LABCORP DIAGNOSTICS

Inflammatory Bowel Disease

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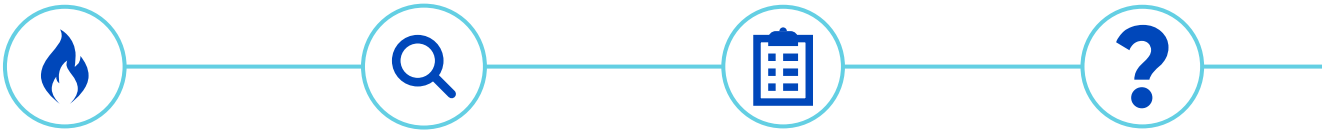
Labcorp's IBD test offerings support complete care decisions

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.



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.

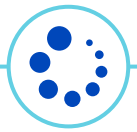
- Expansive network of managed care health plans
- More than 2,000 patient service centers located nationwide
- Integrations with more than 700 EMR/EHRs, PWS and HIE systems
- PhD and MD level client consultation
- Specialized service offerings for IBD, HCV, Celiac Disease and Pathology

PRE-TREATMENT TESTING

→ CBC, Metabolic Panel; Pre-Biologic Screening Profile; Hepatitis C Virus (HCV) Antibody Cascade to Quantitative PCR and Genotyping; Hepatitis B Surface Antigen (HBsAg) Screen, Qualitative; Hepatitis B Surface Antibody, Quantitative: Hepatitis B Core Antibody with Reflex; QuantiFERON®-TB Gold Plus; HLA-DQA1*05

→ CBC, TPMT Enzyme Activity, and/or *TPMT* and *NUDT15* Genotyping

→ CBC
Metabolic Panel



DISEASE ACTIVITY

C-Reactive Protein
Stool Lactoferin
Calprotectin, Fecal

TREATMENT MONITORING

Thiopurine Metabolites

MTX Polyglutamates

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

TREATMENT MANAGEMENT

Adjust dosing and frequency

Identify high and low immunogenicity

Consider co-therapy

Switch Treatment

Responder
Monitor progress
Adjust dosing if indicated

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—DoseASSURE™ Portfolio

Biologic therapeutic drug monitoring (TDM) consists of tandem assays measuring drug and anti-drug antibody concentrations to support improved clinical outcomes and help identify the underlying mechanism of diminished response to therapy.[2-5] *Dose*ASSURE™, Labcorp's portfolio of biologic monitoring assays, may help physicians optimize biological therapy using a personalized, patient-specific approach.

- All biologics have variable pharmacokinetics and the potential to induce an antibody-mediated immune response[6,7]
- TDM helps optimize dosing and frequency of treatment[7,8]
- TDM assists in preventing and managing loss of response due to immunogenicity[9,10]
- TDM can elucidate poor response as due to undertreatment (pharmacokinetic), mechanistic mismatch (pharmacodynamic) or development of anti-drug antibodies (immunogenic)

Biologic Drug Name	Labcorp Test Name	Test No.	Proposed Target Trough Concentrations	Anti-Drug Antibodies Quantitative Range/Result Interpretation
Infliximab Remicade® Avsola™ Renflexis®	Infliximab and Anti-Infliximab Antibody, *Dose*ASSURE™ IFX	**503870**	3 – 7 µg/mL[7]; 5 -10 µg/mL[8]; >4.0 µg/mL for mucosal healing[11] ; ≥10.0 µg/mL may be required for fistula healing[12]	22-10,000+ng/mL Reported as Low, Intermediate, or High Titer
Adalimumab Humira®	Adalimumab and Anti-Adalimumab Antibody, *Dose*ASSURE™ ADL	**503890**	≥7.5 µg/mL[13] >5.85 µg/mL[4]	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[13] >14 µg/mL during maintenance[14]	25-10,000+ 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[15]	40-10,000+ 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[16]	20-10,000+ 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[13]	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[6,7]
- TDM for Biologics is a valuable tool to evaluate doses and to tailor adjustments to your individual patient[6,7]
- 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[3]

Evaluate Immunogenicity (Anti-drug Antibody level)

- Close to half of IBD patients on biologic therapy may develop anti-drug antibodies[5,9,17]
- Anti-drug antibodies can adversely affect the amount of drug in the body[17]
- 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[18-20]

