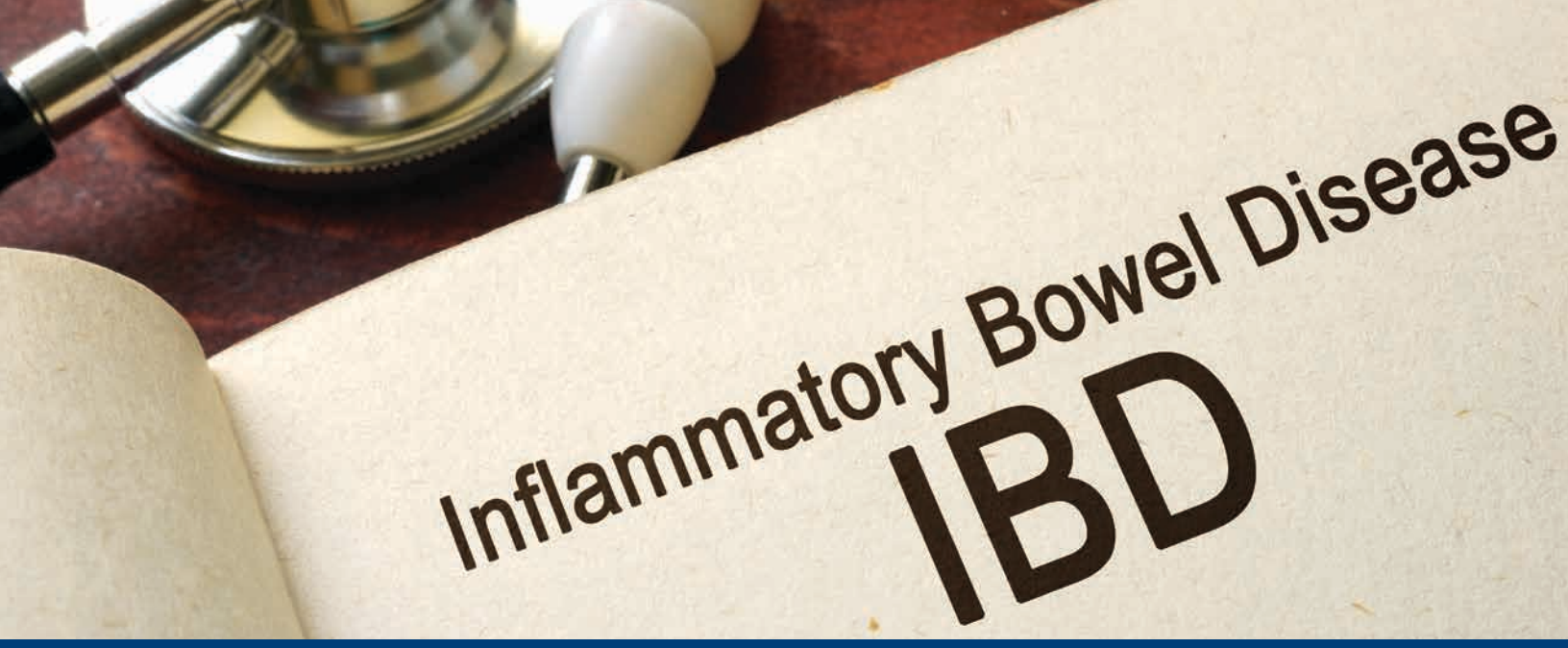
INFLAMMATORY BOWEL DISEASE

LabCorp



Inflammatory Bowel Disease (IBD) is a chronic disease impacting nearly 1.2 million Americans.[1] Developments in treatment, such as biologics, have greatly improved quality of life for patients and advancements in laboratory testing are helping to support diagnosis and optimize therapy. LabCorp offers leading expertise and comprehensive testing services to support physicians in the management of IBD patients.

