A Personalized Approach to Managing Inflammatory Bowel Disease

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Abstract: The management of inflammatory bowel disease (IBD) requires a personalized approach to treat what is a heterogeneous group of patients with inherently variable disease courses. In its current state, personalized care of the IBD patient involves identifying patients at high risk for rapid progression to complications, selecting the most appropriate therapy for a given patient, using therapeutic drug monitoring, and achieving the individualized goal that is most appropriate for that patient. The growing body of research in this area allows clinicians to better predict outcomes for individual patients. Some paradigms, especially within the realm of therapeutic drug monitoring, have begun to change as therapy is targeted to individual patient results and goals. Future personalized medical decisions may allow specific therapeutic plans to draw on serologic, genetic, and microbial data for Crohn's disease and ulcerative colitis patients.

Care of the inflammatory bowel disease (IBD) patient presents unique challenges, as decisions regarding therapy must take into account numerous distinct characteristics of each patient. Beyond the dichotomy between Crohn's disease (CD) and ulcerative colitis (UC), which may be difficult to ascertain in some patients, a number of distinct phenotypes exist within these diseases. IBD can be categorized by existing severity, location and extent, and potential for complications. It may be further categorized according to responsiveness to medical therapy. A number of individualized markers of disease, however, may allow for better prediction of response to therapy and disease course. Decisions for therapy must also be tailored to the comorbidities or risks of an individual patient, such as the risk of hepatosplenic T-cell lymphoma among men younger than 35 years.[1] As such, IBD constitutes an opportunity for personalized medicine, and strategies should be tailored to maximize the success of the current treatment, minimize loss of response to therapy or relapses in the future, and address the risks associated with specific medications for given patients.

Therapeutic Drug Monitoring in Inflammatory Bowel Disease

Although a clinician might have previously considered starting a medication at a standard dose and titrating based upon clinical response, therapeutic drug monitoring (TDM) allows for more accurate adjustment of drug levels in an individual patient. IBD management leads the field of TDM. Clinicians caring for IBD patients have a variety of tests available that have been shown to optimize the efficacy of drugs and minimize toxicity.

TDM is important in the management of patients on thiopurines such as azathioprine (AZA) and 6-mercaptopurine (6-MP) to limit side effects such as myelosuppression and hepatotoxicity. Prior to starting thiopurine therapy, an assay should be conducted of the enzymatic activity of thiopurine methyltransferase (TPMT), a critical enzyme in the degradative pathway of 6-MP/AZA, as this type of assay has been reported to better predict myelosuppression than assays of genotype. In fact, the correlation of genotype with enzymatic activity has been reported to be as low as 65%.[2] An exception to this paradigm would be a patient who recently received a transfusion of red blood cells (RBCs), in which case TPMT genotype would yield more accurate results.[3] Intermediate TPMT enzymatic activity is generally associated with increased efficacy and typically requires lower doses because patients generate higher levels of the active metabolite thioguanine.[4]

Following the initiation of therapy, measurement of the thiopurine metabolites 6-thioguanine nucleotide (6-TGN) and 6-methylmercaptopurine (6-MMP) is useful in multiple ways. Many studies have demonstrated that 6-TGN levels greater than 230 pmol/8×10^8 RBCs are associated with increased efficacy.[5,6] However, supratherapeutic levels, generally above 400 pmol/8×10^8 RBCs,[7] are associated with an increased risk of myelosuppression, which is not necessary for efficacy. 6-MMP can be measured to predict the risk of hepatotoxicity; levels greater than 5700 pmol/8×10^8 RBCs carry a 3-fold risk of hepatotoxicity.[8] Importantly, most patients with 6-MMP levels above 5700 pmol/8×10^8 RBCs do not have hepatotoxicity; thus, the metabolites have to be viewed in the context of the particular patient.

There are other special situations in which TDM for 6-MP metabolites is helpful. Among nonresponders to thiopurines, dose escalation resulted in hepatotoxicity for 24% of patients, with median 6-MMP ribonucleotide levels greater than 12,000 pmol/8×10^8 RBCs and median 6-TGN levels remaining subtherapeutic. In such cases, combining a reduced dose of AZA with allopurinol 100 mg will preferentially shunt 6-MP metabolism toward 6-TGNs.[9] Recent studies have suggested that patients exhibiting 6-MMP:6-TGN ratios of 12:1 to 20:1 do well with the addition of allopurinol.[10,11] These studies have largely been performed in patients on thiopurine monotherapy. For patients on combination therapy of thiopurines and biologics, the question becomes whether therapeutic 6-TGN levels are necessary for increasing trough levels of biologics. A recent study by Yarur and colleagues suggested that for patients on combination therapy of thiopurines and infliximab (Remicade, Janssen), the threshold for increased levels of infliximab was seen with 6-TGN levels above 125 pmol/8×10^8 RBCs, thus obviating the need for therapeutic levels of 6-TGNs.[12]

For anti–tumor necrosis factor (TNF) agents, numerous patient-specific factors, including body mass, concomitant use of immunomodulators, antidrug antibodies (ADAs), inflammatory markers, and albumin, may affect drug levels.[8] Ideally, these factors should be taken into account to decide the starting dose of anti-TNF agents, as is done with TPMT testing. For example, initiation of weekly adalimumab (Humira, AbbVie) provided significantly higher remission rates than standard biweekly adalimumab dosing among CD patients with an elevated baseline C-reactive protein (CRP), but did not result in significantly higher rates of remission in those with lower CRP.[13] Similarly, an elevated baseline CRP also predicted response to high-dose infliximab.[14]

