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Appropriateness of Testing for Anti–Tumor Necrosis Factor Agent and Antibody Concentrations, and Interpretation of Results

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BACKGROUND & AIMS: **The availability of tests for blood concentrations of anti–tumor necrosis factor (TNF) agents and antibodies against these drugs could improve dose selection for patients with inflammatory bowel disease (IBD). However, there is little consensus on when to test and how to interpret test results. We used the RAND/UCLA Appropriateness Method to determine when these tests are appropriate and how to clinically interpret their results.**

METHODS: **We conducted a systematic literature search in November 2013 to identify observational or experimental studies of the measurement of anti-TNF drug and antibody concentrations in patients with IBD and interpretation of their results. We developed 35 scenarios that assessed the appropriateness of testing and 143 scenarios that addressed clinical strategies in response to test results, and presented the findings to an expert panel. The appropriateness of each scenario was rated before and after an in-person meeting with the panel. Panelists rated the appropriateness of various clinical management options including changing therapy within class, switching out of class, adjusting drug dose or interval, adding or adjusting concomitant immune modulators, and doing nothing for each of 6 permutations of high versus low drug concentrations and high, low, or undetectable antibody concentrations. Disagreement was assessed using a validated index.**

RESULTS: **Assessment of anti-TNF drug and antibody concentrations was rated appropriate at the end of induction therapy in primary nonresponders, in secondary nonresponders, at least once during the first year of maintenance therapy, and following a drug holiday. Routine assessment in responders at the end of induction was rated uncertain. In nearly all scenarios, escalation of drug dosing was rated appropriate when drug concentration was low in the absence of antibodies, and switching within class was rated appropriate when antibodies were present. Other recommendations depended on the specific clinical scenario for which the test was obtained.**

CONCLUSIONS: **Based on the RAND/UCLA Appropriateness Method of analysis, an expert panel recommends testing for drug and antibody concentrations in many clinical scenarios. The appropriate timing and best way to respond to anti-TNF drug and antibody testing for IBD depends on the specific clinical scenario. These recommendations can help guide clinicians to best optimize anti-TNF therapy.**

Keywords: Ulcerative Colitis; Crohn's Disease; Treatment; Patient Management.

Abbreviations used in this paper: IBD, inflammatory bowel disease; RAM, RAND/UCLA Appropriateness Method; TNF, tumor necrosis factor.

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Most current article

Anti–tumor necrosis factor (TNF) therapy can heal intestinal inflammation, reduce the likelihood of future complications, and significantly improve quality of life among patients with inflammatory bowel disease (IBD).[1–5] Improved clinical outcomes are associated with higher trough drug concentrations and the absence of antidrug antibodies.[6–8] However, these medications are not universally effective, and are subject to loss of effectiveness over time in most responders. Mechanisms for treatment may be caused by changes in the metabolism of the drug, "mechanistic escape" warranting a different class of therapy, and immunogenicity caused by the development of antidrug antibodies that may be specific to a particular drug. The ability to distinguish these mechanisms of loss of response from one another using drug and antidrug antibody concentrations offers clinicians insight into the appropriateness of clinical management strategies, including discontinuation of the drug with a switch to an alternative anti-TNF or an alternative class of therapy, manipulation of the drug dose or dosing interval, and the addition of a concomitant immunomodulator.[9,10] However, without insight into the mechanisms of treatment failure with these therapies, the provider is left making educated inferences as to the most appropriate management strategy. The availability of commercial assays for the clinical assessment of anti-TNF drug and antibody concentrations offers the practicing clinician an opportunity to tailor management decisions based on a biologically sound rationale. However, further clarity into the optimal ways to use these tests is needed, both in terms of the appropriateness of using these tests and their interpretation in the context of specific clinical scenarios in which they might be used.

There are several different clinical scenarios in which testing for drug and/or antibody concentrations may be appropriate. These include testing routinely after induction treatment[11,12] and routinely during maintenance therapy[13,14] to determine whether an adequate drug dose is being administered, and in patients with primary nonresponse[15,16] and in patients with an initial clinical improvement but with secondary loss of response over time[10] to help determine mechanisms for suboptimal efficacy. Strategies to respond to the results of these tests may depend on the clinical scenario in which the tests are ordered.[17]

To address these areas of uncertainty, we used the RAND/UCLA Appropriateness Method (RAM) to assess the appropriateness of ordering these tests and interpreting their results in patients with IBD receiving anti-TNF therapy.

