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MEDICAL POLICY – 2.04.516

Measurement of Serum Antibodies to Selected Biologic Agents

BCBSA Ref. Policy:	2.04.84	
Effective Date:	Feb. 1, 2024	RELATED MEDICAL POLICIES:
Last Revised:	Jan. 9, 2024	None
Replaces:	2.04.84	

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

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Introduction

Antibodies are a specific type of protein. They are made by the body's immune system. Antibodies help fight germs and other substances inside the body that the immune system sees as harmful. The immune system custom-creates each type of antibody to fight what it sees as invading and destructive things. However, the body can also make antibodies to fight drugs that are intended to treat specific diseases. Blood tests have been developed that try to look at whether a person's body has developed antibodies to the drugs Remicade (infliximab), Humira (adalimumab), Entyvio (vedolizumab), and Stelara (ustekinumab). These blood tests are investigational (unproven). Medical studies so far have not shown that changes in treatment based on the results of these blood tests have improved health results. More and larger studies are needed to show if and how well these types of blood tests work.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Service	Investigational
Measurement of antidrug antibodies and serum tumor necrosis factor blocking agent levels (trough levels)	**Measurement of antidrug antibodies in an individual receiving treatment with a biologic agent*, either alone or as a combination test, which includes the measurement of serum tumor necrosis factor (TNF) blocking agent** levels (trough levels), is considered investigational.** **Note**: *Currently FDA approved biologic agents include infliximab, adalimumab, vedolizumab, and ustekinumab. ** Currently FDA approved tumor necrosis factor blocking agents include infliximab, adalimumab, etanercept, golimumab and certolizumab pegol.
Precision-guided dosing	**Precision-guided dosing testing for optimization of infliximab, adalimumab, and their biosimilars is considered investigational, including but not limited to PredictrPK.**

Coding

According to materials from Prometheus Laboratories on AnserIFX, AnserADA, Anser VDZ, and Anser UST these tests will be reported using 1 unit of either of the following CPT codes:

Code	Description
CPT	
80145	Adalimumab (Humira)
80230	Infliximab (Remicade)
80280	Vedolizumab (Entyvio)
82397	Chemiluminescent assay
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified

Code	Description
80299	Quantitation of therapeutic drug, not elsewhere specified
84999	Unlisted Chemistry Procedure (used to report PredictrPK precision-guided dosing)

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

N/A

Evidence Review

Description

Biologic agents used to treat autoimmune diseases include infliximab, adalimumab, vedolizumab, and ustekinumab. Infliximab (Remicade) is an intravenous tumor necrosis factor α blocking agent approved by the US Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, Crohn disease, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and ulcerative colitis. Adalimumab (Humira) is a subcutaneous tumor necrosis factor α inhibitor that is FDA approved for the treatment of rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, plaque psoriasis, psoriatic arthritis in adults and those with juvenile idiopathic arthritis, hidradenitis suppurativa, and uveitis. Vedolizumab (Entyvio) is an intravenous integrin receptor antagonist that is FDA approved for treatment of ulcerative colitis and Crohn's disease in adults. Ustekinumab (Stelara) is an intravenous and subcutaneous human interleukin-12 and -23 antagonist that is FDA-approved for the treatment of Crohn disease and ulcerative colitis in adults, and psoriatic arthritis and plaque psoriasis in children and adults. Following the primary response to these medications, some individuals become secondary nonresponders. The development of antidrug antibodies (ADA) is considered a cause of this secondary nonresponse.

Background

Infliximab Adalimumab, Vedolizumab, and Ustekinumab in Autoimmune Diseases

Biologic agents (e.g., infliximab, adalimumab, vedolizumab, or ustekinumab) are used to treat multiple inflammatory conditions, including rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis; inflammatory bowel disease (e.g., Crohn disease, ulcerative colitis), ankylosing spondylitis, and plaque psoriasis. These agents are generally given to individuals who fail conventional medical therapy, and they are typically highly effective for the induction and maintenance of clinical remission. However, not all individuals respond, and a high proportion of individuals lose response over time. It is estimated that 1 in 3 individuals do not respond to induction therapy (primary nonresponse); further, among initial responders, response wanes over time in approximately 20% to 60% of individuals (secondary nonresponse). The reasons for therapeutic failures remain a matter of debate but include accelerated drug clearance (pharmacokinetics) and neutralizing agent activity (pharmacodynamics) due to antidrug antibodies (ADA).[1] ADA are also associated with injection-site reactions and acute infusion reactions and delayed hypersensitivity reactions.