TDM has been best studied for infliximab and adalimumab, and includes the measurement of both drug and antibodies to infliximab (ATIs) or antibodies to adalimumab (ATAs). Higher clinical remission rates are seen in patients with detectable trough infliximab levels.[15] Studies have identified concentrations predictive of response ranging from 1.4 to 12.0 μg/mL (Table).[16-19] For adalimumab, cutoffs predictive of remission, as measured by CRP, range from 5.0 to 5.9 μg/mL,[20,21] or from 4.9 to 7.5 μg/mL when assessing mucosal healing.[22,23] Histologic remission, however, may require even higher levels of adalimumab.[23] In the CLASSIC (Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease) I and II studies, a wide variation of adalimumab levels was seen among individual patients, with substantial overlap noted between responders and nonresponders.[24] The variation in cutoff values reported and the variation in the ability of levels to predict response may reflect the heterogeneity in defining response and the inherently flawed dimension of clinical response as distinct from endoscopic and histologic response. The timing of drug level measurement may also be critical to the ability of a drug level to predict response, as studies have suggested that trough concentrations more accurately predict clinical remission than peak concentrations.[25] A recent abstract suggests that levels of infliximab

Table. Characterization of Anti-TNF Levels and Response Outcomes

Study	Drug	Therapeutic Level	Time of Measurement	Test Type	Definition of Response Outcome
Afif et al[16]	Infliximab	Cutoff: 1.4 μg/mL	Trough	ELISA	Clinical response: cessation of diarrhea, abdominal cramping, or fistula closure
		Cutoff: 12.0 μg/mL	4 weeks after infusion	ELISA	Clinical response: cessation of diarrhea, abdominal cramping, or fistula closure
Bortlik et al[17]	Infliximab	Cutoff: 3.0 μg/mL	Trough	ELISA	Sustained clinical response: no need for surgery, no new immunomodulator, no corticosteroids, and no dose increase of infliximab
Van Moerkercke et al[18]	Infliximab	Median: 5.77 μg/mL	Trough	ELISA	Mucosal healing Complete healing: disappearance of all lesions Partial healing: clear endoscopic improvement
Baert et al[19]	Infliximab	Cutoff: 12.0 μg/mL	4 weeks after infusion	ELISA	Duration of clinical response
Papamichael et al[27]	Infliximab	Cutoff: 22.5 μg/mL	Week 2	ELISA	Short-term mucosal healing (Mayo 0-1 endoscopic subscore) after induction
Imaeda et al[20]	Adalimumab	Cutoff: 5.9 μg/mL	Trough	ELISA	CRP level ≤0.3 mg/dL
Yarur et al[21]	Adalimumab	Cutoff: 5.0 μg/mL	Random	HMSA	CRP elevation
Roblin et al[22]	Adalimumab	Cutoff: 4.85 μg/mL	Trough	ELISA	Clinical remission UC: Mayo score <3 CD: CDAI <150
		Cutoff: 4.9 μg/mL	Trough	ELISA	Mucosal healing UC: Mayo endoscopic subscore 0-1 CD: disappearance of all ileocolonic ulcerations
Yarur et al[23]	Adalimumab	Cutoff: 7.5 μg/mL	Trough	HMSA	Endoscopic healing: lack of inflammatory findings in intestinal mucosa
		Cutoff: 7.8 μg/mL	Trough	HMSA	Histologic remission: lack of histologic inflammation on biopsies

CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; ELISA: enzyme-linked immunosorbent assay; HMSA, homogenous mobility shift assay; TNF, tumor necrosis factor; UC, ulcerative colitis.

measured at week 4 can be used to predict trough levels.[26] The implication is that a clinician can see the level early enough to make dose adjustments rather than wait for a trough. As a corollary, high infliximab concentrations (>22.5 μg/mL) measured at week 2 of induction may predict short-term mucosal healing.[27] Thus, in general, higher levels are needed to induce mucosal healing, and it may be possible to measure these levels early during induction, rather than wait for loss of response.

What has been learned about TDM for anti-TNF agents may also apply to other monoclonal antibody–based biologic therapies for IBD. Studies of vedolizumab (Entyvio, Takeda) have shown that higher trough levels resulted in increased rates of clinical response and remission in UC and CD patients.[28,29] Although an assay is not currently commercially available for measuring vedolizumab in serum, future care of the IBD patient treated with vedolizumab may include monitoring drug levels to optimize response.

