP3A subfamily members expressed in the liver and intestine. The majority of people express CYP3A4,² and its main clinical importance is drug-induced inhibition that results in reduced metabolism of concomitant drugs. The relevance of CYP3A4 to gastroenterology was demonstrated by cardiac arrhythmias experienced by patients receiving the gastroprokinetic agent cisapride in combination with inhibitors of CYP3A4.⁵⁶

Two genetic variants of *CYP3A4* are commonly described: *CYP3A4-V*, located in the promoter region of the nifedipine-specific response element of the gene,⁵⁷ and *CYP3A4*1B* (*CYP3A4A*>G 290 bp upstream of the transcription start site). The *CYP3A4*1B* variant is characterized by increased levels of *CYP3A4* transcription and high levels of drug metabolism;⁵⁸ *CYP3A4*1B* carriers therefore need higher doses of tacrolimus when compared with noncarriers.⁵⁹ Cyclosporin clearance was found to be higher in *CYP3A4*1B* carriers, but the genetic effect was modest (9%);⁶⁰ thus, genotyping is unlikely to be helpful in predicting immunosuppressive dosing, as other unknown factors seem to contribute more substantially to oral bioavailability.

Grapefruit juice acts as an inhibitor of drug metabolism, especially for CYP3A4 substrates in the small intestine. A single glass of grapefruit juice per day might increase bioavailability, potentiate action, and cause adverse effects of drugs, especially for those with a low therapeutic index.^{61,62} Grapefruit juice constituents can also stimulate or inhibit P-glycoprotein activity. Thus, functional interactions exist between CYP3A and P-glycoprotein in the intestinal mucosa.

CYP3A5—*CYP3A5* expression is polymorphic, with substantial population differences. *CYP3A5* is expressed by less than 10% of white populations, whereas it is expressed by the majority of people in other populations.² For African-Americans *CYP3A5* expression might be greater than that of *CYP3A4*,² which reflects alterations in the frequency of the functional *CYP3A5*1* allele. The substrate specificity of CYP3A5 is similar to that of CYP3A4.² *CYP3A5* polymorphism is largely unexplored in gastrointestinal clinical practice, although one investigation found no effect of CYP3A5 on the response of patients with corticosteroid-resistant ulcerative colitis to tacrolimus.¹⁵

Genotyping cytochrome P450—Genotyping of CYP is generally not applied in gastrointestinal clinical practice because of the lack of appreciation of the potential effect of variation in phase I drug metabolism among gastroenterologists. In addition, virtually no clinical trial or prospective study evidence has shown that genotyping predicts adverse effects or non-response when applied to the treatment of nonmalignant gastrointestinal diseases. Equivalent drugs are available if there is no clinical response (such as other analgesics to replace codeine for pain relief, and rabeprazole as a PPI to be used with clopidogrel in patients with coronary stents who experience reflux esophagitis). Finally, in

the case of functional gastrointestinal diseases, such as IBS, the consequence of nonresponse is rarely serious and, therefore, the therapeutic effect of genotyping CYP in patients prescribed psychoactive medications would be minimal.

Phase II metabolism

Among phase II metabolic reactions, which involve conjugation with endogenous substituents, the one relevant to nonmalignant gastrointestinal conditions is thiopurine *S*-methyltransferase (TPMT). During TPMT metabolism, 6-mercaptopurine (6-MP) is converted to 6-thioinosine monophosphate (6-TIMP) by hypoxanthineguanine phosphoribosyltransferase (HGPRT), and 6-TIMP is further metabolized to 6-thioguanine nucleotides (6-TGNs) (Figure 2). Alternative pathways of 6-MP inactivation are catalyzed by xanthine oxidase (to thiouric acid), and by TPMT (to 6-methyl mercaptopurine; 6-MMP). The relative activities of TPMT, xanthine oxidase and HGPRT determine the amount of active 6-TGN relative to other 6-MP metabolites.⁶³ Dose escalation of 6-MP might result in conversion of 6-TIMP to 6-MMP ribonucleotides (6-MMPR) by TPMT;⁶⁴ a high 6-MMPR to 6-TGN ratio is associated with hepatotoxicity.