Methods

Study Design

RAM uses an iterative approach to combine the best available evidence with expert opinion using a modified Delphi panel.[18–20] This structured methodology includes a literature review presented to an expert panel followed by 2 rounds of anonymous panel ratings. The second round of ratings is conducted after an in-person moderated discussion among participants, which is focused on areas of disagreement in the first round of voting.

Literature Review

We conducted a systematic literature search in November 2013 to identify observational or experimental studies of the measurement and interpretation of anti-TNF drug and antibody concentrations among patients with IBD. We also conducted targeted reviews to specifically address the following topics: association of infliximab, adalimumab, and certolizumab pegol drug and antibody concentrations with outcomes in Crohn's disease; association of infliximab, adalimumab, and certolizumab pegol drug and antibody concentrations with outcomes in ulcerative colitis; therapeutic drug monitoring and dose optimization during maintenance therapy; restarting anti-TNF therapy after a drug holiday; and pharmacokinetics of infliximab, adalimumab, and certolizumab pegol. These reviews were compiled into a comprehensive monograph that was distributed to all panelists before the first round of ratings (Supplementary Material).

Clinical Scenarios

The survey was divided into 2 sections. In Section I, panelists rated the appropriateness of ordering drug/antibody concentration tests. Variables that were assessed were selected on the basis of their potential influence on pharmacokinetics and clinical decision-making, including the drug clearance, type of anti-TNF agent, smoking status, and disease phenotype and behavior. These variables were assessed in 6 different scenarios including routinely after induction, routinely during maintenance therapy in primary nonresponders, in secondary nonresponders, and when restarting after a drug holiday.

In Section II, panelists rated the appropriateness of various clinical interventions in response to a specific result of drug/antibody testing for a given clinical scenario, or chapter. Panelists rated 6 permutations of drug and antibody test results (all combinations of low/high drug concentration and undetectable/low/high antibody concentration) in the following chapters: (1) at the end of induction therapy (routinely), (2) at the end of induction therapy in primary nonresponders, (3) in secondary nonresponders (ie, in patients losing response), (4) during maintenance therapy (at a regular interval), and (5) in patients reinitiating anti-TNF therapy after an extended "drug holiday." For each permutation of drug/antibody concentration within each chapter, panelists rated the appropriateness of the following 6 clinical interventions

to the anti-TNF regimen: (1) switch to another agent within the anti-TNF class, (2) switch to another agent within the anti-TNF class and add an immunomodulatory, (3) switch outside of the anti-TNF class, (4) increase the anti-TNF dose or decrease the interval, (5) add/adjust immunomodulatory, and (6) do nothing.

Definitions and Assumptions

Definitions of terms were provided at the outset of each round of ratings and at the in-person meeting as listed next. "Normal drug clearance": no obvious factors associated with rapid or slower drug clearance. "Abnormal drug clearance": one or more factors leading to rapid or delayed drug clearance. "The end of induction (infliximab)": 14 weeks. "The end of induction (adalimumab)": 6 weeks. "Primary nonresponder": no clinical response to induction doses. "Secondary nonresponder": initial response to induction doses, but with clinical loss of response thereafter. "Drug holiday": delay (intentional or unintentional) of at least 3 doses (same for both infliximab and adalimumab). "Drug below threshold": drug concentrations that are undetectable or "just above" levels of detection, but below the threshold considered to be therapeutic, specific to each drug, and determined through a review of the literature. "Antibodies: high level": antibody levels associated with lower drug concentrations and lower clinical efficacy. "Antibodies: low level": detectable antibody levels thought to be transient or nonneutralizing, and not necessarily associated with decreased drug concentrations or clinical efficacy. Published cutoff values for drug and antibody concentrations associated with clinical efficacy were reviewed with the panelists but were not specified for scenario ratings given that several cutoffs have been proposed and that they may vary across laboratories and assays. All panelists reviewed and agreed with these definitions and assumptions before the moderated discussion.

We assumed testing was performed using the validated homogeneous mobility shift assay, allowing for measurement of antibodies in the presence of drug. Consistent with RAM methodology, panelists were specifically asked not to consider cost in the decision to order testing or in acting on test results.