LabCorp's IBD test offering supports complete care decisions

Inflammation Status

- CBC
- Metabolic Panel
- C-Reactive Protein
- Sed Rate
- Calprotectin, Fecal
- Stool Lactoferin

IBD Diagnosis

GI Pathology
Colonoscopy or
Other Endoscopy

Indeterminate or Patient non-compliance

IBD Specific Serology
- ASCA
- ANCA

+

- Anti-Glycan Antibodies

Risk Assessment

Co-Morbidity
- Clostridium difficile
- Stool Culture
- CMV

Crohn's Prognostic
- Anti-Glycan Antibodies

Treatment Decision

- Biologic
- Thiopurine
- Methotrexate

Non-Responder
Switch treatment
Add co-therapy

Single-Source Laboratory Solution for the Gastroenterology Specialist

Through specialized GI testing, a national service network, and multiple connectivity options, LabCorp makes it easier for gastroenterologists to manage their laboratory needs.

- Expansive network of managed care health plans
- Nearly 2000 patient service centers located nationwide
- Integrations with more than 700 EMR/EHRs, PWS, and HIE systems
- PhD and MD level client consultation
- Specialized service offerings for IBD, HCV, Celiac Disease, and Pathology

Pre-Treatment Testing

- CBC
- Metabolic Panel
- QuantiFERON Gold TB
- Hepatitis B Screening

- CBC
- TPMT Enzymes and/or TPMT Genetics

- CBC
- Metabolic Panel

Disease Activity

- C-Reactive Protein
- Stool Lactoferin
- Calprotectin, Fecal

Responder
Monitor progress
Adjust dosing if indicated

Treatment Monitoring

- Thiopurine Metabolites

- MTX Polyglutamates

- Biologic Drug Concentration and Antibody Testing (*Dose*ASSURE™)

Quantify active drug levels,
Identify immunogenicity,
Adjust dosing and frequency,
Consider co-therapy,
Switch Treatment

IBD Treatment Monitoring

Patient response to IBD treatments may be highly variable but new Therapeutic Drug Monitoring (TDM) assays can help optimize therapy using a personalized, patient-specific approach.

Monitoring Biologics — *Dose*ASSURE™ Portfolio

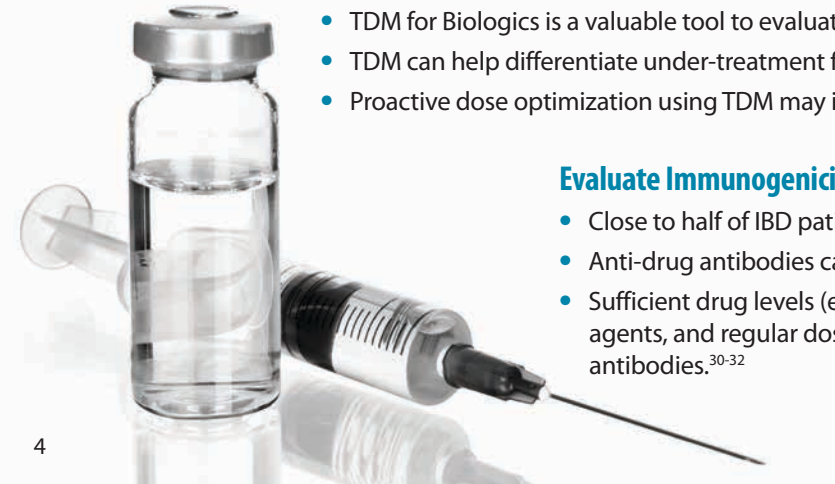
Biologics monitoring assays measure both drug concentration and anti-drug antibodies to support improved clinical outcomes and characterize those patients who may have diminished response to therapy.[21,29,15,27] *Dose*ASSURE™, LabCorp's portfolio of biologics monitoring assays, may help physicians optimize biological therapy using a personalized, patient-specific approach.