Xanthine oxidase—The gene encoding xanthine oxidase (also called xanthine dehydrogenase) was originally considered not to be polymorphic,⁶⁵ but it is now appreciated that hepatic xanthine oxidase activity is reduced in 20% of white people (affecting females more than males), 11% of Japanese and 4% of Spanish people.^{66–68} Several studies have identified genetic polymorphisms in the gene encoding xanthine oxidase⁶⁹ and its promoter region that might determine inter-individual differences in expression of this gene.⁷⁰ Xanthine oxidase levels are also reduced by allopurinol and methotrexate, which might increase the bioavailability of 6-MP and so potentially increase the efficacy (and risk of toxicity) of 6-MP.

TPMT—TPMT is polymorphic and is the major heritable factor causing variation in response to azathioprine, which is nonenzymatically converted to 6-MP, and 6-MP itself.² TPMT deficiency explains myelotoxicity associated with thiopurines; however, it is not responsible for other adverse effects of these medications, including pancreatitis and hepatotoxicity.

The variant TPMT alleles (*TPMT**2, *TPMT**3A, *TPMT**3B, *TPMT**3C, *TPMT**3D, *TPMT**4, *TPMT**5, *TPMT**6, *TPMT**7, and *TPMT**10 alleles) result from SNPs.⁷¹ These variant alleles are associated with lower TPMT enzyme activity, preferential metabolism of 6-MP to 6-TGN by HGPRT and a higher potential for myelotoxicity than nonvariant alleles.² The most frequently encountered variant alleles are *TPMT**2, *TPMT**3A, *TPMT**3B and *TPMT**3C. TPMT genotype and enzyme activity are well correlated. Indeed, deficiency can normally be explained by two variant alleles in the genotype; the presence of *TPMT**2, *TPMT**3A, or *TPMT**3C is highly sensitive (95%) and specific (100%) for intermediate activity.⁷² Among white and African-American populations, 89% of people have high TPMT activity (>10 U/ml red blood cells), 11% have intermediate activity (5–10 U/ml), and 0.3% have low activity (<5 U/ml).⁷³ Among Chinese populations, ~3% of people have low or intermediate activity.⁷⁴ Lower TPMT enzyme activity was found in fewer Afro-Caribbeans than in white people and people from South Asia.⁷⁵ Other populations also seem to have a small proportion of people with variants predictive of low TPMT enzyme activity including, for example, 2.6% among Southern Iranians⁷⁶ and Turkish patients,⁷⁷ <1% among Jordanians,⁷⁸ 1.6% in Han Chinese⁷⁹ (with no significant differences among Han, Jing, Yao and Uyghur Chinese⁸⁰) and 6.8% among Mexicans.⁸¹ By contrast, a relatively high prevalence of variants predictive of intermediate TPMT activities were identified in specific ethnic groups in Israel, specifically, the Druze and Ethiopian Jews.⁸²

As the phenotype (as determined by an assay of TPMT activity) and genotype are well correlated, no consensus has been reached with regards to the utility of determining TPMT genotype in patients with IBD on a routine basis. One decision analysis suggested that pretreatment testing for TPMT activity is cost effective.⁸³ By contrast, in another study, the majority of individuals (73%) with Crohn's disease who developed bone marrow suppression were not carriers of variant alleles.⁸⁴ Therefore, TPMT genotyping or phenotyping might not replace the need for blood monitoring for myelosuppression in these patients. Monitoring white blood cell counts regularly (monthly for the first 3 months and then quarterly) might be the most cost-effective strategy. Nevertheless, the FDA and American Gastroenterological Association medical position statement recommend TPMT genotype or phenotype testing prior to the initiation of therapy with azathioprine or 6-MP in patients with IBD, as a Grade B recommendation.⁸⁵