HLA-DQA1*05 Variant Associated with Immunogenicity Risk for IFX/ADL Antibodies [167680]

- HLA-DQA1*05 genotype is associated with a 75% higher risk of anti-infliximab or anti-adalimumab antibodies and a 67% risk of loss of response compared to non-carriers[21]
- Informs treatment decisions when immunomodulators may pose a risk for adverse events or there is consideration to de-escalate combination therapy
- Aids in ruling out the risk of immunogenicity

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[22]
- Assists with evaluating unresponsive patients[22]
- Thiopurine drug monitoring helps avoid potential toxicity in responsive patients[22]
- Approximately 30% – 40% of RA patients do not adequately respond to methotrexate treatment[23]

Drug Name	Labcorp Test	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**		Total MTX PG is the sum of Methotrexate PG1 through PG5. Total MTX PG greater than 74 nmol/L at 3 months is consistent with therapeutic efficacy.[24] MTX PG1 is the unmodified/native circulating parent drug. MTX PG2 and long-chain MTX polyglutamates (MTX PG3, MTX PG4, MTX PG5) are formed and retained intracellularly.[24] Clinical response may be mediated by long-chain MTX PGs.[25]

TPMT genetic and TPMT enzyme activity testing are available prior to Thiopurine treatment to identify patients who may be at risk for drug toxicity and to determine patient-specific dosing.

IBD Diagnosis

A combination of clinical findings and 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 → **Up to 97% specificity in differentiating ulcerative colitis (UC) from Crohn's disease (CD)[26,27]**

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

Anti-Glycan Antibodies →

Up to 85.5% sensitivity in identifying CD[28]

- Proprietary antibody testing utilizing IBDx technology (provided by Glycominds)
- 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[29]**

Overcome Diagnostic Challenges

The markers examined in Labcorp's IBD Expanded Diagnostic Profile may help clarify diagnosis and expedite therapeutic decisions.[26-31]

- Aid in the prompt recognition of IBD[30]
- 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[30]
- Assist in the evaluation of patients with indeterminate colitis or IBD unclassified[32,33]

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.[2,26,27,30,34-40] Our profile may help physicians:

- Gain prognostic insight by identifying CD patients at risk for progression to complicated disease[2,26,27,30,34-40]
- Stratify patients into disease severity/phenotypic subtypes[2,26,27,30,34-40]
- Evaluate candidates for colectomy or IPAA and their post-surgical prognosis[33,41]

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

IBD Disease Activity

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

A meta-analysis of C-Reactive Protein (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.[42] 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	Test No.	Optimum Cut-off	Sensitivity[42]	Specificity[42]	PPV*[42]	NPV*[42]
C-Reactive Protein (CRP), Quantitative	**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, Quantitative	**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 Name	Test No.
Adalimumab and Anti-Adalimumab Antibody, *Dose*ASSURE™ ADL	**503890**
C-Reactive Protein (CRP), Quantitative	**006627**
Calprotectin, Fecal	**123255**
Certolizumab and Anti-Certolizumab Antibody, *Dose*ASSURE™ CTZ	**504627**
Clostridioides difficile Toxin Gene, NAA	**183988**
Complete Blood Count (CBC) With Differential	**005009**
Crohn's Prognostic Profile	**162020**
Golimumab and Anti-Golimumab Antibody, *Dose*ASSURE™ GOL	**504563**
Hepatitis B Surface Antigen	**006510**
Hepatitis B Core Antibody, IgM	**016881**
HLA-DQA1*05 Variant Associated With Immunogenicity Risk for IFX/ADL Antibodies	**167680**
Inflammatory Bowel Disease (IBD) Expanded Profile	**162045**

Test Name	Test No.
Infliximab and Anti-Infliximab Antibody, *Dose*ASSURE™ IFX	**503870**
Lactoferrin, Fecal, Quantitative	**123016**
Metabolic Panel (14), Comprehensive	**322000**
Methotrexate Polyglutamates	**504104**
Pre-Biologic Screening Profile	**144441**
QuantiFERON®-TB Gold Plus	**182879**
Sedimentation Rate, Modified Westergren	**005215**
Stool Culture	**008144**
Thiopurine Metabolites	**503800**
Thiopurine Methyltransferase (TPMT), Enzyme Activity, Erythrocytes	**510750**
TPMT and *NUDT15* Genotyping	**512300**
Ustekinumab and Anti-Ustekinumab Antibody, *Dose*ASSURE™ UST	**504594**
Vedolizumab and Anti-Vedolizumab Antibody, *Dose*ASSURE™ VDZ	**504567**

