

Infliximab (Avsola®, Inflectra®, Remicade®, & Renflexis®) (for Mississippi Only)

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[Instructions for Use](#)

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Related Policy

- [Maximum Dosage and Frequency](#)

Application

This Medical Benefit Drug Policy only applies to the state of Mississippi.

Coverage Rationale

This policy refers to the following infliximab products:

- Avsola® (infliximab-axxq)
- Inflectra® (infliximab-dyyb)
- Remicade® (infliximab)
- Renflexis® (infliximab-abda)
- Any FDA-approved infliximab biosimilar product not listed here*

*Any U.S. Food and Drug Administration approved and launched infliximab biosimilar product not listed by name in this policy will be considered non-preferred until reviewed by UnitedHealthcare.

Preferred Product

Inflectra® (infliximab-dyyb) and Avsola® (infliximab-axxq) are the preferred infliximab products. Coverage will be provided for Inflectra® or Avsola® contingent on the coverage criteria in the [Diagnosis-Specific Criteria](#) section.

Coverage for Renflexis® (infliximab-abda), Remicade® (infliximab), or other non-preferred infliximab product will be provided contingent on the criteria in this section and the coverage criteria in the [Diagnosis-Specific Criteria](#) section. In order to continue coverage, members already on Renflexis, Remicade, or other non-preferred infliximab product will be required to change therapy to Inflectra® (infliximab-dyyb) or Avsola® (infliximab-axxq) unless they meet the criteria in this section.

Preferred Product Criteria

Treatment with Remicade, Renflexis, or other non-preferred infliximab biosimilar products, is medically necessary for the indications outlined in this policy when both of the following criteria are met:

- **One** of the following:
 - **Both** of the following:
 - Documentation of a trial of at least 14 weeks of Inflectra or Avsola resulting in minimal clinical response to therapy and residual disease activity; **and**
 - Physician attests that, in their clinical opinion, the clinical response would be expected to be superior with Remicade, Renflexis, or other infliximab biosimilar product than experienced with Inflectra and Avsola
 - or**
 - **Both** of the following:
 - Documentation of intolerance, contraindication, or adverse event to Inflectra or Avsola; **and**
 - Physician attests that, in their clinical opinion, the same intolerance, contraindication, or adverse event would not be expected to occur with Remicade, Renflexis, or other infliximab biosimilar product
- and**
- Patient has not had a loss of a favorable response after established maintenance therapy with Inflectra, Avsola, or other infliximab biosimilar product

Diagnosis-Specific Criteria

“Infliximab” will be used to refer to all infliximab products.

Infliximab is proven and medically necessary for the treatment of:

- **Ankylosing spondylitis when all of the following criteria are met:**^{1,57,62}
 - For **initial therapy**, **all** of the following:
 - Diagnosis of ankylosing spondylitis (AS); **and**
 - **One** of the following:
 - History of failure to **two** NSAIDs (e.g., ibuprofen, naproxen) at the maximally indicated doses, each used for at least 4 weeks, unless contraindicated or clinically significant adverse effects are experienced; **or**
 - Patient has been previously treated with a targeted immunomodulator FDA-approved for the treatment of ankylosing spondylitis [e.g., adalimumab, Enbrel (etanercept), Cimzia (certolizumab), Simponi (golimumab), Xeljanz (tofacitinib), Rinvoq (upadacitinib)]; **or**
 - Patient is currently on Infliximab
 - and**
 - Infliximab is dosed according to U.S. Food and Drug Administration (FDA) labeled dosing for ankylosing spondylitis; **and**
 - Patient is **not** receiving infliximab in combination with any of the following:
 - Biologic disease-modifying antirheumatic drug (DMARD) [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
 - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]
 - and**
 - Prescribed by or in consultation with a rheumatologist; **and**
 - Initial authorization is for no more than 12 months
- For **continuation of therapy**, **all** of the following:
 - Documentation of positive clinical response to infliximab; **and**
 - Infliximab is dosed according to U.S. FDA labeled dosing for ankylosing spondylitis; **and**
 - Patient is **not** receiving infliximab in combination with any of the following:
 - Biologic disease-modifying antirheumatic drug (DMARD) [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
 - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]
 - and**
 - Reauthorization is for no more than 12 months