TPMT and TGN levels in blood might help to predict the responsiveness of patients to treatment. The odds of achieving complete remission with azathioprine are ~5 times lower if TPMT levels are >14 U/ml red blood cells when compared with TPMT levels of 10–13.9 U/ml.⁸⁶ High 6-TGN levels are associated with an improved response^{87,88} and reduced disease activity⁸⁹ among pediatric and adult patients with IBD, including those with colonic and fistulizing Crohn's disease;⁷⁵ nonresponders tend to have low 6-TGN levels.⁹⁰

In a prospective study of 207 patients with IBD who were given 2 mg/kg of azathioprine, those whose mean 6-TGN level was >100 pmol per 8×10^8 red blood cells over a period of 6 months were significantly more likely to respond to treatment.⁹¹ In addition, those patients whose baseline TPMT activity was <35 pmol/h/mg/Hb (compared with >35 pmol/h/mg/Hb) were also more likely to respond to treatment with azathioprine (81% and 43%, respectively).

Some centers monitor the serum levels of 6-MMPR in addition to 6-TGN, and use the ratio between 6-TGN and 6-MMPR to predict response. For example, in a study of 51 patients with IBD, 37 patients developed suboptimal 6-TGN and preferential 6-MMPR levels following dose escalation with azathioprine or 6-MP.⁶⁴

TPMT genotyping—Genotyping of *TPMT* is generally not applied in clinical practice, as it does not offer a clear advantage over either phenotyping (specifically measurement of 6-TGN and 6-MMPR levels) to predict patient outcome or simple blood counts to monitor for myelotoxicity.

Gastrointestinal disease

IBD

In 102 patients with IBD who were being treated with methotrexate, four polymorphisms in three genes were analyzed: these polymorphisms were *SLC19A1*80G>A, *GGH452G*>T, *MTHFR*677C>T and *MTHFR*1298A>C.⁸⁴ Patients homozygous for the *MTHFR*1298C alleles (but not *SLC19A1*80G>A or *GGH452G*>T) were more likely to experience myelosuppression than those homozygous for *MTHFR*1298A alleles.^{84,92}

Tumor necrosis factor (TNF) exerts its biological effect through binding two different cell-surface receptors: TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2), which are encoded by *TNFRSF1A* and *TNFRSF1B*, respectively.^{93,94} Variants in the genes encoding TNF⁹⁵ and the TNF receptors⁹⁶ suggest that homozygosity for the polymorphism in exon 6 of *TNFRSF1B* (Arg196Arg) is associated with a poor response to infliximab. However, this finding was not confirmed in a second study.⁹⁷ No clear effect of *TNFRSF1A* and *TNFRSF1B* polymorphisms (*TNFRSF1A*36A>G and *TNFRSF1B*587A>G) was observed in

the response of patients with IBD to infliximab.⁶³ Two further studies found that three SNPs in the *NOD2* gene could not effectively predict the response of patients with IBD to infliximab.^{98,99}

Multiple studies have investigated the effect of different genetic variants on the response of patients with Crohn's disease to infliximab. Indeed, *FCGR3A* encodes the receptor for IgG, which is expressed on macrophages and natural killer cells, therefore regulating the binding of IgG to these cells, and so leads to cell-specific functions such as phagocytosis. In one study, patients with Crohn's disease were treated with infliximab for 3 months; carriers of the *FCGR3A*4985G>T variant had a positive response in measurements of C-reactive protein (a biomarker of inflammation).¹⁰⁰ In the ACCENT I trial,¹⁰¹ the reduction in Crohn's disease activity index in patients with Crohn's disease who carried the *FCGR3A*4985G>T variant was less convincing.

Another gene that has been investigated as a possible predictor of response to infliximab is the *IBD5* gene, which is located on chromosome 5q31. The *IBD5* homozygous mutant genotype was associated with a reduction in the Crohn's disease activity index in patients with Crohn's disease, and a similar trend was identified in patients with ulcerative colitis.¹⁰² Pharmacogenetic studies evaluating the response of patients with Crohn's disease to adalimumab and etanercept have not been reported to date.