Low levels of anti-TNF agents are associated with developing ADAs and preceded the formation of ATIs and ATAs.[30,31] Once they are generated, however, ATIs and ATAs increase drug clearance of anti-TNF agents and are associated with lower serum drug levels as well as active disease and loss of response.[32,33] It therefore becomes imperative to prevent patients from developing ATIs or ATAs. This can be accomplished by proactive, rather than reactive, drug monitoring. Using this strategy, patients

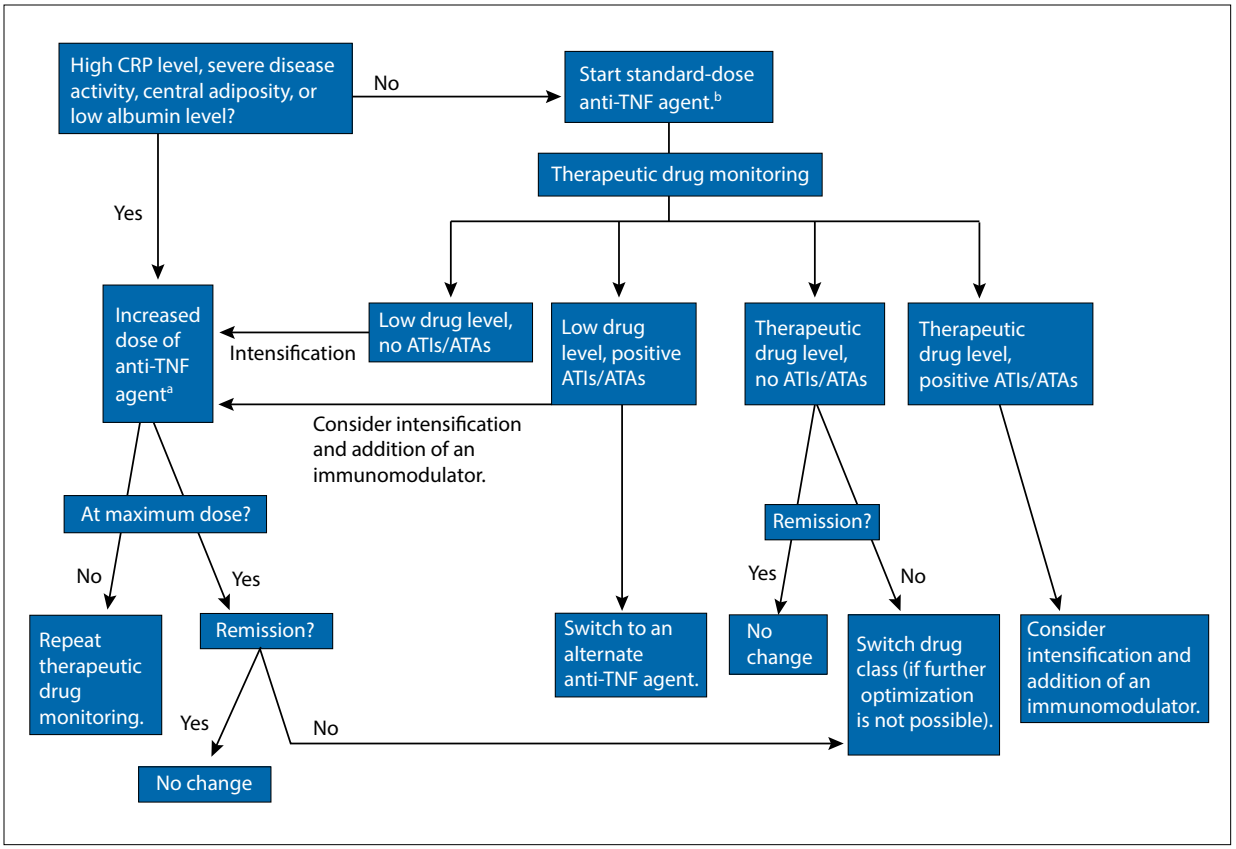

Figure. An algorithm for therapeutic adjustments in patients treated with anti-TNF agents.

[a]Increased doses include infliximab 10 mg/kg or adalimumab 40 mg weekly. [b]Standard-dose anti-TNF agents include infliximab 5 mg/kg every 8 weeks or adalimumab 40 mg every other week.

ATAs, antibodies to adalimumab; ATIs, antibodies to infliximab; CRP, C-reactive protein; TNF, tumor necrosis factor.

were shown to have a greater probability of remaining on infliximab than patients receiving standard of care.[34] Measurement of trough levels as early as week 14 of therapy has also been shown to predict long-term outcomes.[35] Together, these studies suggest that proactive, early assessment of trough levels of biologic therapies will allow for dose optimization and may maximize the likelihood of persistent remission for an individual patient. A summary of this strategy is presented in the Figure.

With knowledge of an individual patient's serum levels and ATI/ATA status, a clinician may guide therapeutic decisions accordingly. In the case of subtherapeutic serum drug levels and the absence of ATIs or ATAs, experts have advocated a strategy of intensification, in which dosage is increased or the intervals between administrations are decreased.[16,36] According to this schema, those with detectable ATIs or ATAs should be switched to an alternate anti-TNF agent[37] because most patients with ADAs do not respond to dose escalation.[14] Vande Casteele and colleagues, however, have shown that ATIs may be transient, which was the case in 28% of their study cohort.[38] Some data have even suggested that the initiation of an immunomodulator[39] or the intensification[40] of therapy may result in the suppression of ATIs.