Detection of Antidrug Antibodies

The detection and quantitative measurement of ADA is difficult, owing to drug interference and identifying when antibodies likely have a neutralizing effect. First-generation assays, (i.e., enzyme-linked immunosorbent assays [ELISA]) can measure only ADA in the absence of detectable drug levels, due to the interference of the drug with the assay. Other techniques available for measuring antibodies include the radioimmunoassay method, and more recently, the homogenous mobility shift assay using high-performance liquid chromatography. Disadvantages of the radioimmunoassay method are associated with the complexity of the test and prolonged incubation time, along with safety concerns related to the handling of radioactive material. The homogenous mobility shift assay measures ADA when infliximab is present in serum. Studies evaluating the validation of results among different assays are lacking, making interstudy comparisons difficult. One retrospective study by Kopylov et al (2012), which evaluated 63 individuals, demonstrated comparable diagnostic accuracy between 2 different ELISA methods in individuals with inflammatory bowel disease (i.e., double-antigen ELISA and antihuman lambda chain-based ELISA.)[2] This study did not include an objective clinical and endoscopic scoring system for validation of results.

Treatment Options for Secondary Nonresponse to Biologic Agents

A diminished or suboptimal response to infliximab, adalimumab, vedolizumab or ustekinumab can be managed in several ways: shortening the interval between doses, increasing the dose, switching to a different biologic agent (in individuals who continue to have a loss of response after receiving the increased dose), or switching to a non-biologic agent.

PredictrPK

PredictrPK IFX or ADA are tests that hels healthcare providers with biologic dose optimization by using individualized pharmacokinetic modeling. According to the Prometheus site, "PredictrPK IFX combines serology markers, patient-specific variables, current dosing information, and a proprietary machine-learning algorithm to provide individualized actionable insights to optimize the dose and interval for inflammatory bowel disease (IBD) patients treated with infliximab (IFX) or IFX biosimilars"

Summary of Evidence

For individuals who have rheumatoid arthritis, psoriatic arthritis, or juvenile idiopathic arthritis; inflammatory bowel disease (e.g., Crohn disease, ulcerative colitis); ankylosing spondylitis; or plaque psoriasis who receive evaluation for serum antibodies to infliximab, adalimumab, vedolizumab, or ustekinumab, the evidence includes multiple systematic reviews, randomized controlled trials, and observational studies. Relevant outcomes are test validity, change in disease status, health status measures, quality of life, and treatment-related morbidity. Antibodies to biologic agents develop in a substantial proportion of treated individuals and are believed to neutralize or enhance clearance of the drugs. Considerable evidence has demonstrated an association between ADA and secondary nonresponse as well as injection-site and infusion-site reactions. The clinical usefulness of measuring ADA hinges on whether test results inform management changes, thereby leading to improved outcomes, compared with management directed by symptoms, clinical assessment, and standard laboratory evaluation. Limited evidence has described management changes after measuring ADA. A randomized controlled trial did not find a difference in relapse rates with therapeutic drug monitoring of inflximab using trough levels and antidrug antibodies compared to standard therapy without monitoring these levels. A small randomized controlled trial in individuals with Crohn disease

and other inflammatory diseases comparing antidrug antibody-informed management of relapse with standard dose escalation did not demonstrate improved outcomes with the antidrug antibody-informed approach. Additionally, many assays—some having significant limitations, have been used in studies; ADA threshold values that are informative for discriminating treatment responses have not been established. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

A search of **ClinicalTrials.gov** in September 2023 did not identify any ongoing or unpublished trials that would likely influence this review.

Practice Guidelines and Position Statements

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

Guidelines or position statements will be considered for inclusion if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Gastroenterology

In 2019, the American College of Gastroenterology published a guideline on ulcerative colitis (UC).[30] The guideline stated: "In patients with moderately to severely active UC who are responders to anti-TNF [tumor necrosis factor] therapy and now losing response, we suggest measuring serum drug levels and antibodies (if there is not a therapeutic level) to assess the reason for loss of response (conditional recommendation, very low quality of evidence)."