In a comprehensive summary of pharmacogenetics studies for all classes of drugs used in patients with IBD, Vermeire *et al.*¹⁰³ noted few studies with consistent findings. Moreover, the authors stated that the observed associations require confirmation in further studies. As mentioned above, *TPMT* testing prior to starting treatment with thiopurines is the only genetic test approved for IBD in clinical practice, but the most common strategy employed is the measurement of 6-TGN levels, rather than *TPMT* genotyping.¹⁰³

IBS

Serotonin—Serotonin (5-hydroxytryptamine; 5-HT) receptor sub-types, 5-HT₁, 5-HT₃, and 5-HT₄ are located in the gut;¹⁰⁴ alterations in 5-HT and its receptors affect gut function. 5-HT in synaptic spaces stimulates these receptors until it is actively cleared by a serotonin transporter protein (called SERT, encoded by *SLC6A4*) that is located on the ends of presynaptic neurons. *SLC6A4* spans 31 kb and consists of 14 exons (Figure 3).^{105,106} The two main *SLC6A4* allelic variants studied are the rs25531 SNP (A/G) and a 44 bp insertion or deletion polymorphism in the promoter region (5HTT-LPR; serotonin transporter protein linked polymorphic region). The insertion or deletion of repeated elements results in a long (L) or a short (S) allele. Compared with *SLC6A4**L, *SLC6A4**S results in lower transcriptional efficiency, decreased SERT expression and, therefore, decreased uptake of serotonin in a lymphoblast cell line.¹⁰⁷ Mechanistically, the *SLC6A4**SS homozygous genotype should result in high levels of serotonin in the synapse (owing to low uptake) with resulting diarrhea. Indeed, mice lacking SERT have accelerated colonic motility.¹⁰⁸

The association of SERT-P polymorphisms (5HTT-LPR or rs25531) with IBS or its subgroups is still controversial, although *SLC6A4**S is associated with increased pain on rectal distension in patients with IBS.¹⁰⁹ In addition, the decreased expression of *SLC6A4* mRNA in the rectal mucosa of patients with IBS (diarrhea-predominant IBS [IBS-D] and constipation-predominant IBS [IBS-C] documented in one paper¹¹⁰ was not replicated in another report.¹¹¹

Alosetron (a 5-HT₃ receptor antagonist) retards colonic transit¹¹² and is effective in treating IBS-D. Conversely, the 5-HT₄ agonist, tegaserod, accelerates colonic transit¹¹³ and was used to treat chronic constipation and IBS-C, until its withdrawal from the market. Although

genetic variants in serotonin receptors (including, 5-HT_{3E} receptor and the related microRNA-510) have been reported in association with IBS-D,¹¹⁴ their relevance to pharmacogenetics has yet to be determined.

A pharmacogenetics study explored whether the 5HTT-LPR polymorphism predicts the response of patients with IBS-D to treatment with alosetron.¹¹⁵ In patients who have the *SLC6A4**LL homozygous genotype, greater slowing of colonic transit was observed, compared with those who have the *SLC6A4**SS genotype. Consistent with this finding, tegaserod was associated with a worse response (overall and bowel function) in *SLC6A4**LL patients.¹¹⁶ These data are consistent with the hypothesis (Figure 4) that the *SLC6A4**LL genotype results in transcription of normal *SLC6A4* and clearance of 5-HT from the synaptic cleft; as less 5-HT is present in the synaptic cleft, less 5-HT needs to be inhibited by alosetron at the 5-HT₃ receptors and less endogenous 5-HT is available to aid tegaserod in its attempt to stimulate the 5-HT₄ receptors.