For patients with therapeutic levels of drug and no ATIs/ATAs but without clinical response, switching classes of medications may be reasonable[37] (although this should be considered carefully). Intensification may also be successful in these cases. In fact, 70% of patients with therapeutic drug levels had a clinical response to dose intensification.[41] This may reflect the variability among patients with respect to their own therapeutic levels. A lack of response despite therapeutic serum levels may be due to a high inflammatory burden within the gastrointestinal tract, as higher anti-TNF concentrations in tissue may be necessary in the face of greater inflammation at the tissue level.[42]

Nonetheless, intensification with the use of TDM has resulted in significantly higher rates of clinical response, fewer hospitalizations, and fewer flares as

compared to dosage adjustments based upon clinical assessment alone.[43] In summary, TDM can be valuable for optimizing the most effective medications and allows individualization of doses.

Traditionally Used Serologies and Emerging Biomarkers for Guiding Management in Inflammatory Bowel Disease

Although serologies have long been used to aid in the diagnosis of UC and CD, they and other biomarkers may also be of great utility in predicting disease outcomes for an individual patient. A recent study found that anti–*Saccharomyces cerevisiae* antibody (ASCA) immunoglobulin A and G (IgA and IgG) and the flagellin antibodies anti–A4-Fla2 and anti-FlaX predict complicated CD years before diagnosis.[44] Dubinsky and colleagues also demonstrated an increased frequency of internal penetrating and stricturing disease and the need for surgery with increasing levels of ASCA, anti–outer membrane protein C (anti-OmpC), and anti-CBir1 flagellin in a prospectively ascertained cohort of pediatric patients.[45] Serologies may also predict postoperative recurrence of CD. For example, after measuring antineutrophil cytoplasmic antibody (ANCA), ASCA, anti-OmpC, anti-CBir1, anti–A4-Fla2, and anti-FlaX, a positive anti-FlaX or a negative ANCA predicted higher rates of postoperative recurrence of CD.[46] Whereas serologies may be helpful to predict phenotype in CD patients, they are generally not helpful in predicting response to anti-TNF agents.[47] Recent proteomic analysis of patient serum has suggested that numerous additional targets such as apolipoprotein A1, apolipoprotein E, complement C4B, plasminogen, serotransferrin, beta-2 glycoprotein 1, and clusterin are upregulated in patients with limited response to infliximab as compared to patients in remission.[48] Although not currently standard practice, knowledge of a patient's serology results may guide medication choices or prompt a clinician to pursue a more aggressive strategy.

Genetic Testing in Inflammatory Bowel Disease Care

One hundred sixty-three loci have been linked to IBD, including 30 CD-specific loci and 23 UC-specific loci.[49] However, these genes represent only 23% and 16% of the heritability of CD and UC, respectively, and are thus of limited utility in predicting who will develop IBD.[50]

Genetic testing for IBD and its future clinical use may prove to be of greater benefit in predicting disease course. An example of this potential can be seen in CD with *NOD2*, for which more than 27 variants have been reported (although 3 of these predict most clinical behavior).[51] *NOD2* variants have been associated with fibrostenotic CD, an earlier need for surgery, and the risk of postoperative recurrence of CD.[52-55] A prior meta-analysis showed a specificity of 98% for complicated CD in those with 2 mutant *NOD2* alleles, leading to the recommendation that more aggressive treatment strategies should be considered for these patients.[56]

Studies have addressed genotype-phenotype associations with other CD susceptibility loci such as *ATG16L1, IRGM*, and *IL23R*. These studies have shown more variable results, prompting debate about their utility.[57] Alternatively, the contribution of overall genetic burden of risk alleles (as opposed to associations with individual polymorphisms) in contributing to CD risk has been shown to predict subphenotypes such as ileal involvement. The genetic burden of these risk alleles in CD patients, however, did not show a significant association with complicated disease behavior after adjusting for confounding with ileal location, causing some physicians to question the utility of genetic testing in clinical practice.[58]

Although prior studies of UC[59,60] have suggested loci conferring increased risk of severe disease, the utility of genetic testing for UC remains unclear following more recent studies that did not show an association between UC disease course and UC-specific loci.[61]

The risk of harmful side effects of IBD therapies may also be identified through genetic testing. A genome-wide association study found a 2.5-fold risk of pancreatitis in IBD patients taking thiopurines who had the single nucleotide polymorphism rs2647087 within the class II human leukocyte antigen region. An association of polymorphisms of *IL23R* has also been reported for psoriasiform reactions to infliximab.[62] As genetic testing becomes more accessible, it may become easier to predict, and therefore easier to avoid, side effects such as these or other rare events, including drug-induced liver injury with anti-TNF agents, for which genetic risk factors have not yet been identified.[63]

Assessing risk in IBD patients by means of genetic testing may also provide clinically meaningful information when combined with additional patient data. For example, a model evaluating *NOD2* genotype and serologies for IBD (ASCA-IgA, ASCA-IgG, anti-OmpC, anti-CBir1, anti–*Pseudomonas fluorescens*-associated sequence I2 [anti-I2], and perinuclear antineutrophil cytoplasmic antibody) has predicted complicated CD with high accuracy.[51] Analysis of a model combining genetic and clinical risk factors showed a significantly increased success rate in predicting the need for surgery as compared to a purely genetic model.[64] This approach may be of particular value, as genetic information for a patient does not exist in a vacuum in clinical practice and would accompany a clinician's knowledge of the patient's clinical risk fac-

tors. Combined genetic and microbial analysis has also supported the role of human genetic factors in microbial alterations in specific IBD populations, including a microbial shift characterized by a decrease in *Clostridium* groups XIVa and IV as well as an increase in Actinobacteria and Proteobacteria associated with patients carrying *NOD2* risk alleles.[65] Given the multifactorial influences on IBD expression, combining information from these modalities may provide improved accuracy in predicting outcomes for individual patients.