- All biologics have variable phamacokinteics and the potential to induce an antibody-mediated immune response[19,20]
- TDM helps optimize dosing and frequency of treatment[20-22]
- TDM assists in preventing and managing loss of response due to immunogenicity[23,24]
- TDM has been shown to be cost-effective and may direct more appropriate care.[20]

Biologic Drug Name	LabCorp Test	LabCorp Test No.	Proposed Target Trough Concentrations	Anti-Drug Antibodies Quantitative Range/Result Interpretation
Infliximab Remicade® Inflectra® Renflexis®	Infliximab and Anti-Infliximab Antibody (Serial Monitor), *Dose*ASSURE™ IFX	503870	3 – 7 µg/mL[20]; 5 -10 µg/mL[22]; >4.0 µg/mL for mucosal healing[25]; ≥10.0 µg/mL may be required for fistula healing[37]	22- 10,000+ng/mL Reported as Low, Intermediate, or High Titer
Adalimumab Humira®	Adalimumab and Anti-Adalimumab Antibody (Serial Monitor), *Dose*ASSURE™ ADL	503890	≥7.5 µg/mL[26] >5.85 µg/mL[27]	25-10,000+ ng/mL Reported as Low, Intermediate, or High Titer
Vedolizumab Entyvio®	Vedolizumab and Anti-Vedolizumab Antibody, *Dose*ASSURE™ VDZ	504567	>30 µg/mL at week 6[26] >14 µg/mL during maintenance[36]	25-10,000+ ng/mL Stratification into low to high titer has yet to be determined.
Golimumab Simponi®	Golimumab and Anti-Golimumab Antibody, *Dose*ASSURE™ GOL	504563	≥4.27 µg/mL correlated with greater response and remission[38]	20-10,000+ ng/mL Stratification into low to high titer has yet to be determined.
Ustekinumab Stelara®	Ustekinumab and Anti-Ustekinumab Antibody, *Dose*ASSURE™ UST	504594	>4.5 µg/mL has been associated with greater rate of endoscopic response[39]	40-10,000+ ng/mL Stratification into low to high titer has yet to be determined.
Certolizumab Cimzia®	Certolizumab and Anti-Certolizumab Antibody, *Dose*ASSURE™ CTZ	504627	≥20 µg/mL correlated to higher remission rate[26]	40-10,000+ ng/mL Stratification into low to high titer has yet to be determined.

Patient-specific clinical context must be taken into account when evaluating drug and anti-drug antibody. Serial measurements over time may be helpful.
NOTE: These target ranges were those used in landmark studies and do not necessarily translate into general recommendations for individual patients.

Trough collections are recommended in most cases.