Appropriateness Panel

The panel consisted of members of the Building Research in Inflammatory Bowel Disease Globally (BRIDGe; www.BRIDGeIBD.com), and recognized, published leaders in the field of therapeutic drug monitoring in IBD. After receiving the literature summary that was prepared by several participants, the panelists were instructed to confidentially rate the scenarios on the basis of their own expertise in the context of the available literature. The panelists then convened 2 weeks later at a moderated in-person session (January 2014, Scottsdale, AZ). During this meeting scenarios were discussed in detail, after which panelists confidentially rerated each scenario; agreement was not required.

Analysis

Appropriateness was rated on a scale of 1–9 for each scenario (1–3, inappropriate; 4–6, uncertain; and 7–9, appropriate). "Appropriate" was defined as when the expected positive health benefits exceeded the potential negative health consequences, whereas "inappropriate" was considered to reflect that the expected health consequences outweighed potential benefit. Median scores were calculated and rounded up, so that a median score of 3.5 was rated as uncertain and a median score of 6.5 was rated as appropriate. To quantify the level of agreement, the RAND/UCLA disagreement index was calculated using a standard published equation.[18] A disagreement index greater than 1.0 indicates extreme variation, whereas disagreement index values less than 1.0 reflect agreement. Scenarios in which ratings met criteria for disagreement were rated "uncertain" even if the median score rating was "inappropriate" or "appropriate."

Results

The Appropriateness of Checking Drug and Antibody Concentrations

Panelists did not distinguish between whether patients were receiving infliximab or adalimumab when rating the appropriateness of checking drug/antibody levels for any scenario. Panelists did not rate scenarios for patients using certolizumab pegol because of the lack of a commercially available drug assay. Ratings suggested that it is "appropriate" to check drug/antibody levels in the following scenarios: (1) after induction in primary nonresponders; (2) in secondary nonresponders (ie, loss of response); (3) during maintenance therapy, at least once during the first year; and (4) whenever restarting a drug after a drug holiday. However, there was uncertainty about whether to check levels in patients routinely after induction therapy.

Regarding assessment of antibody levels at the time of restarting anti-TNF therapy after a drug holiday (defined as missing 3 or more scheduled doses), panelists rated that checking levels after the first reinduction dose was "appropriate" and that checking levels before the first dose was "uncertain." However, panelists agreed that if antidrug antibodies were found before or after the first dose, then further drug should not be given because of the risk of an allergic reaction with additional dosing, and that a switch to an alternative therapy (either in-class or out-of-class) is appropriate.

Table 1. End of Induction, Responding to Therapy

Drug concentration	Antibody concentration	Intervention	Rating
Low	Undetectable	Switch within class	Inappropriate
		Switch outside of class	Inappropriate
		Increase dose or decrease dose interval	Appropriate
		Do nothing	Inappropriate
	Low[a]	Switch within class	Uncertain
		Switch outside of class	Inappropriate
		Increase dose or decrease dose interval	Appropriate
		Do nothing	Inappropriate
	High[a]	Switch within class	Appropriate
		Switch outside of class	Uncertain
		Increase dose or decrease dose interval	Uncertain
		Do nothing	Inappropriate
Adequate	Undetectable	Switch within class	Inappropriate
		Switch outside of class	Inappropriate
		Increase dose or decrease dose interval	Inappropriate
		Do nothing	Appropriate
	Low[a]	Switch within class	Inappropriate
		Switch outside of class	Inappropriate
		Increase dose or decrease dose interval	Inappropriate
		Do nothing	Uncertain
	High[a]	Switch within class	Uncertain
		Switch outside of class	Uncertain
		Increase dose or decrease dose interval	Inappropriate
		Do nothing	Uncertain

[a]If antibodies are positive, consider optimizing or adding immunomodulator in addition to other change in therapy.

The Appropriateness of Interventions in Response to Testing

Panelists rated the appropriateness of various interventions in response to the results of drug concentrations (undetectable, low, or adequate) and antibody concentrations (undetectable, low, or high) for each scenario (Tables 1–4). Overall, panelists rated the appropriateness of 4 interventions (switch within class, switch outside of class, increase dose or interval, do nothing) for each of 6 possible combinations of drug/antibody results in 4 discrete circumstances, for a total of 96 scenarios. There was a high degree of agreement among the panelists, with only 7 of 96 scenarios meeting criteria for disagreement. Overall, 21 interventions were rated "appropriate," 23 were rated "uncertain" or exhibited disagreement and were thus assigned a rating of "uncertain," and 52 interventions were rated "inappropriate." Panelists agreed that if antibodies were positive, optimizing or adding an immunomodulator was generally appropriate in conjunction with other interventions. Readers can view the panel's appropriateness ratings for all scenarios on a web-based platform after identifying the relevant clinical context (http://www.bridgeibd.com/anti-tnf-optimizer).