The Role of the Microbiota in Personalized Inflammatory Bowel Disease Care

While a complete review of the literature evaluating the microbiota of IBD patients is beyond the scope of this article, it is important to note that advances in microbial analysis have the potential to guide the future care of IBD patients. In fact, the microbiome may be particularly helpful in predicting disease severity in IBD patients. The depletion of *Faecalibacterium prausnitzii,* a butyrate-producing species from the Firmicutes phylum, has been widely reported in CD,[66-68] and has been shown to be decreased in patients with active disease.[69] A relative paucity of *F prausnitzii,* as well as the butyrate-producing species *Roseburia hominis*, has also been shown to correlate with increasing disease severity in UC.[70] Using microbiome sequencing, other researchers have suggested that alterations in the microbiota in the setting of disease flares may be patient-specific.[71] However, the ability to sequence the microbiomes of IBD patients and monitor them for change may ultimately provide a more personalized model for prediction of flares.

Microbial analysis also has the potential to further inform therapeutic decisions in IBD. In fact, corticosteroid responsiveness in IBD has been predicted by the presence of increasing microbial diversity.[72] Similarly, a decrease in bacteria associated with dysbiosis, such as *Escherichia coli*, has been observed in CD patients following treatment with adalimumab.[73] Dysbiosis may also ultimately guide decisions for the continuation of medication, as a low proportion of *F prausnitzii* and a low rate of *Bacteroides* have been shown to predict CD relapse after discontinuation of infliximab.[74]

The role that unique microbial profiles play in IBD may also be seen in fecal microbiota transplantation (FMT). Although studies have shown mixed success with FMT for IBD,[75,76] closer evaluation of the microbiota of these patients may provide a clue as to the pathogenesis and potential treatment of IBD. Initial findings by Moayyedi and colleagues[75] indicated that FMT did not have a significant effect; however, the inclusion of 22 patients who received FMT from a single donor resulted in a statistically significant benefit, suggesting that donor microbiota characteristics may vastly alter outcomes.[77] In a second trial, patients deriving benefit from FMT acquired microbial signatures similar to those of their donors,[76] suggesting that the transfer of specific bacterial flora or compounds they produce may be the key to successful FMT in IBD patients. Mouse models showed that the intragastric transfer of *F prausnitzii* cultures or their supernatants significantly decreased colitis severity,[78] further supporting this concept. With further identification of specific microbial profiles that may serve as crucial transferrable elements in FMT, future testing may provide for the proper selection of ideal candidates and donors for the procedure or even potential microbial therapeutics.

Conclusion

Current strategies allow clinicians to better target drugs and optimize therapies based upon drug levels and identifiable risk factors for an aggressive disease course. Prospective studies will continue to fill in details of when to test and what levels are needed to achieve the outcome of deep remission with clinical and endoscopic healing. The emerging understanding of genetics and the gut microbiota will also play a role in defining the risks of disease complications, response to therapy, and even risks of therapies. The future of IBD management will include many personalized data points to better predict outcomes for individual patients and to precisely tailor therapy.

Dr Abreu has been a consultant for AbbVie Laboratories, Prometheus Laboratories, Takeda, UCB, Pfizer, Janssen, and Eli Lilly. She is also an advisory board member and lecturer for AbbVie Laboratories, and is a scientific advisory board member for Celgene Corporation. Dr Kingsley has no relevant conflicts of interest to disclose.

References

1. Kotlyar DS, Osterman MT, Diamond RH, et al. A systematic review of factors that contribute to hepatosplenic T-cell lymphoma in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2011;9(1):36-41.e1.
2. 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 Ther*. 2007;25(9):1069-1077.
3. Schwab M, Schaeffeler E, Marx C, Zanger U, Aulitzky W, Eichelbaum M. Shortcoming in the diagnosis of TPMT deficiency in a patient with Crohn's disease using phenotyping only. *Gastroenterology*. 2001;121(2):498-499.
4. Gardiner SJ, Gearry RB, Begg EJ, Zhang M, Barclay ML. Thiopurine dose in intermediate and normal metabolizers of thiopurine methyltransferase may differ three-fold. *Clin Gastroenterol Hepatol*. 2008;6(6):654-660.
5. Dubinsky MC, Lamothe S, Yang HY, et al. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. *Gastroenterology*. 2000;118(4):705-713.
6. Osterman MT, Kundu R, Lichtenstein GR, Lewis JD. Association of 6-thioguanine nucleotide levels and inflammatory bowel disease activity: a meta-analysis. *Gastroenterology*. 2006;130(4):1047-1053.