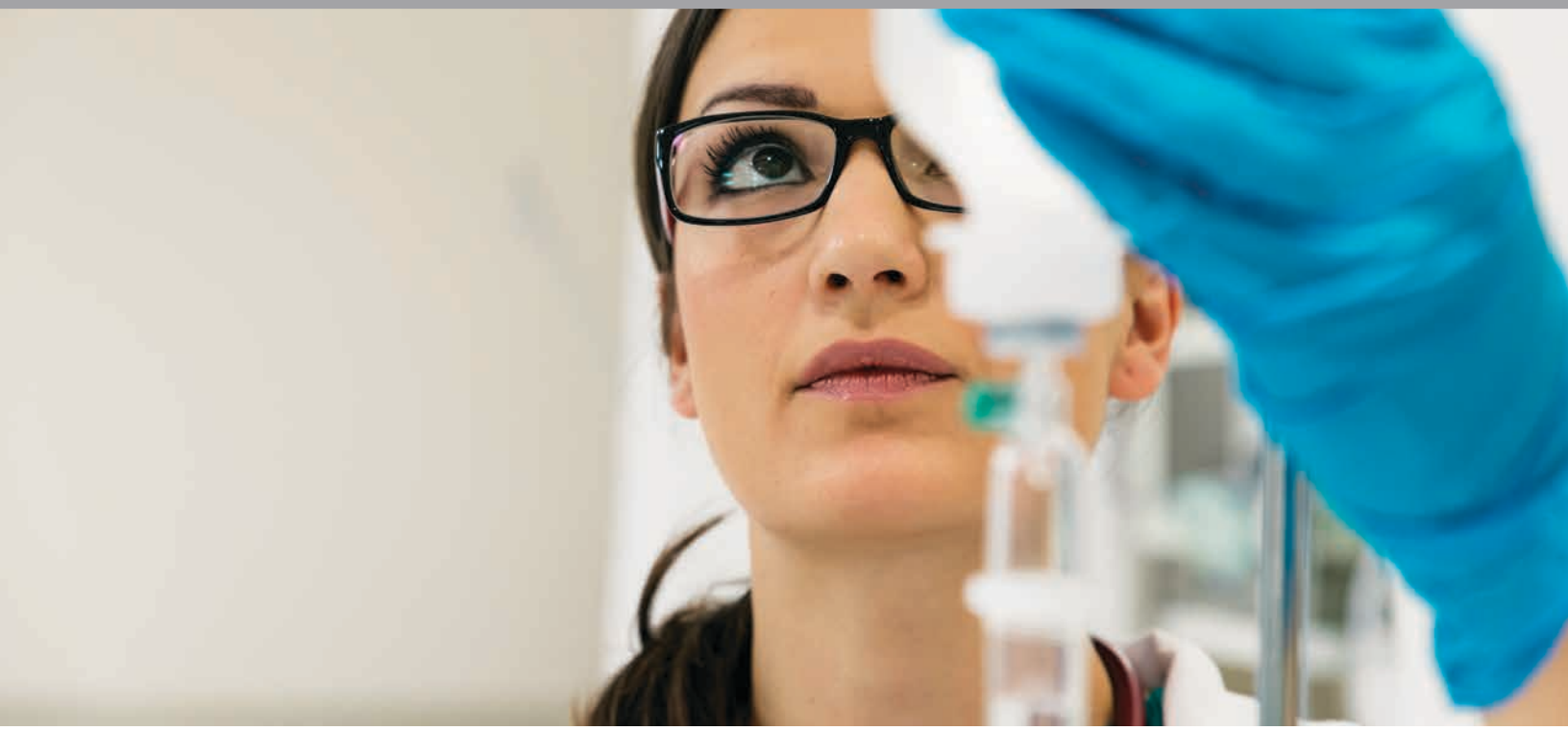


Optimize Biologics Drug Concentrations

- Dosing by weight and empiric dose adjustments are inefficient and suboptimal[19,20]
- TDM for Biologics is a valuable tool to evaluate doses and to tailor adjustments to your individual patient.[19,20]
- TDM can help differentiate under-treatment from other causes of lack of response.
- Proactive dose optimization using TDM may improve clinical scores and prolong duration of anti-TNF therapy.[21]

Evaluate Immunogenicity (Anti-drug Antibody level)

- Close to half of IBD patients on biologic therapy may develop anti-drug antibodies.[23,28,29]
- Anti-drug antibodies can adversely affect the amount of drug in the body.[28]
- Sufficient drug levels (e.g. infliximab >3µg/mL), concomitant use of immunomodulating agents, and regular dosing may protect against the risk of developing anti-drug antibodies.[30-32]



Monitoring Immunomodulators

Monitoring drug levels for Immunomodulators supports dosing decisions, assessing patient compliance, and determining effectiveness of treatment.