In 2018, the American College of Gastroenterology published a guideline on Crohn disease (CD).[31] Although acknowledging that a detailed review of therapeutic drug monitoring was beyond the scope of the guideline, it stated: "If active CD is documented, then assessment of biologic drug levels and antidrug antibodies (therapeutic drug monitoring) should be considered."

American Gastroenterology Association Institute

In 2017, the American Gastroenterology Association Institute published guidelines on therapeutic drug monitoring in inflammatory bowel disease (IBD).[32] The guidelines note that:

> "In the presence of sufficient trough concentrations, results of antibody testing should not guide treatment decisions. If the trough concentration is low (below the suggested threshold, in patients with active IBD) and no anti-drug antibodies are present, then the index drug should be optimized using any of the following techniques: shortening the dosing interval and/or increasing the drug dose, and/or adding an immunomodulator agent. If there is no detectable drug (zero trough concentration) and high-titer anti-drug antibodies are present, then the patient should consider switching to a different drug within the class or to a different drug class. If there is no detectable drug and low-titer antibodies are present, then one can consider trying to optimize the index drug by shortening the dosing interval and/or increasing the drug dose, and/or adding an immunomodulator agent. Typically, optimizing the drug will be attempted before changing to a different drug within the class or switching to a new drug class, although some might opt to change to a different drug within the class or switch to a new drug class. It should be noted that the reporting of anti-drug antibodies is variable between commercial assays, with some assays being very sensitive for detecting very-low-titer antibodies of limited clinical significance. Uniform thresholds for clinically relevant antibody titers are lacking. At this time, it is unclear how antibodies affect drug efficacy when both active drug and antibodies are detected. In cases of low trough concentrations and low or high anti-drug antibodies, the evidence to clarify optimal management is lacking."

The guidelines did not address therapeutic drug monitoring in individuals treated with vedolizumab or ustekinumab.

National Institute for Health and Care Excellence

In 2016, the National Institute for Health and Care Excellence (NICE) issued guidance on therapeutic monitoring of tumor necrosis factor (TNF) α inhibitors in the treatment of individuals with Crohn disease.[33] The Institute recommended that laboratories monitoring TNF-α inhibitors in individuals with Crohn disease who have lost response to the treatment should "work with clinicians to collect data through a prospective study, for local audit, or for submission to an existing registry."

In 2019, the NICE issued guidance on therapeutic monitoring of TNF-α inhibitors in the treatment of individuals with rheumatoid arthritis.[34] The Institute stated: "Enzyme-linked immunosorbent assay (ELISA) tests for therapeutic monitoring of tumour necrosis factor (TNF)-alpha inhibitors (drug serum levels and antidrug antibodies) show promise but there is currently insufficient evidence to recommend their routine adoption in rheumatoid arthritis." It also recommended that "laboratories currently using ELISA tests for therapeutic monitoring of TNF-alpha inhibitors in rheumatoid arthritis should do so as part of research and further data collection."

Medicare National Coverage

There is no national coverage determination.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

Prometheus Laboratories, a College of American Pathologists-accredited lab under the Clinical Laboratory Improvement Amendments, offers four non-radio-labeled, fluid-phase homogenous mobility shift assay tests called AnserIFX (for infliximab), AnserADA (for adalimumab), AnserVDZ for vedolizumab, and AnserUST (for ustekinumab). The tests measure both serum drug concentrations and ADA. They are not based on an ELISA test and can measure ADA in the presence of detectable drug levels, improving on a major limitation of the ELISA method.