7. Hindorf U, Lindqvist M, Hildebrand H, Fagerberg U, Almer S. Adverse events leading to modification of therapy in a large cohort of patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2006;24(2):331-342.
8. Yarur AJ, Abreu MT, Deshpande AR, Kerman DH, Sussman DA. Therapeutic drug monitoring in patients with inflammatory bowel disease. *World J Gastroenterol*. 2014;20(13):3475-3484.
9. Sparrow MP, Hande SA, Friedman S, et al. Allopurinol safely and effectively optimizes tioguanine metabolites in inflammatory bowel disease patients not responding to azathioprine and mercaptopurine. *Aliment Pharmacol Ther*. 2005;22(5):441-446.
10. Seinen ML, van Asseldonk DP, de Boer NK, et al. The effect of allopurinol and low-dose thiopurine combination therapy on the activity of three pivotal thiopurine metabolizing enzymes: results from a prospective pharmacological study. *J Crohns Colitis*. 2013;7(10):812-819.
11. Friedman A, Brookes JD, Ward MG, et al. Final thiopurine metabolite levels and shunter status can be predicted after six weeks of thiopurine therapy—biochemical outcomes from the EATME study. *Gastroenterology*. 2015;148(4):S861.
12. Yarur AJ, Kubiliun MJ, Czul F, et al. Concentrations of 6-thioguanine nucleotide correlate with trough levels of infliximab in patients with inflammatory bowel disease on combination therapy. *Clin Gastroenterol Hepatol*. 2015;13(6):1118-1124.e3.
13. Hendler SA, Cohen BL, Colombel JF, Sands BE, Mayer L, Agarwal S. High-dose infliximab therapy in Crohn's disease: clinical experience, safety, and efficacy. *J Crohns Colitis*. 2015;9(3):266-275.
14. Sandborn WJ, Colombel JF, D'Haens G, et al. Association of baseline C-reactive protein and prior anti-tumor necrosis factor therapy with need for weekly dosing during maintenance therapy with adalimumab in patients with moderate to severe Crohn's disease. *Curr Med Res Opin*. 2013;29(5):483-493.
15. Maser EA, Villela R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. *Clin Gastroenterol Hepatol*. 2006;4(10):1248-1254.
16. Afif W, Loftus EV Jr, Faubion WA, et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. *Am J Gastroenterol*. 2010;105(5):1133-1139.
17. Bortlik M, Duricova D, Malickova K, et al. Infliximab trough levels may predict sustained response to infliximab in patients with Crohn's disease. *J Crohns Colitis*. 2013;7(9):736-743.
18. Van Moerkercke W, Ackaert C, Compernolle G, et al. High infliximab trough levels are associated with mucosal healing in Crohn's disease. *Gastroenterology*. 2010;138(5):S60.
19. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med*. 2003;348(7):601-608.
20. Imaeda H, Takahashi K, Fujimoto T, et al. Clinical utility of newly developed immunoassays for serum concentrations of adalimumab and anti-adalimumab antibodies in patients with Crohn's disease. *J Gastroenterol*. 2014;49(1):100-109.
21. Yarur AJ, Deshpande AR, Sussman DA, et al. Serum adalimumab levels and antibodies correlate with endoscopic intestinal inflammation and inflammatory markers in patients with inflammatory bowel disease. *Gastroenterology*. 2013;144(5):S774-S775.
22. Roblin X, Marotte H, Rinaudo M, et al. Association between pharmacokinetics of adalimumab and mucosal healing in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol*. 2014;12(1):80-84.e2.
23. Yarur AJ, Jain A, Hauenstein SI, et al. Higher adalimumab levels are associated with histologic and endoscopic remission in patients with Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis*. 2016;22(2):409-415.
24. Chiu YL, Rubin DT, Vermeire S, et al. Serum adalimumab concentration and clinical remission in patients with Crohn's disease. *Inflamm Bowel Dis*. 2013;19(6):1112-1122.
25. Vande Casteele N, Mould DR, Gils A, et al. Adequate trough concentrations and sustained TNF suppression early on during induction therapy with adalimumab predict remission in anti-TNF naïve Crohn's disease patients. *Gastroenterology*. 2015;148(4):S854-S855.
26. Hoekman DR, Lowenberg M, Mathot RA, et al. Non-trough IFX concentrations reliably predict trough level and accelerate dose-adjustment in Crohn's disease. *Gastroenterology*. 2015;148(4):S107.
27. Papamichael K, Vande Casteele N, Billiet T, et al. Early therapeutic drug monitoring for prediction of short-term mucosal healing in patients with ulcerative colitis treated with infliximab. *Gastroenterology.* 2015;148(4):S848.
28. Feagan BG, Rutgeerts P, Sands BE, et al; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2013;369(8):699-710.
29. Sandborn WJ, Feagan BG, Rutgeerts P, et al; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2013;369(8):711-721.