- Utilize during treatment to help reach and maintain therapeutic goal[33]
- Assists with evaluating unresponsive patients[33]
- Thiopurine drugs monitoring helps avoid potential toxicity in responsive patients[33]
- Approximately 30% – 40% of RA patients do not adequately respond to methotrexate treatment[34]

Drug Name	LabCorp Test	LabCorp Test No	Target Concentrations	
Purinethol® Azasan® Imuran® Tabloid®	Thiopurine Metabolites	503800	**6-TGN** **6-MMPN**	**Suboptimal dosing:** <235 pmol 6-TG/8x108 RBC **Optimal dosing:** 235-450 pmol 6-TG/8x108 RBC **Increasing risk for myelotoxicity and leukopenia:** >450 pmol 6-TGN/8x108 RBC **Hepatotoxicity risk:** >5700 pmol 6-MMP/8x108 RBC
Rasuvo® Rheumatrex® DosePack® Otrexup® Trexall®	Methotrexate Polyglutamates	504104		The minimal concentrations of MTX-polyglutamates associated with a significantly decreased disease activity score (DAS28) at three months were: – 20 nmol/L MTX-PG3 – 50 nmol/L Total-PGS (MTX-PG 1–5) 85% of patients having a significant reduction (-2) grades of their DAS did so prior to reaching a: – Total MTX-PG (1–5) of 150 nmol/L – MTX-PG2 of 22 nmol/L – MTX-PG3 of 60 nmol/L 15% of eventual responders required higher levels.

TPMT genetic and TPMT activity testing is additionally available to assess dosing prior to Thiopurine treatment, as well as to identify patients who may be at risk for drug toxicity.

IBD Diagnosis

A combination of clinical findings, endoscopic, histopathologic, radiologic, and laboratory testing is used to establish the diagnosis of IBD.

Diagnostic challenges arise when clinical presentation is indolent, invasive procedures are not obtainable, or results are inconclusive. Novel serological markers for IBD offer improved sensitivity and specificity to aid in differential diagnosis and provide valuable prognostic information about disease behavior.

IBD Expanded Diagnostic Profile (LabCorp Test No: 162045)

Testing includes five IBD specific antibody markers*

- gASCA *Antisaccharomyces cerevisiae* antibodies
- ACCA *Antichitobioside* carbohydrate antibodies
- ALCA *Antilaminaribioside* carbohydrate antibodies
- AMCA *Antimannobioside* carbohydrate antibodies

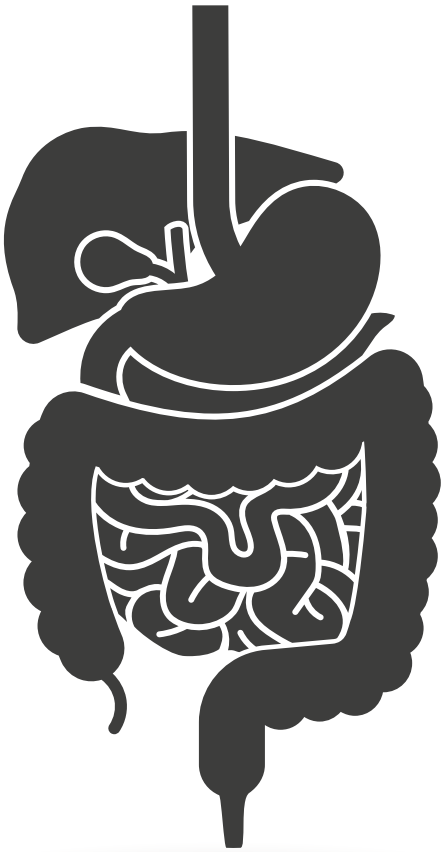
Anti-Glycan Antibodies → **Up to 97% specificity in differentiating UC from CD**[2,3]

Up to 85.5% sensitivity in identifying CD[4] **using multiple markers**

- Proprietary antibody testing utilizing IBDx technology
- Over a decade of scientific research demonstrating clinical value of Anti-Glycan Antibodies
- Stratifies into 3 prognostic levels of CD severity

pANCA Atypical perinuclear anti-neutrophil cytoplasmic antibodies → **Up to 70% sensitivity in identifying patients with UC**[5]

IBD Expanded Diagnostics Profile was developed to be both clinically appropriate and cost-effective for patients.