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History

Date	Comments
10/09/12	New Policy (2.04.84 Measurement of Serum Antibodies to Infliximab, Adalimumab, and Vedolizumab). Measurement of antibodies to infliximab, either alone or as a

Date	Comments
	combination test which includes the measurement of serum infliximab levels, is considered investigational.
11/11/13	Replace Policy. Policy reviewed with literature search through July 2013; references 2, 6-12 added. Title changed to add "…and Adalimumab." "Measurement of antibodies to adalimumab in a patient receiving adalimumab, either alone or as a combination test which includes the measurement of serum adalimumab levels" added to the policy statement; considered investigational. Brand names added to policy for clarity.
12/17/14	Annual Review. Brand and generic drug names moved to a table in the Policy Guidelines section. Policy updated with literature review through September 10, 2014. References 4-5, 15-18, 22, 25-30 added. Policy statements unchanged.
12/08/15	Annual Review. Policy updated with literature review through September 30, 2015; references 1, 7-8, 12-18, and 30-32 added. Policy statements unchanged, although section titles added.
12/01/16	Annual Review, approved November 8, 2016. Policy updated with literature review through September 2016. Policy statement unchanged.
02/01/17	Annual Review, approved January 10, 2017. Policy updated with literature review through November 3, 2016; references 4 and 33 added. Policy statements unchanged.
11/10/17	Policy moved to new format; no changes to policy statement.
02/01/18	Annual Review, approved January 16, 2018. Policy updated with literature review through September 2017; references 14, 21-23, and 38-42 added. Added criteria to policy statement for vedolizumab test Anser VDZ as investigational.
02/01/19	Policy renumbered from 2.04.84 to 2.04.516, approved January 4, 2019. This policy replaces policy 2.04.84. Policy created with literature review through September 2018. Measurement of antibodies to infliximab, adalimumab, vedolizumab, and ustekinumab is considered investigational.
04/01/19	Interim Review, approved March 12, 2019. Reference 36 added. Added criteria to policy statement for ustekinumab test, Anser UST as investigational. Title changed from "Measurement of Serum Antibodies to Infliximab, Adalimumab, and Vedolizumab" to "Measurement of Serum Antibodies to Infliximab, Adalimumab, Vedolizumab, and Ustekinumab". History section updated.
10/04/19	Coding update, added CPT code 80299.
01/01/20	Coding update, added CPT codes 80145, 80230, and 80280 (new codes effective 1/1/20).
02/01/20	Annual Review, approved January 9, 2020. Policy updated with literature review through November 2019; no references added. Policy title changed to "Measurement of Serum Antibodies to Selected Biologic Agents" from" Measurement of Serum Antibodies to Infliximab, Adalimumab, Vedolizumab, and Ustekinumab." Policy statement unchanged.

Date	Comments
02/01/21	Annual Review, approved January 6, 2021. Policy updated with literature review through October 13, 2020; no references added. Minor edits to policy statements for greater clarity. Added CPT codes 82397 and 83520 for reference when billed with specific antibody CPT codes.
02/01/22	Annual Review, approved January 10, 2022. Policy updated with literature review through October 5, 2021; references added. Policy statement unchanged.
08/17/22	Minor update to history section. Added previous history from policy 2.04.84 Measurement of Serum Antibodies to Infliximab, Adalimumab, and Vedolizumab.
02/01/23	Annual Review, approved January 9, 2023. Policy updated with literature review through September 12, 2022; no references added. Minor editorial refinements to policy statements; intent unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.
02/01/24	Annual Review, approved January 9, 2024. Policy updated with literature review through September 27, 2023; Reference added. Modified policy statements for each biologic agent to a more general all-encompassing policy statement, " Measurement of antidrug antibodies in an individual receiving treatment with a biologic agent (e.g., infliximab, adalimumab, vedolizumab, or ustekinumab), either alone or as a combination test, which includes the measurement of serum tumor necrosis factor (TNF) blocking agent (e.g., infliximab, adalimumab, etanercept, golimumab and certolizumab pegol) levels (trough levels), is considered investigational. Policy intent unchanged. Added policy statement that precision-guided dosing testing for optimization of infliximab, adalimumab, and their biosimilars is considered investigational.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

Discrimination is Against the Law

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Washington residents: You can also file a civil rights complaint with the Washington State Office of the Insurance Commissioner, electronically through the Office of the Insurance Commissioner Complaint Portal available at https://www.insurance.wa.gov/file-complaint-or-check-your-complaint-status, or by phone at 800-562-6900, 360-586-0241 (TDD). Complaint forms are available at https://fortress.wa.gov/oic/onlineservices/cc/pub/complaintinformation.aspx.

Alaska residents: Contact the Alaska Division of Insurance via email at insurance@alaska.gov, or by phone at 907-269-7900 or 1-800-INSURAK (in-state, outside Anchorage).