30. Seow CH, Newman A, Irwin SP, Steinhart AH, Silverberg MS, Greenberg GR. Trough serum infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. *Gut*. 2010;59(1):49-54.
31. Karmiris K, Paintaud G, Noman M, et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. *Gastroenterology*. 2009;137(5):1628-1640.
32. Nanda KS, Cheifetz AS, Moss AC. Impact of antibodies to infliximab on clinical outcomes and serum infliximab levels in patients with inflammatory bowel disease (IBD): a meta-analysis. *Am J Gastroenterol*. 2013;108(1):40-47.
33. Velayos FS, Sheibani S, Lockton S, et al. Prevalence of antibodies to adalimumab (ATA) and correlation between ATA and low serum drug concentration on CRP and clinical symptoms in a prospective sample of IBD patients. *Gastroenterology*. 2013;144(5):S91.
34. Vaughn BP, Martinez-Vazquez M, Patwardhan VR, Moss AC, Sandborn WJ, Cheifetz AS. Proactive therapeutic concentration monitoring of infliximab may improve outcomes for patients with inflammatory bowel disease: results from a pilot observational study. *Inflamm Bowel Dis*. 2014;20(11):1996-2003.
35. Singh N, Rosenthal CJ, Melmed GY, et al. Early infliximab trough levels are associated with persistent remission in pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2014;20(10):1708-1713.
36. Bendtzen K, Ainsworth M, Steenholdt C, Thomsen OØ, Brynskov J. Individual medicine in inflammatory bowel disease: monitoring bioavailability, pharmacokinetics and immunogenicity of anti-tumour necrosis factor-alpha antibodies. *Scand J Gastroenterol*. 2009;44(7):774-781.
37. Colombel JF, Feagan BG, Sandborn WJ, Van Assche G, Robinson AM. Therapeutic drug monitoring of biologics for inflammatory bowel disease. *Inflamm Bowel Dis*. 2012;18(2):349-358.
38. Vande Casteele N, Gils A, Singh S, et al. Antibody response to infliximab and its impact on pharmacokinetics can be transient. *Am J Gastroenterol*. 2013;108(6):962-971.
39. Ben-Horin S, Waterman M, Kopylov U, et al. Addition of an immunomodulator to infliximab therapy eliminates antidrug antibodies in serum and restores clinical response of patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2013;11(4):444-447.
40. Ungar B, Chowers Y, Yavzori M, et al; ABIRISK consortium. The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab. *Gut*. 2014;63(8):1258-1264.
41. Vermeire S, Gabriels F, Ballet V, et al. The effect of dose escalation on trough levels in patients who lost response to infliximab. *Gut*. 2010;59(S3):A81.
42. Yarur AJ, Jain A, Sussman DA, et al. The association of tissue anti-TNF drug levels with serological and endoscopic disease activity in inflammatory bowel disease: the ATLAS study. *Gut*. 2016;65(2):249-255.
43. Kelly OB, O'Donnell S, Stempak JM, et al. Dose optimization of infliximab using therapeutic drug monitoring is more effective than dose optimization based on clinical assessment alone in patients with active inflammatory bowel disease. *Gastroenterology*. 2015;148(4):S856.
44. Choung RS, Stockfisch TP, Princen F, et al. Longitudinal status of serological markers predict Crohn's disease phenotype before diagnosis: a "PREDICTS" study. *Gastroenterology*. 2015;148(4):S22.
45. Dubinsky MC, Kugathasan S, Mei L, et al; Western Regional Pediatric IBD Research Alliance; Pediatric IBD Collaborative Research Group; Wisconsin Pediatric IBD Alliance. Increased immune reactivity predicts aggressive complicating Crohn's disease in children. *Clin Gastroenterol Hepatol*. 2008;6(10):1105-1111.
46. Hamilton AL, Kamm MA, Selvaraj F, et al. Serological antibodies for the prediction of post-operative recurrent Crohn's disease results from the POCER study. *Gastroenterology*. 2015;148(4):S116.
47. Prideaux L, De Cruz P, Ng SC, Kamm MA. Serological antibodies in inflammatory bowel disease: a systematic review. *Inflamm Bowel Dis*. 2012;18(7):1340-1355.
48. Gazouli M, Anagnostopoulos AK, Papadopoulou A, et al. Serum protein profile of Crohn's disease treated with infliximab. *J Crohns Colitis*. 2013;7(10):e461-e470.
49. Jostins L, Ripke S, Weersma RK, et al; International IBD Genetics Consortium (IIBDGC). Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature*. 2012;491(7422):119-124.
50. Lees CW, Barrett JC, Parkes M, Satsangi J. New IBD genetics: common pathways with other diseases. *Gut*. 2011;60(12):1739-1753.
51. Lichtenstein GR, Targan SR, Dubinsky MC, et al. Combination of genetic and quantitative serological immune markers are associated with complicated Crohn's disease behavior. *Inflamm Bowel Dis*. 2011;17(12):2488-2496.