Overcome Diagnostic Challenges

The markers examined in LabCorp's IBD Expanded Diagnostic Profile may help clarify diagnosis and expedite therapeutic decisions.[2-7]

- Aid in the prompt recognition of IBD[6]
- Aid in differentiating between IBD and non-IBD[1] forms of colitis
- Assist in the differential diagnosis of UC vs CD in both adults and children[6]
- Assist in the evaluation of patients with indeterminate colitis or IBD unclassified[8,9]

Support Crohn's Disease Prognosis and Treatment Decisions

The markers examined in LabCorp's IBD Expanded Diagnostic profile have been shown to be highly specific predictors of aggressive disease behavior in Crohn's Disease.[2,3,6,10-17] Our profile may help physicians:

- Gain prognostic insight by identifying CD patients at risk for progression to complicated disease[2,3,6,10-17]
- Stratify patients into disease severity/phenotypic subtypes[2,3,6,10-17]
- Evaluate candidates for colectomy or IPAA and their post-surgical prognosis[9,18]

IBD Disease Activity

Non-invasive biomarkers may be useful in assessing and monitoring disease activity in Inflammatory Bowel Disease.

A meta-analysis of CRP, fecal calprotectin and stool lactoferrin yielded the pooled sensitivities and specificities, odds ratios, and positive and negative predictive values listed in the chart below.[35] Based on these findings, a negative fecal calprotectin in patients with symptoms consistent with IBD may rule out endoscopically active disease with a NPV of 86%. Conversely, a positive CRP result may rule in endoscopically active disease with a PPV of 86%.

Diagnostic Accuracy for Endoscopically Active Disease

Biomarker	LabCorp Test No	Optimum Cut-off	Sensitivity[35]	Specificity[35]	PPV*[35]	NPV*[35]
C-reactive Protein (CRP), quant.	006627	5.0 mg/L	0.49	0.92	0.86	0.64
Calprotectin, fecal	123255	50 µg/g	0.88	0.73	0.76	0.86
Lactoferrin, fecal quant.	123016	7.25 mg/L	0.82	0.79	0.80	0.82

*where average pre-test probabilities of endoscopically active disease are 50%.

IBD and Related Testing

Test No.	Test Name
503890	Adalimumab and Anti-Adalimumab Antibody (Serial Monitor), *Dose*ASSURE™ ADL
006627	C-Reactive Protein (CRP), Quantitative
123255	Calprotectin, Fecal
504627	Certolizumab and Anti-Certolizumab Antibody, *Dose*ASSURE™ CTZ
183988	Clostridium difficile Toxin Gene, NAA
005009	Complete Blood Count (CBC) With Differential
162020	Crohn's Prognostic Profile
504563	Golimumab and Anti-Golimumab Antibody, *Dose*ASSURE™ GOL
006510	Hepatitis B Surface Antigen
016881	Hepatitis B Core Antibody, IgM
162045	IBD Expanded Diagnostic Profile
503870	Infliximab and Anti-Infliximab Antibody (Serial Monitor), *Dose*ASSURE™ IFX
322000	Metabolic Panel (14), Comprehensive
504104	Methotrexate Polyglutamates
182873	QuantiFERON®-TB Gold
005215	Sedimentation Rate, Modified Westergren
008144	Stool Culture
503800	Thiopurine Metabolites
510750	Thiopurine Methyltransferase (TPMT), Enzyme Activity
504142	Thiopurine Methyltransferase (TPMT) Genotyping
504594	Ustekinumab and Anti-Ustekinumab Antibody, *Dose*ASSURE™ UST
504567	Vedolizumab and Anti-Vedolizumab Antibody, *Dose*ASSURE™ VDZ