Language Assistance

ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 800-722-1471 (TTY: 711).

PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nang walang bayad. Tumawag sa 800-722-1471 (TTY: 711).

注意：如果您使用繁體中文，您可以免費獲得語言援助服務。請致電 800-722-1471 (TTY：711）。

CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 800-722-1471 (TTY: 711).

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ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода. Звоните 800-722-1471 (телетайп: 711).

LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 800-722-1471 (TTY: 711).

MO LOU SILAFIA: Afai e te tautala Gagana fa'a Sāmoa, o loo iai auaunaga fesoasoan, e fai fua e leai se totogi, mo oe, Telefoni mai: 800-722-1471 (TTY: 711).

ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ, ໂດຍບໍ່ເສັຽຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 800-722-1471 (TTY: 711).

注意事項：日本語を話される場合、無料の言語支援をご利用いただけます。800-722-1471 （TTY:711）まで、お電話にてご連絡ください。

PAKDAAR: Nu saritaem ti Ilocano, ti serbisyo para ti baddang ti lengguahe nga awanan bayadna, ket sidadaan para kenyam. Awagan ti 800-722-1471 (TTY: 711).

УВАГА! Якщо ви розмовляєте українською мовою, ви можете звернутися до безкоштовної служби мовної підтримки. Телефонуйте за номером 800-722-1471 (телетайп: 711).

ប្រយ័ត្ន៖ បើសិនជាអ្នកនិយាយ ភាសាខ្មែរ, សេវាជំនួយផ្នែកភាសា ដោយមិនគិតឈ្នួល គឺអាចមានសំរាប់បំរើអ្នក។ ចូរ ទូរស័ព្ទ 800-722-1471 (TTY: 711)។

ማስታወሻ: የሚናገሩት ቋንቋ ኣማርኛ ከሆነ የትርጉም እርዳታ ድርጅቶች፣ በነጻ ሊያግዝዎት ተዘጋጀተዋል፡ ወደ ሚከተለው ቁጥር ይደውሉ 800-722-1471 (መስማት ለተሳናቸው፡ 711).

XIYYEEFFANNAA: Afaan dubbattu Oroomiffa, tajaajila gargaarsa afaanii, kanfaltiidhaan ala, ni argama. Bilbilaa 800-722-1471 (TTY: 711).

ملحوظة: إذا كنت تتحدث اذكر اللغة، فإن خدمات المساعدة اللغوية تتوافر لك بالمجان. اتصل برقم 800-722-1471 (رقم هاتف الصم والبكم: 711).

ਧਿਆਨ ਦਿਓ: ਜੇ ਤੁਸੀਂ ਪੰਜਾਬੀ ਬੋਲਦੇ ਹੋ, ਤਾਂ ਭਾਸ਼ਾ ਵਿੱਚ ਸਹਾਇਤਾ ਸੇਵਾ ਤੁਹਾਡੇ ਲਈ ਮੁਫਤ ਉਪਲਬਧ ਹੈ। 800-722-1471 (TTY: 711) 'ਤੇ ਕਾਲ ਕਰੋ।

เรียน: ถ้าคุณพูดภาษาไทยคุณสามารถใช้บริการช่วยเหลือทางภาษาได้ฟรี โทร 800-722-1471 (TTY: 711).

ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zur Verfügung. Rufnummer: 800-722-1471 (TTY: 711).

UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer 800-722-1471 (TTY: 711).

ATANSYON: Si w pale Kreyòl Ayisyen, gen sèvis èd pou lang ki disponib gratis pou ou. Rele 800-722-1471 (TTY: 711).

ATTENTION : Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 800-722-1471 (ATS : 711).

ATENÇÃO: Se fala português, encontram-se disponíveis serviços linguísticos, grátis. Ligue para 800-722-1471 (TTY: 711).

ATTENZIONE: In caso la lingua parlata sia l'italiano, sono disponibili servizi di assistenza linguistica gratuiti. Chiamare il numero 800-722-1471 (TTY: 711).

توجه: اگر به زبان فارسی گفتگو می کنید، تسهیلات زبانی بصورت رایگان برای شما فراهم می باشد. با 800-722-1471 (TTY: 711) تماس بگیرید.