End of induction, responding to therapy

At the end of induction, in patients responding to therapy but with low drug levels and low or undetectable antibodies, increasing the anti-TNF dose or frequency was considered appropriate, whereas "doing nothing" was inappropriate (Table 1). However, if antibodies were high then switching within class was the only appropriate intervention. When drug concentration was adequate but antibodies were high, there was no "appropriate" scenario, although several scenarios were rated "uncertain" and adding an immunomodulator (or increasing the immunomodulator dose to a therapeutic dose if the patient was already on one) was recommended.

End of induction, primary nonresponse

Assessment of drug and antibody concentrations was considered "appropriate" at the end of the induction period in patients without response (Table 2). In this scenario, if the drug concentration was low, and no antibodies were present, then the only "appropriate" recommendation would be to increase the dose or shorten the interval. In conjunction with that intervention, consideration for optimizing or adding an immunomodulator was recommended. However, if antibodies were found to be high with a low drug concentration, then switching within class would be considered "appropriate," switching out of class "uncertain," and increasing the dose would be considered "inappropriate." In scenarios where drug concentrations were adequate, switching out of class would be considered "appropriate" regardless of antibody concentration, whereas switching within class was rated "uncertain."

Table 2. End of Induction, Primary Nonresponder

Drug concentration	Antibody concentration	Intervention	Rating
Low	Undetectable	Switch within class	Inappropriate
		Switch outside of class	Inappropriate
		Increase dose or decrease dose interval	Appropriate
		Do nothing	Inappropriate
	Low[a]	Switch within class	Uncertain
		Switch outside of class	Uncertain
		Increase dose or decrease dose interval	Appropriate
		Do nothing	Inappropriate
	High[a]	Switch within class	Appropriate
		Switch outside of class	Uncertain
		Increase dose or decrease dose interval	Inappropriate
		Do nothing	Inappropriate
Adequate	Any value	Switch within class	Uncertain
		Switch outside of class	Appropriate
		Increase dose or decrease dose interval	Inappropriate
		Do nothing	Inappropriate

[a]If antibodies are positive, consider optimizing or adding immunomodulator in addition to other change in therapy.

Loss of Response

Assessment of drug and antibody concentrations was considered appropriate in patients with an initial response to anti-TNF therapy but with subsequent loss of response despite adherence to maintenance dosing (Table 3). In this scenario, if the drug concentration were found to be low, then increasing the dose or frequency (with consideration of optimizing or adding an immunomodulator) would be "appropriate" if antibodies were undetectable or low. However, if antibodies were high, then this intervention would be "inappropriate," and switching within class would be "appropriate." In this scenario, if the drug concentration were adequate, then switching out of class would be "appropriate" regardless of antibody status, and switching within class would additionally be an "appropriate" intervention if antibodies were high.

During Maintenance, in Responders

In patients responding to maintenance therapy, assessment of drug and antibody concentrations was rated "appropriate" at least once during the first year of maintenance therapy (Table 4). If drug concentrations were low with low or absent antibodies, increasing the dose or decreasing the interval would be appropriate. However, in those patients doing well on maintenance

Table 3. Secondary Nonresponse (Loss of Response)

Drug concentration	Antibody concentration	Intervention	Rating
Low	Undetectable	Switch within class	Inappropriate
		Switch outside of class	Inappropriate
		Increase dose or decrease dose interval	Appropriate
		Do nothing	Inappropriate
	Low[a]	Switch within class	Uncertain
		Switch outside of class	Uncertain
		Increase dose or decrease dose interval	Appropriate
		Do nothing	Inappropriate
	High[a]	Switch within class	Appropriate
		Switch outside of class	Uncertain
		Increase dose or decrease dose interval	Inappropriate
		Do nothing	Inappropriate
Adequate	Undetectable or Low[a]	Switch within class	Uncertain
		Switch outside of class	Appropriate
		Increase dose or decrease dose interval	Inappropriate
		Do nothing	Inappropriate
	High[a]	Switch within class	Appropriate
		Switch outside of class	Appropriate
		Increase dose or decrease dose interval	Inappropriate
		Do nothing	Inappropriate

[a]If antibodies are positive, consider optimizing or adding immunomodulator in addition to other change in therapy.