References

1. Kappelman MD, Moore KR, Allen JK, Cook SF. Recent trends in the prevalence of Crohn's disease and ulcerative colitis in a commercially insured US population. *Dig Dis Sci.* 2013;58(2):519-525.
2. Dotan I, et al. Antibodies Against Laminaribioside and Chitobioside Are Novel Serologic Markers in Crohn's Disease. *Gastroenterol.* 2006;131:366-378.
3. Ferrante M, et al. New serological markers in inflammatory bowel disease are associated with complicated disease behavior. *Gut.* 2007;56:1394-13403.
4. Malickova K, et al. Anticarbohydrate antibodies as markers of inflammatory bowel disease in a Central European cohort. *Eur J Gastroenterol Hepatol.* 2010;22:144-150.
5. Quinton JF, et al. Anti-Saccharomyces cerevisiae mannan antibodies combined with antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease: prevalence and diagnostic role. *Gut.* 1998;42:788-791.
6. Bonneau J, et al. Systematic review: New serological markers (anti-glycan, anti-GP2, anti-GM-CSF Ab) in the prediction of IBD patient outcomes. *Autoimmunity Reviews.* 2015;14:231-245.
7. Linskens RK, et al. Evaluation of serological markers to differentiate between ulcerative colitis and Crohn's disease: pANCA, ASCA and agglutinating antibodies to anaerobic coccoid rods. *Eur J Gastroenterol Hepatol.* 2002;14(9):1013-8.
8. Joossens S, et al. The Value of Serologic Markers in Indeterminate Colitis: A Prospective Follow-Up Study. *Gastroenterol.* 2002;122:1242-1247.
9. Tremaine WJ. Diagnosis and Treatment of Indeterminate Colitis. *Gastroenterol Hepatol.* 2011;7(12):826-828
10. Papp M, et al. New Serological Markers for Inflammatory Bowel Disease Are Associated With Earlier Age at Onset, Complicated Disease Behavior, Risk for Surgery, and NOD2/CARD15 Genotype in a Hungarian IBD Cohort. *Am J Gastroenterol.* 2008;103:665-681.
11. Rieder F, et al. Clinical Utility of Anti-glycan Antibodies in Pediatric Crohn's Disease in Comparison with an Adult Cohort. *Inflamm Bowel Dis.* 2012;18:1221-1231.
12. Rieder F, et al. Association of the Novel Serologic Anti-glycan Antibodies Anti-laminarin and Anti-chitin with Complicated Crohn's Disease Behavior. *Inflamm Bowel Dis.* 2010;16:263-274.
13. Koutroubakis IE, et al. Antiglycan Antibodies in Greek Patients with Inflammatory Bowel Disease. *Dig Dis Sci.* 2010;56:845-852.
14. Simondi D, et al. Antiglycan Antibodies as Serological Markers in the Differential Diagnosis of Inflammatory Bowel Disease. *Inflamm Bowel Dis.* 2008;14:645-651.
15. Seow CH, et al. Novel Anti-Glycan Antibodies Related to Inflammatory Bowel Disease Diagnosis and Phenotype. *Am J Gastroenterol.* 2009;104:1426-1434.
16. Rieder F, et al. Serum Anti-Glycan Antibodies Predict Complicated Crohn's Disease Behavior: A Cohort Study. *Inflamm Bowel Dis.* 2010;16:1367-75.
17. Kaul A, et al. Serum Anti-glycan Antibody Biomarkers for Inflammatory Bowel Disease Diagnosis and Progression: A Systematic Review and Meta-analysis. *Inflamm Bowel Dis.* 2012;18(10):1872-1884.
18. Ferrante M, et al. Development of pouchitis following ileal pouch-anal anastomosis (IPAA) for ulcerative colitis: A role for serological markers and microbial pattern recognition receptor genes. *J Crohns Colitis.* 2008;2(2):142-151.
19. Vaughn BP, et al. Biologic Concentration Testing in Inflammatory Bowel Disease. *Inflamm Bowel Dis.* 2015;21:1435-4142.