Bile acids—Variation in the genes encoding klotho β and, perhaps, FGFR4 (*KLB* and *FGFR4*, respectively), both of which are involved in bile acid synthesis, is associated with accelerated colonic transit in patients with IBS-D (Figure 5).¹¹⁷ In addition, variation in the genes that control the synthesis of these two proteins influences the colonic transit response to chenodeoxycholic acid in patients with IBS-C¹¹⁸ and in patients with IBS-D who are treated with the bile acid sequestrant colestevam hydrochloride.¹¹⁹

Motility disorders

Metoclopramide

The antiemetic and gastroprokinetic agent metoclopramide binds to dopamine D1, D2 and D3 receptors, is a substrate for CYP2D6, as well as a competitive inhibitor of the CYP2D6 isoform and is analogous to neuroleptic agents such as haloperidol and chlorpromazine.¹²⁰ In one study, two patients genotyped as CYP2D6 poor metabolizers experienced acute dystonic reactions when receiving metoclopramide.¹²¹ Concomitant use of such antiemetic and gastroprokinetic agents might increase plasma concentrations of either drug, and so predispose patients to the development of tardive dyskinesia. In addition, the *DRD3* Ser9Gly variant leads to a greater binding affinity of dopamine for D3 receptors than do non-variants.¹²² A meta-analysis demonstrated that, in non-Asians, tardive dyskinesia associated with antipsychotic medication is more likely to occur in patients who have the *DRD3* Ser9Gly amino acid change than in patients who do not have this variant;¹²³ however, an association between this SNP and metoclopramide has not yet been reported.

Domperidone

An unexpected association was found between the genetic variant rs3814589 in *KCNH2* and an effective response of patients with symptoms of gastroparesis to the dopaminergic agent, domperidone.¹⁷ The mechanism of interaction between the variant voltage-gated inwardly rectifying potassium channel (which is altered as a result of the *KCNH2* variation) and domperidone requires further elucidation. Such potassium channels might be relevant in the gut, through a potential effect on intestinal motility, or in the heart, where they might predispose individuals to cardiac arrhythmias.

Genotyping in motility disorders—Genotyping is generally not applied in clinical practice because of the lack of clinical trial evidence that it predicts adverse effects or nonresponse, except in the case of tegaserod for patients with IBS-C.¹²⁴ Tegaserod, however, is no longer available in most countries, such as the USA¹²⁵ and Canada, because of the report of adverse cardiovascular events, even though observational,¹²⁶ case-control¹²⁷

and mechanistic¹²⁸ studies do not identify tegaserod as a risk factor for cardiovascular complications.

Recommendations—On the basis of the deliberations of two expert working groups in pharmacogenetics,^{129,130} an editorial¹³¹ was published that included a list of questions that should be considered to qualify a pharmacogenomic test for clinical practice. These considerations include: the relationship between the test result and response to drug therapy; validation of initial results; the frequency of the genomic variant in the patient population of interest; the availability of a clear course of action based on the test result; and the understanding of patient outcomes (both potential benefits and harms) that might result from modification of the drug therapy.

A summary of the discussed nonmalignant gastrointestinal conditions, drugs, genes, polymorphisms and their clinical effects is provided in Table 1. On the basis of these criteria and the responses to the questions posed in the algorithm of Gardiner and Begg⁹ (Box 2 and Box 3), pharmacogenetics testing is not routinely used in the management of nonmalignant gastrointestinal diseases. Such tests and (in the future) genome-wide association studies would probably require assessment of cost utility and efficacy to achieve the reimbursement being implemented in clinical management of nonmalignant gastrointestinal diseases, rather than only demonstrating noninferiority.¹³²

Conclusion

Although pharmacogenetics testing is not recommended for most nonmalignant gastrointestinal diseases, drug treatment of these illnesses could be enhanced and individualized by knowledge of the genetic factors that influence drug absorption, metabolism and the targets (such as proteins, receptors and signaling pathways) of therapy. On the basis of current information, physicians and patients require education on pharmacogenetics; in addition, the CYP genotypes (particularly, *CYP2C19*, *CYP2C9*, *CYP2D6* and *CYP3A4*) should be incorporated into the electronic medical record of every patient to enhance the efficacy and individualization of treatment and to avoid adverse effects from drugs.