Table 4. During Maintenance Therapy (in Responders)

Drug concentration	Antibody concentration	Intervention	Rating
Low	Undetectable or Low[a]	Switch within class	Inappropriate
		Switch outside of class	Inappropriate
		Increase dose or decrease dose interval	Appropriate
		Do nothing	Inappropriate
	High[a]	Switch within class	Appropriate
		Switch outside of class	Uncertain
		Increase dose or decrease dose interval	Uncertain
		Do nothing	Inappropriate
Adequate	Undetectable	Switch within class	Inappropriate
		Switch outside of class	Inappropriate
		Increase dose or decrease dose interval	Inappropriate
		Do nothing	Appropriate
	Low[a]	Switch within class	Inappropriate
		Switch outside of class	Inappropriate
		Increase dose or decrease dose interval	Inappropriate
		Do nothing	Uncertain
	High[a]	Switch within class	Uncertain
		Switch outside of class	Inappropriate
		Increase dose or decrease dose interval	Inappropriate
		Do nothing	Uncertain

[a]If antibodies are positive, consider optimizing or adding immunomodulator in addition to other change in therapy.

therapy who have low drug concentration but high concentration of antibodies, switching within class would be appropriate, "doing nothing" would be inappropriate, and other interventions were rated uncertain. However, in cases where there were adequate drug and high antibody concentrations, there was no obvious appropriate intervention, with "doing nothing" and "switching within class" both rated as uncertain.

Discussion

Our study has several important findings. First, we determined that ordering tests for drug and antibody concentrations is appropriate in 4 clinical scenarios: (1) secondary loss of response, (2) primary nonresponse, (3) during the first year of maintenance therapy, and (4) restarting after a drug holiday (after the initial dose); but ordering these tests after induction was "uncertain." Second, we determined that the appropriateness of various interventions in response to test results varies across scenarios, reinforcing the concept that these tests must always be interpreted in the specific context in which they were ordered. Finally, we found very little disagreement among the panelist appropriateness ratings, even though the RAM does not require consensus and the ratings are intended to reflect panelist opinion in the context of the available literature.

An area of active investigation is the determination of actual cutoff values of drug concentrations used to determine treatment efficacy. These values may differ across individual drugs, disease phenotype, and clinical endpoints, and may vary across assays. For example, although adalimumab trough concentrations have been associated with normalization of C-reactive protein and clinical remission,[21] it may be that higher concentrations may associate with mucosal healing.[22] Minimum infliximab concentrations associated with clinical efficacy in Crohn's disease have ranged from 3 to 5 μg/mL,[6] although these targets warrant prospective validation. In ulcerative colitis, increasing infliximab trough concentrations have been associated with improved clinical efficacy. In a similar vein, antibody concentrations were qualitatively defined as "low" or "high" to account for the potential to overcome "low level" or "transient" antibodies with higher drug dosing.[23] We therefore grouped drug and antibody concentrations using qualitative and not quantitative categories. In so doing, we intended for our findings to be broadly relevant across various assays, which may have different clinically meaningful cutoff values for treatment efficacy and antibody concentrations.

Our study has several limitations. First, there is little prospective evidence to support the clinical use of drug and antibody testing for many scenarios. The RAM is well-suited for such topics, so as to elicit recommendations from experts in the context of the best available evidence regardless of the quality of the evidence. Second, the variability across assays with respect to reliability, validity, and clinical correlations warranted qualitative, not quantitative definitions of the antibody cutoffs for categorization as "high" and "low." As new assays emerge, the "low" and "high" cutoff values for both drug and antibody concentrations remain disparate and poorly defined; this can frustrate the clinician and patient attempting to interpret results accordingly. Third, panelists were instructed to not include "cost" as a

consideration for the appropriateness of ordering these tests. This was intentional, and in accordance with the RAM,[18] but may limit the generalizability of these recommendations to "real world" settings where the costs of these tests may not be covered by payors. Nonetheless, these tests have been shown to be cost-effective across various pricings, given the cost-savings gained with optimized therapy that reduces complications, hospitalizations, and surgery.[24,25]