52. Brant SR, Picco MF, Achkar JP, et al. Defining complex contributions of NOD2/CARD15 gene mutations, age at onset, and tobacco use on Crohn's disease phenotypes. *Inflamm Bowel Dis*. 2003;9(5):281-289.
53. Abreu MT, Taylor KD, Lin YC, et al. Mutations in NOD2 are associated with fibrostenosing disease in patients with Crohn's disease. *Gastroenterology*. 2002;123(3):679-688.
54. Cleynen I, González JR, Figueroa C, et al. Genetic factors conferring an increased susceptibility to develop Crohn's disease also influence disease phenotype: results from the IBDchip European Project. *Gut*. 2013;62(11):1556-1565.
55. Alvarez-Lobos M, Arostegui JI, Sans M, et al. Crohn's disease patients carrying Nod2/CARD15 gene variants have an increased and early need for first surgery due to stricturing disease and higher rate of surgical recurrence. *Ann Surg*. 2005;242(5):693-700.
56. Adler J, Rangwalla SC, Dwamena BA, Higgins PD. The prognostic power of the NOD2 genotype for complicated Crohn's disease: a meta-analysis. *Am J Gastroenterol*. 2011;106(4):699-712.
57. Jung C, Colombel JF, Lemann M, et al. Genotype/phenotype analyses for 53 Crohn's disease associated genetic polymorphisms. *PLoS One*. 2012;7(12):e52223.
58. Ananthakrishnan AN, Huang H, Nguyen DD, Sauk J, Yajnik V, Xavier RJ. Differential effect of genetic burden on disease phenotypes in Crohn's disease and ulcerative colitis: analysis of a North American cohort. *Am J Gastroenterol*. 2014;109(3):395-400.
59. Nam SY, Kim N, Kim JS, Lim SH, Jung HC, Song IS. Heat shock protein gene 70-2 polymorphism is differentially associated with the clinical phenotypes of ulcerative colitis and Crohn's disease. *J Gastroenterol Hepatol*. 2007;22(7):1032-1038.
60. Guo C, Ahmad T, Beckly J, et al. Association of caspase-9 and RUNX3 with inflammatory bowel disease. *Tissue Antigens*. 2011;77(1):23-29.
61. Waterman M, Knight J, Dinani A, et al. Predictors of outcome in ulcerative colitis. *Inflamm Bowel Dis*. 2015;21(9):2097-2105.
62. Sherlock ME, Walters T, Tabbers MM, et al. Infliximab-induced psoriasis and psoriasiform skin lesions in pediatric Crohn disease and a potential association with IL-23 receptor polymorphisms. *J Pediatr Gastroenterol Nutr*. 2013;56(5):512-518.
63. Shelton E, Chaudrey K, Sauk J, et al. New onset idiosyncratic liver enzyme elevations with biological therapy in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2015;41(10):972-979.
64. Dubinsky MC, Kugathasan S, Kwon S, et al. Multidimensional prognostic risk assessment identifies association between IL12B variation and surgery in Crohn's disease. *Inflamm Bowel Dis*. 2013;19(8):1662-1670.
65. Frank DN, Robertson CE, Hamm CM, et al. Disease phenotype and genotype are associated with shifts in intestinal-associated microbiota in inflammatory bowel diseases. *Inflamm Bowel Dis*. 2011;17(1):179-184.
66. Sokol H, Pigneur B, Watterlot L, et al. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proc Natl Acad Sci U S A*. 2008;105(43):16731-16736.
67. Swidsinski A, Loening-Baucke V, Vaneechoutte M, Doerffel Y. Active Crohn's disease and ulcerative colitis can be specifically diagnosed and monitored based on the biostructure of the fecal flora. *Inflamm Bowel Dis*. 2008;14(2):147-161.
68. Wang W, Chen L, Zhou R, et al. Increased proportions of Bifidobacterium and the Lactobacillus group and loss of butyrate-producing bacteria in inflammatory bowel disease. *J Clin Microbiol*. 2014;52(2):398-406.
69. Sokol H, Seksik P, Furet JP, et al. Low counts of Faecalibacterium prausnitzii in colitis microbiota. *Inflamm Bowel Dis*. 2009;15(8):1183-1189.
70. Machiels K, Joossens M, Sabino J, et al. A decrease of the butyrate-producing species Roseburia hominis and Faecalibacterium prausnitzii defines dysbiosis in patients with ulcerative colitis. *Gut*. 2014;63(8):1275-1283.
71. Wills ES, Jonkers DM, Savelkoul PH, Masclee AA, Pierik MJ, Penders J. Fecal microbial composition of ulcerative colitis and Crohn's disease patients in remission and subsequent exacerbation. *PLoS One*. 2014;9(3):e90981.
72. Michail S, Durbin M, Turner D, et al. Alterations in the gut microbiome of children with severe ulcerative colitis. *Inflamm Bowel Dis*. 2012;18(10):1799-1808.
73. Busquets D, Mas-de-Xaxars T, López-Siles M, et al. Anti-tumour necrosis factor treatment with adalimumab induces changes in the microbiota of Crohn's disease. *J Crohns Colitis*. 2015;9(10):899-906.
74. Rajca S, Grondin V, Louis E, et al. Alterations in the intestinal microbiome (dysbiosis) as a predictor of relapse after infliximab withdrawal in Crohn's disease. *Inflamm Bowel Dis*. 2014;20(6):978-986.
75. Moayyedi P, Surette MG, Kim PT, et al. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a randomized controlled trial. *Gastroenterology*. 2015;149(1):102-109.e6.
76. Rossen NG, Fuentes S, van der Spek MJ, et al. Findings from a randomized controlled trial of fecal transplantation for patients with ulcerative colitis. *Gastroenterology*. 2015;149(1):110-118.e4.
77. Grinspan AM, Kelly CR. Fecal microbiota transplantation for ulcerative colitis: not just yet. *Gastroenterology*. 2015;149(1):15-18.
78. Martín R, Chain F, Miquel S, et al. The commensal bacterium Faecalibacterium prausnitzii is protective in DNBS-induced chronic moderate and severe colitis models. *Inflamm Bowel Dis*. 2014;20(3):417-430.