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Key points

- Genetic variations can affect drug absorption, efflux, metabolism and the ability of drugs to interact with their target proteins
- Drug interactions might result from concomitant use of medications that alter the function of cytochrome P450 enzymes
- Activity of the platelet function inhibitor, clopidogrel, is affected by medications (including PPIs) that alter CYP2C19 function; the clinical impact of coadministration of clopidogrel and PPIs, however, is unclear
- Thiopurine dosage in patients with IBD is typically monitored with blood counts and, if necessary, 6-thioguanine or other metabolite levels, rather than genotyping the thiopurine methyltransferase gene
- Genotyping is generally not applied in clinical management of nonmalignant gastrointestinal diseases because of the lack of clinical trial evidence that it predicts adverse effects or nonresponse
- In nonmalignant gastrointestinal diseases, pharmacogenetics might facilitate individualized medicine in the future

Review Criteria

The literature search was based on PubMed searches from 1965 onwards, including the terms “diarrhea”, “constipation”, “irritable bowel syndrome”, “functionalgastrointestinal disorder”, “motility”, “metoclopramide”, “domperidone”, “tegaseord”, “alosetron”, “bile acid”, “inflammatory bowel disease”, “Crohn's disease”, “ulcerative colitis”, “thiopurines”, “thiopurine methyl transferase”, “TNF- α ”, “infliximab”, “ethanercept”, “adalimumab”, “reflux esophagitis”, “clopidogrel”, “proton pump inhibitors”, “ethnicity”, “cytochrome P450” “treatment”, “codeine”, “opiate-induced constipation” and “opiate bowel dysfunction”. The search focused predominantly on full-text papers published in the English language. Abstracts were included when critically relevant and when not already available as full-text articles. The reference lists of published articles were reviewed to identify further references of potential interest.

Figure 1. Distribution of *CYP2* altered activity variants in different geographic regions. **a** | *CYP2C9*. **b** | *CYP2C19*. **c** | *CYP2D6*. Permission obtained from Wolters Kluwer Health © Sistonen, J. *et al. Pharmacogenet. Genomics* **19**, 170–179 (2009).

Figure 2.

Overview of thiopurine metabolism. Azathioprine is nonenzymatically converted to 6-MP. Xanthine oxidase catalyzes hepatic first-pass oxidation of 6-MP to 6-thiouric acid (inactive). 6-MP then moves into systemic circulation. 6-TGNs are active metabolites of 6-MP that do not undergo oxidation by xanthine oxidase and are produced by HGPRT. By contrast, TPMT inactivates 6-MP, and produces therapeutically inactive 6-MMP. TPMT competes with HGPRT for 6-MP substrate. The 6-TGNs produced have therapeutic and potentially toxic hematologic effects by integrating into DNA (and interrupting replication), and by inhibiting *de novo* purine synthesis. 6-MMP is further metabolized to the potentially hepatotoxic 6--MMP ribonucleotides by guanosine 5'-monophosphate synthase. Abbreviations: 6-MMP, 6-methylmercaptopurine; 6-MP, 6-mercaptopurine; 6-TGN, 6-thioguanine nucleotides; HGPRT, hypoxanthine guanine phosphoribosyltransferase; TPMT, thiopurine methyl transferase. Permission obtained from Elsevier Inc. © Givens, R. C. & Watkins, P. B. *Gastroenterology* **125**, 240–248 (2003).

Figure 3.

Structure of *SLC6A4*. The coding (pink) exons and noncoding and intronic areas (blue) of *SLC6A4*; note the 5HTT-LPR polymorphism is ~1.4 kb upstream and the intronic VNTR near exon 2. A polymorphism in intron 2 of *SLC6A4* consists of a 17 bp VNTR, termed STin2 VNTR. Abbreviations: 5HTT-LPR, serotonin transporter protein linked polymorphic region; VNTR, variable number of tandem repeats. Permission obtained from Murphy, D. L., Lerner, A., Rudnick, G. & Lesch, K. P. *Mol. Interv.* **4**, 109–123 (2004).

Figure 4.