References

1. Kappelman MD, et al. 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. Seow CH, et al. Novel Anti-Glycan Antibodies Related to Inflammatory Bowel Disease Diagnosis and Phenotype. Am J Gastroenterol. 2009;104:1426-1434.
3. Vande Casteele N, et al. Trough Concentrations of Infliximab Guide Dosing for Patients With Inflammatory Bowel Disease. Gastroenter. 2015;148:1320-1329.
4. 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.
5. Vande Casteele N, et al. Antibody Response to Infliximab and its Impact on Pharmacokinetics can be Transient. Am J Gastroenterol. 2013;108:962-971.
6. Vaughn BP, et al. Biologic Concentration Testing in Inflammatory Bowel Disease. Inflamm Bowel Dis. 2015;21:1435-4142.
7. Ordas, et al. Therapeutic Drug Monitoring of Tumor Necrosis Factor Antagonists in Inflammatory Bowel Disease. Clin Gastroenterol Hepatol. 2012;10:1079-1087.
8. 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.
9. Ungar B, et al. The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab. Gut. 2014;63:1258-1264.
10. American Gastroenterological Association. Guidelines for the Identification, Assessment and Initial Medical Treatment in Crohn's Disease. https://www.gastro.org/IBDcarepathway
11. 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.
12. 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.
13. 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.
14. 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
15. 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.
16. 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.
17. 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
18. Colombel JR et al. Infliximab, Azathioprine, or Combination Therapy for Crohn's Disease. N Engl J Med. 2010 362(15):1383-1395.
19. 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
20. 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
21. Solitano V, et al. HLA-DQA1 05 Genotype and immunogenicity to tumor necrosis factor-A antagonists: A systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2023;21(12):3019-3029.e5. doi:10.1016/j.cgh.2023.03.044
22. Chevaux JB, et al. Optimizing thiopurine therapy in inflammatory bowel disease. Inflamm Bowel Dis. 2011 Jun 17 (^): 1428-1435.
23. denBroeder AA, et al. Dose de-escalation strategies and role of therapeutic drug monitoring of biologics in RA. Rheumatol. 2010; 49:1801-1803
24. de Rotte MCFJ, et al. Methotrexate polyglutamates in erythrocytes are associated with lower disease activity in patients with rheumatoid arthritis. Ann Rheum Dis. 2015 Feb;74(2):408-414.
25. Danila MI, et al. Measurement of erythrocyte methotrexate polyglutamate levels: Ready for clinical use in rheumatoid arthritis? Curr Rheumatol Rep. 2010 Oct;12(5):342-347.
26. Dotan I, et al. Antibodies Against Laminaribioside and Chitobioside Are Novel Serologic Markers in Crohn's Disease. Gastroenterol. 2006;131:366-378.
27. Ferrante M, et al. New serological markers in inflammatory bowel disease are associated with complicated disease behavior. Gut. 2007;56:1394-13403.
28. 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.
29. 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.
30. 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.
31. 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.
32. Joossens S, et al. The Value of Serologic Markers in Indeterminate Colitis: A Prospective Follow-Up Study. Gastroenterol. 2002;122:1242-1247.
33. Tremaine WJ. Diagnosis and Treatment of Indeterminate Colitis. Gastroenterol Hepatol. 2011;7(12):826-828
34. 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.
35. 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.
36. 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.
37. Koutroubakis IE, et al. Antiglycan Antibodies in Greek Patients with Inflammatory Bowel Disease. Dig Dis Sci. 2010;56:845-852.
38. Simondi D, et al. Antiglycan Antibodies as Serological Markers in the Differential Diagnosis of Inflammatory Bowel Disease. Inflamm Bowel Dis. 2008;14:645-651.
39. Rieder F, et al. Serum Anti-Glycan Antibodies Predict Complicated Crohn's Disease Behavior:A Cohort Study. Inflamm Bowel Dis. 2010;16:1367-75.
40. 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.
41. 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.
42. 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.

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