It is hoped that our current recommendations for the appropriateness of testing will be used to inform policies governing payment for these tests where they are not currently covered. Although we attempted to cover a broad range of clinical scenarios, it was not possible to include all factors that may influence decision-making, such as phenotype of Crohn's disease, prior surgery, and patient preferences. We attempted to include variables for which some published evidence was available to guide clinical decision-making. Finally, our scenarios required some assumptions and definitions that were based on the literature, when available, but also relied on guidance from the panelists where the literature is lacking, consistent with the RAM relying on panelist expertise in the context of the available literature. For example, the timing of "post-induction" infliximab trough assessment is supported by several studies,[11,12] whereas the evidence for adalimumab is lacking.

We believe our findings are rigorously derived and can serve as a practical clinical guide. These recommendations help to clarify the most appropriate use of drug and antibody tests by delineating when they should be ordered, and how the results should be interpreted. To further assist the clinician at the point of care, we have developed a web-based application that can be accessed for free and used to input results of drug and antibody concentration testing in addition to the specific clinical scenario. The application then shows how the expert panel rated the appropriateness of various therapeutic interventions for that particular circumstance (http://www.bridgeibd.com/anti-tnf-optimizer). These recommendations should not replace clinical judgment, but might assist the clinician at the point of care in tailoring management to individual patient circumstances.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2016.05.010.

References

1. D'Haens GR, Panaccione R, Higgins PD, et al. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: when to start, when to stop, which drug to choose, and how to predict response? Am J Gastroenterol 2011;106:199–212; quiz 213.
2. Sandborn WJ. Crohn's disease evaluation and treatment: clinical decision tool. Gastroenterology 2014;147:702–705.
3. Sandborn WJ, Rutgeerts P, Feagan BG, et al. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. Gastroenterology 2009;137:1250–1260.
4. Feagan BG, Panaccione R, Sandborn WJ, et al. Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. Gastroenterology 2008;135:1493–1499.
5. Feagan BG, Sandborn WJ, Lazar A, et al. Adalimumab therapy is associated with reduced risk of hospitalization in patients with ulcerative colitis. Gastroenterology 2014;146:110–118 e3.
6. Vande Casteele N, Khanna R, Levesque BG, et al. The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn's disease. Gut 2014;64:1539–1545.
7. Baert F, Kondragunta V, Lockton S, et al. Antibodies to adalimumab are associated with future inflammation in Crohn's patients receiving maintenance adalimumab therapy: a post hoc analysis of the Karmiris trial. Gut 2016;65:1126–1131.
8. 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;108:40–47; quiz 48.
9. Hazlewood GS, Rezaie A, Borman M, et al. Comparative effectiveness of immunosuppressants and biologics for inducing and maintaining remission in Crohn's disease: a network meta-analysis. Gastroenterology 2015;148:344–354 e5; quiz e14–15.
10. 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;105:1133–1139.
11. 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;20:1708–1713.
12. Cornillie F, Hanauer SB, Diamond RH, et al. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. Gut 2014;63:1721–1727.
13. Vaughn BP, Martinez-Vazquez M, Patwardhan VR, et al. 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;20:1996–2003.
14. Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology 2015;148:1320–1329 e3.
15. Ainsworth MA, Bendtzen K, Brynskov J. Tumor necrosis factor-alpha binding capacity and anti-infliximab antibodies measured by fluid-phase radioimmunoassays as predictors of clinical efficacy of infliximab in Crohn's disease. Am J Gastroenterol 2008;103:944–948.
16. Papamichael K, Gils A, Rutgeerts P, et al. Role for therapeutic drug monitoring during induction therapy with TNF antagonists