Hypothetical explanations for the association of alosetron treatment with slow colonic transit in *SLC6A4**LL carriers and diarrhea-predominant IBS, and the worse clinical response to tegaserod in patients who are *SLC6A4**LL carriers with constipation-predominant IBS. The *SLC6A4**LL homozygous carrier status is associated with optimal function of the reuptake transporter protein SERT. Therefore, less 5-HT remains in the synapse that needs to be inhibited by alosetron at the 5-HT₃ receptor, and therefore the same dose of alosetron will be more effective at inhibiting the accelerated colonic transit in diarrhea-predominant IBS. Conversely, with less 5-HT at the synapse, the same dose of tegaserod will be less effective at stimulating the 5-HT₄ receptors, resulting in lower impact of tegaserod on symptoms in constipation-predominant IBS. Abbreviations: 5-HT, 5-hydroxytryptamine; SERT, serotonin transporter protein.

Figure 5.

Genetic variation in proteins involved in bile acid synthesis is associated with colonic transit in patients with IBS. Among the proteins involved in the feedback regulation of bile acid synthesis, genetic variation in *KLB* rs17618244 is associated with colonic transit at 24 h in patients with IBS. In addition, the diarrhea-predominant IBS subgroup exhibited the strongest association of *KLB* rs17618244 with faster colonic transit at 24 h.¹¹⁷ Klotho β is encoded by *KLB* and is one of the two proteins on the hepatocyte membrane which, together with FGFR4, mediate the intracellular signaling of the ileal hormone FGF19 to downregulate cytochrome P450 7A1 (CYP7A1) activity and thereby suppress bile acid synthesis. The *KLB* GG genotype leads to amino acid change Arg728Gln and results in increased degradation of klotho β and defective feedback regulation of bile acid synthesis by FGF19. The data are consistent with the hypothesis that the hepatocyte synthesizes and secretes more bile acid into the biliary and digestive tracts in patients with the *KLB* GG genotype and, hence, the associated acceleration of colonic transit due to the stimulation of colonic secretion and motility by the higher concentration of bile acid reaching the colon. Permission obtained from Elsevier Inc. © from Wong, B. S. *et al. Gastroenterology* **140**, 1934–1942 (2011).

Table 1

Gastrointestinal conditions, drugs, genes and polymorphisms

Condition	Drug	Protein (gene)	Alleles or polymorphisms	Clinical effects
IBD	Azathioprine, 6-MP	Thiopurine-S- methyltransferase (<i>TPMT</i>)	<i>TPMT</i> *2, <i>TPMT</i> *3A, <i>TPMT</i> *3B, <i>TPMT</i> *3C, <i>TPMT</i> *3D, <i>TPMT</i> *4, <i>TPMT</i> *5, <i>TPMT</i> *6, <i>TPMT</i> *7 and <i>TPMT</i> *10	High, intermediate, low metabolizers predict drug dosing needs
	Methotrexate	Methylenetetrahydrofolate reductase (<i>MTHFR</i>)	<i>MTHFR</i> 1298A>C	<i>MTHFR</i> 1298CC patients experience more adverse effects
GERD <i>H. pylori</i> infection	PPIs	Cytochrome P450 2C19 (<i>CYP2C19</i>)	<i>CYP2C19</i> *2, <i>CYP2C19</i> *3, <i>CYP2C19</i> *4, <i>CYP2C19</i> *5	Wild-type predicts slower healing of esophagitis and lower cure rates of <i>H. pylori</i> infection <i>CYP2C19</i> *5 result in decreased metabolism of drug
Diarrhea- predominant IBS	Alosetron	Serotonin transporter (<i>SLC6A4</i>)	5HTT-LPR	Patients with diarrhea and <i>SLC6A4</i> *LL homozygotes may predict better response and slowing of colonic transit
Constipation-predominant IBS	Tegaserod	Serotonin transporter (<i>SLC6A4</i>)	5HTT-LPR	Patients with diarrhea and <i>SLC6A4</i> *LL homozygotes may predict worse clinical response

Abbreviations: 5HTT-LPR, serotonin transporter protein linked polymorphic region; 6-MP, 6-mercaptopurine. Permission obtained from Saito, Y. A. & Camilleri, M. Clinical application of pharmacogenetics in gastrointestinal diseases. *Expert Opin. Pharmacother.* **7**, 1857–1869 (2006).