20. Ordas, et al. Therapeutic Drug Monitoring of Tumor Necrosis Factor Antagonists in Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol.* 2012;10:1079-1087.
21. Vande Casteele N, et al. Trough Concentrations of Infliximab Guide Dosing for Patients With Inflammatory Bowel Disease. *Gastroenter.* 2015;148:1320-1329.
22. Vaughn BP, 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.
23. Ungar B, et al. The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab. *Gut.* 2014;63:1258-1264.
24. American Gastroenterological Association. Guidelines for the Identification, Assessment and Initial Medical Treatment in Crohn's Disease. https://www.gastro.org/IBDcarepathway
25. Imaeda H, et al. Relationship between serum infliximab trough levels and endoscopic activities in patients with Crohn's disease under scheduled maintenance treatment. *Am J Gastroenterol.* 2014; 49:674-682.
26. Vande Casteele N, et al. American Gastroenterological Association Institute Technical Review on the Role of Therapeutic Drug Monitoring in the Management of Inflammatory Bowel Diseases. *Gastroenterol.* 2017;153:835–857.
27. Mazor Y, 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.
28. Steenholdt C, et al. Clinical Implications of Variations in Anti-infliximab Antibody Levels in Patients with Inflammatory Bowel Disease. *Inflamm Bowel Dis.* 2012 Vol 18(12):2209-2217
29. Vande Casteele N, et al. Antibody Response to Infliximab and its Impact on Pharmacokinetics can be Transient. *Am J Gastroenterol.* 2013;108:962-971.
30. Colombel JR et al. Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease. *N Engl J Med.* 2010 362(15):1383-1395.
31. Brandse JR, et al. Insufficient Infliximab Exposure Predisposes to Immunogenicity and Enhanced Clearnace of Infliximab in IBD. *J Crohns Colitis.* 2016; 150(4 suppl 1): S144
32. Hanauer SB, et al. Incidence and Importance of Antibody Responses to Infliximab After Maintenance or Episodic Treatment in Crohn's Disease. *Clin Gastroenterol Hepatol.* 2004; 2:542-553
33. Chevaux, JB, Peyrin-Biroulet L, Sparrow MP. *Inflamm Bowel Dis.* 2011 Jun 17 (^): 1428-1435.
34. denBroeder AA, et al. Dose de-escalation strategies and role of therapeutic drug monitoring of biologics in RA. *Rheumatol.* 2010; 49:1801-1803.
35. Mosli MH, et al. C-Reactive Protein, Fecal Calprotectin, and Stool Lactoferrin for Detection of Endoscopic Activity in Symptomatic Inflammatory Bowel Disease Patients: A Systematic Review and Meta-Analysis. *Am J Gastroenterol.* 2015;110(6):802-819.
36. Dreesen E, et al. Evidence to Support Monitoring of Vedolizumab Trough Concentrations in Patients With Inflammatory Bowel Diseases. *Clin Gastroenterol Hepatol.* 16(12):1937-46.
37. Yarur A, et al. Higher Infliximab Trough Levels Are Associated With a Higher Rate of Perianal Fistula Healing in Patients With Crohn's Disease. *Gastroenterol.* 2016;150(4):S105-S106.
38. Sandborn WJ, et al. Subcutaneous Golimumab Induces Clinical Response and Remission in Patients with Moderate-to-Severe Ulcerative Colitis. *Gastroenterol.* 2014;20:S1-S3.38.
39. Battat R, et al. Association Between Ustekinumab Trough Concentrations and Clinical, Biomarker, and Endoscopic Outcomes in Patients With Crohn's Disease. *Clin Gastroenterol Hepatol.* 2017;15:1427–1434.

LabCorp

www.LabCorp.com

If you have any questions, please contact your local LabCorp representative at **888-522-2677**, or visit **www. LabCorp.com**.