in IBD: evolution in the definition and management of primary nonresponse. Inflamm Bowel Dis 2015;21:182–197.
17. Djulbegovic B, Hozo I, Lyman GH. Linking evidence-based medicine therapeutic summary measures to clinical decision analysis. MedGenMed 2000;2:E6.
18. Brook RH. The RAND/UCLA Appropriateness Method. Clinical practice guideline development: methodology perspectives. Rockville, MD: Public Health Service: AHCR, 1994.
19. Melmed GY, Spiegel BM, Bressler B, et al. The appropriateness of concomitant immunomodulators with anti-tumor necrosis factor agents for Crohn's disease: one size does not fit all. Clin Gastroenterol Hepatol 2010;8:655–659.
20. Cheifetz AS, Melmed GY, Spiegel B, et al. Setting priorities for comparative effectiveness research in inflammatory bowel disease: results of an international provider survey, expert RAND panel, and patient focus groups. Inflamm Bowel Dis 2012; 18:2294–2300.
21. Mazor Y, Almog R, Kopylov U, et al. Adalimumab drug and antibody levels as predictors of clinical and laboratory response in patients with Crohn's disease. Aliment Pharmacol Ther 2014; 40:620–628.
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;12:80–84 e2.
23. 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; 11:444–447.
24. Steenholdt C, Brynskov J, Thomsen OO, et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. Gut 2014; 63:919–927.
25. Velayos FS, Kahn JG, Sandborn WJ, et al. A test-based strategy is more cost effective than empiric dose escalation for patients with Crohn's disease who lose responsiveness to infliximab. Clin Gastroenterol Hepatol 2013;11:654–666.

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Conflicts of interest
These authors disclose the following: Gil Y. Melmed has received research funding from Pfizer, Prometheus, and Shire; and is a consultant for Abbvie, Given Imaging, Luitpold Pharmaceuticals, Jannsen, UCB, Celgene, Takeda, Genentech, and Pfizer. Peter M. Irving is on the Advisory Board and Speaker's Bureau for Abbvie, MSD, and Takeda. Jennifer Jones has served as a speaker for Jansen, Merck, Schering-Plough, Abbot, and Abbvie; and has participated in advisory boards for Janssen, Abbott, and Takeda. Gilaad G. Kaplan has served as a speaker for Janssen, Merck, Schering-Plough, and Abbvie; has participated in advisory board meetings for Jansen and Abbvie; and has received research support from GlaxoSmithKline, Merck, Abbvie, and Shire. Miles P. Sparrow has received research support from Ferring Pharmaceuticals and Abbott Pharmaceuticals; and is on the Advisory Board of Janssen, Takeda, and Hospira Pharmaceuticals. Brian Bressler is on the Advisory Board of Abbvie, Janssen, Takeda, Shire, Genentech, Ferring, and Warner Chillcott; the Speaker's Bureau of Abbvie, Janssen, Takeda, and Forrest Laboratory; is a consultant for Celltrion and Pendopharm; and has received research support from Abbvie, Amgen, BMS, Genentech, Janssen, BI, and GlaxoSmithKline. Adam S. Cheifetz has served on advisory boards for Abbvie and Janssen and consulting for Takeda, UCB, and Prometheus. Shane M. Devlin has served on Speaker's Bureau and as a consultant for Takeda, Janssen, and Abbvie. Niels Vande Casteelle is a Postdoctoral Fellow of the Research Foundation - Flanders, Belgium (grant number 1260714N); has received consultancy fees from Janssen Biologics, MSD, UCB, Pfizer, Takeda; and has received speaker's fees from Abbott/AbbVie. Diane Mould is president of Projections Research Inc, a consulting company working with the pharmaceutical industry. Jean-Fred Colombel has served as consultant, advisory board member, or speaker for Abbvie, ABScience, Amgen, Bristol Meyers Squibb, Celltrion, Danone, Ferring, Genentech, Giuliani SPA, Given Imaging, Janssen, Immune Pharmaceuticals, Merck & Co, Millenium Pharmaceuticals Inc, Nutrition Science Partners Ltd, Pfizer Inc, Prometheus Laboratories, Protagonsit, Receptos, Sanofi, Schering Plough Corporation, Second Genome, Takeda, Teva Pharmaceuticals, UCB Pharma, Vertex, and Dr. August Wolff GmbH & Co. Marla Dubinsky is a consultant for Abbvie, Janssen, Takeda, and UCB. William J. Sandborn has served as a consultant for Janssen, Abbvie, UCB Pharma, Amgen, Genentech, Pfizer, and Medimmune/AstraZencea; and has received research support from Janssen, Abbvie, Amgen, Genentech, and Pfizer. Corey A. Siegel has received research funding from Abbvie, Janssen, Takeda, and UCB; delivered CME lectures for Abbvie, Janssen, Merck, and Takeda; and served as an advisor/consultant for Abbvie, Amgen, Janssen, Lilly, Pfizer, Takeda, and Theradiag. The remaining authors disclose no conflicts.

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