- **Crohn's disease when all of the following criteria are met:**^{1,3-5,41,57,61}
 - For **initial therapy**, **all** of the following:
 - Diagnosis of moderately to severely active Crohn's disease; **and**
 - **One** of the following:
 - Disease is considered high risk (e.g. fistulizing, structuring, luminal, perianal, extensive disease, growth delay); **or**
 - History of failure to one of the following conventional therapies at up to maximally indicated doses within the last 3 months, unless contraindicated or clinically significant adverse effects are experienced:
 - Corticosteroids (e.g., prednisone, methylprednisolone, budesonide)
 - 6-mercaptopurine (Purinethol)
 - Azathioprine (Imuran)
 - Methotrexate (Rheumatrex, Trexall)
 - Patient has been previously treated with a targeted immunomodulator FDA-approved for the treatment of Crohn's disease [e.g., adalimumab, Cimzia (certolizumab), Stelara (ustekinumab), Skyrizi (risankizumab), Rinvoq (upadacitinib)]; **or**
 - Patient is currently on Infliximab
 - and**
 - Infliximab is dosed according to U.S. FDA labeled dosing for Crohn's disease; **and**
 - Patient is **not** receiving infliximab in combination with any of the following:
 - Biologic disease-modifying antirheumatic drug (DMARD) [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Entyvio (vedolizumab)]
 - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]
 - and**
 - Prescribed by or in consultation with a gastroenterologist; **and**
 - Initial authorization is for no more than 12 months
 - For **continuation of therapy**, **all** of the following:
 - Documentation of positive clinical response to infliximab; **and**
 - Infliximab is dosed according to U.S. FDA labeled dosing for Crohn's disease; **and**
 - Patient is **not** receiving infliximab in combination with any of the following:
 - Biologic disease-modifying antirheumatic drug (DMARD) [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Entyvio (vedolizumab)]
 - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]
 - and**
 - Reauthorization is for no more than 12 months
- **Noninfectious uveitis when all of the following criteria are met:**^{12-14,15,17}
 - For **initial therapy**, **all** of the following:
 - Diagnosis of refractory noninfectious uveitis that is causing or threatening vision loss (e.g., noninfectious uveitis associated with Behçet's or Reiter's syndromes); **and**
 - History of failure, contraindication, or intolerance to **all** of the following:
 - Topical corticosteroids; **and**
 - Systemic corticosteroids; **and**
 - Immunosuppressive drugs (e.g., azathioprine, cyclosporine, or methotrexate)
 - and**
 - Infliximab is dosed no higher than 5 mg/kg, administered at week 0, 2, 6, and every 8 weeks thereafter; **and**
 - Patient is **not** receiving infliximab in combination with any of the following:
 - Biologic disease-modifying antirheumatic drug (DMARD) [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
 - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]
 - and**
 - Prescribed by or in consultation with **one** of the following:
 - Rheumatologist
 - Ophthalmologist

- Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]
- Phosphodiesterase 4 (PDE4) inhibitor [e.g., Otezla (apremilast)]

and

- Reauthorization is for no more than 12 months

- **Psoriatic arthritis when all of the following criteria are met:**^{1,57,61}

- For **initial therapy**, **all** of the following:

- Diagnosis of psoriatic arthritis (PsA); **and**
- **One** of the following:
 - History of failure to a 3-month trial of methotrexate at the maximally indicated dose, unless contraindicated or clinically significant adverse effects are experienced; **or**
 - Patient has been previously treated with a targeted immunomodulator FDA-approved for the treatment of psoriatic arthritis [e.g., adalimumab, Enbrel (etanercept), Cimzia (certolizumab), Simponi (golimumab), Orencia (abatacept), Stelara (ustekinumab), Skyrizi (risankizumab), Tremfya (guselkumab), Cosentyx (secukinumab), Taltz (ixekizumab), Xeljanz (tofacitinib), Olumiant (baricitinib), Rinvoq (upadacitinib), Otezla (apremilast)]; **or**
 - Patient is currently on Infliximab

and

- Infliximab is dosed according to U.S. FDA labeled dosing for psoriatic arthritis; **and**
- Patient is **not** receiving infliximab in combination with any of the following:
 - Biologic disease-modifying antirheumatic drug (DMARD) [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
 - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]
 - Phosphodiesterase 4 (PDE4) inhibitor [e.g., Otezla (apremilast)]

and

- Prescribed by or in consultation with **one** of the following:
 - Rheumatologist
 - Dermatologist

and

- Initial authorization is for no more than 12 months

- For **continuation of therapy**, **all** of the following:

- Documentation of positive clinical response to infliximab; **and**
- Infliximab is dosed according to U.S. FDA labeled dosing for psoriatic arthritis; **and**
- Patient is **not** receiving infliximab in combination with any of the following:
 - Biologic disease-modifying antirheumatic drug (DMARD) [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
 - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]
 - Phosphodiesterase 4 (PDE4) inhibitor [e.g., Otezla (apremilast)]

and

- Reauthorization is for no more than 12 months

- **Rheumatoid arthritis when all of the following criteria are met:**^{1,57,61}

- For **initial therapy**, **all** of the following:

- Diagnosis of moderately to severely active rheumatoid arthritis (RA); **and**
- **One** of the following:
 - History of failure intolerance to a 3-month trial of **one** non-biologic disease modifying anti-rheumatic drug (DMARD) (e.g., methotrexate, leflunomide, sulfasalazine, hydroxychloroquine) at maximally indicated doses within the last 6 months, unless contraindicated or clinically significant adverse effects are experienced; **or**
 - Patient has been previously treated with a targeted immunomodulator FDA-approved for the treatment of rheumatoid arthritis [e.g., adalimumab, Enbrel (etanercept), Cimzia (certolizumab), Simponi (golimumab), Orencia (abatacept), Xeljanz (tofacitinib), Olumiant (baricitinib), Rinvoq (upadacitinib)]; **or**
 - Patient is currently on Infliximab

and

- Infliximab is dosed according to U.S. FDA labeled dosing for rheumatoid arthritis; **and**

- Patient is **not** receiving infliximab in combination with any of the following:
 - Biologic disease-modifying antirheumatic drug (DMARD) [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
 - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]
 - and**
 - Prescribed by or in consultation with a rheumatologist; **and**
 - Initial authorization is for no more than 12 months
 - For **continuation of therapy**, all of the following:
 - Documentation of positive clinical response to infliximab; **and**
 - Infliximab is dosed according to U.S. FDA labeled dosing for rheumatoid arthritis; **and**
 - Patient is **not** receiving infliximab in combination with any of the following:
 - Biologic disease-modifying antirheumatic drug (DMARD) [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
 - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]
 - and**
 - Reauthorization is for no more than 12 months
- **Sarcoidosis when all of the following criteria are met:**^{6,25,39-40,46,52}
 - For **initial therapy**, all of the following:
 - Diagnosis of sarcoidosis; **and**
 - History of failure, contraindication, or intolerance to corticosteroids (e.g., prednisone, methylprednisolone); **and**
 - History of failure, contraindication, or intolerance to one immunosuppressant (e.g., methotrexate, cyclophosphamide, azathioprine); **and**
 - Infliximab is dosed no higher than 10 mg/kg, administered at week 0, 2, then once every 4 to 6 weeks thereafter; **and**
 - Patient is **not** receiving infliximab in combination with any of the following:
 - Biologic disease-modifying antirheumatic drug (DMARD) [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
 - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]
 - and**
 - Initial authorization is for no more than 12 months
 - For **continuation of therapy**, all of the following:
 - Documentation of positive clinical response to infliximab; **and**
 - Infliximab is dosed no higher than 10 mg/kg, administered every 8 weeks; **and**
 - Patient is **not** receiving infliximab in combination with either of the following:
 - Biologic disease-modifying antirheumatic drug (DMARD) [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Simponi (golimumab)]
 - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]
 - and**
 - Reauthorization is for no more than 12 months
- **Ulcerative colitis when all of the following criteria are met:**^{1,57,61}
 - For **initial therapy**, all of the following:
 - Diagnosis of moderately to severely active ulcerative colitis (UC); **and**
 - One of the following:
 - History of failure, contraindication, or intolerance to at least one conventional therapy (e.g., 6-mercaptopurine, aminosalicylate, azathioprine, corticosteroids); **or**
 - Patient has been previously treated with a targeted immunomodulator FDA-approved for the treatment of ulcerative colitis as documented by claims history or submission medical records (Document drug, date, and duration of therapy) [e.g., adalimumab, Simponi (golimumab), Stelara (ustekinumab), Xeljanz (tofacitinib), Rinvoq (upadacitinib)]; **or**
 - Patient is currently on infliximab
 - Infliximab is dosed according to U.S. FDA labeled dosing for UC; **and**
 - Patient is **not** receiving infliximab in combination with any of the following:

- Biologic disease-modifying antirheumatic drug (DMARD) [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Entyvio (vedolizumab)]
- Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]

and

- Prescribed by or in consultation with a gastroenterologist; **and**
 - Initial authorization is for no more than 12 months
 - For **continuation of therapy**, **all** of the following:
 - Documentation of positive clinical response to infliximab; **and**
 - Infliximab is dosed according to U.S. FDA labeled dosing for UC; **and**
 - Patient is **not** receiving infliximab in combination with any of the following:
 - Biologic disease-modifying antirheumatic drug (DMARD) [e.g., Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab), Entyvio (vedolizumab)]
 - Janus kinase inhibitor [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib)]
- and**
- Reauthorization is for no more than 12 months

- **Acute graft-versus-host disease (GVHD) when all of the following criteria are met:**^{69,70}

- For **initial therapy**, **all** of the following:
 - Diagnosis of steroid-refractory acute GVHD; **and**
 - **One** of the following:
 - Patient is receiving infliximab in combination with systemic corticosteroids
 - Patient is intolerant to systemic corticosteroid therapy
- and**
- Initial authorization is for no more than 4 doses
 - For **continuation of therapy**, **all** of the following:
 - Documentation of positive clinical response; **and**
 - Patient continues to experience acute GVHD; **and**
 - **One** of the following:
 - Patient is receiving infliximab in combination with systemic corticosteroids
 - Patient is intolerant to systemic corticosteroid therapy
- and**
- Reauthorization is for no more than 4 doses

- **Immune checkpoint inhibitor-related toxicities when all of the following criteria are met:**⁶⁷

- For **initial therapy**, **all** of the following:
 - Patient has recently received checkpoint inhibitor therapy [e.g., Keytruda (Pembrolizumab), Opdivo (Nivolumab)];
- and**
- Diagnosis of **one** of the following:
 - Moderate (G2) or severe (G3-4) immunotherapy-related diarrhea or colitis
 - Severe (G3-4) immunotherapy-related pneumonitis
 - Severe (G3) or life-threatening (G4) immunotherapy-related acute renal failure/elevated serum creatinine.
 - Severe (G3-4) immunotherapy-related uveitis
 - Life threatening (G4) immunotherapy-related myocarditis, pericarditis, arrhythmias, impaired ventricular function, or conduction abnormalities
 - Severe immunotherapy-related inflammatory arthritis
 - Moderate, severe, or life-threatening immunotherapy-related, steroid-refractory myalgias or myositis (muscle weakness)
- and**
- Patient has had inadequate improvement in toxicities or symptoms despite systemic corticosteroid therapy of [adequate dose and duration for the diagnosis](#); **and**
 - **One** of the following:
 - Patient is receiving infliximab in combination with systemic corticosteroids
 - Patient is intolerant to systemic corticosteroid therapy
- and**

- Initial authorization is for no more than 4 doses
- For **continuation of therapy**, all of the following:
 - Documentation of positive clinical response; **and**
 - Patient continues to experience toxicities from treatment with immune checkpoint inhibitor therapy; **and**
 - One of the following:
 - Patient is receiving infliximab in combination with systemic corticosteroids
 - Patient is intolerant to systemic corticosteroid therapy
- and**
- Reauthorization is for no more than 4 doses

There may be other conditions that qualify as serious, rare diseases for which the use of infliximab may be appropriate.

Infliximab is unproven and not medically necessary for the treatment of:

- Hidradenitis suppurative
- Juvenile idiopathic arthritis (juvenile rheumatoid arthritis)
- Myelodysplastic syndromes
- Reiter’s syndrome
- Sjogren’s syndrome
- Still’s disease
- Undifferentiated spondyloarthritis
- Wegener’s granulomatosis

Infliximab is unproven for the treatment of the above conditions because statistically robust randomized controlled trials are needed to address the issue of whether infliximab has sufficient superiority in clinical efficacy compared to other available treatments to justify the inherent clinical risk in the use of a monoclonal antibody anti-tumor necrosis factor agent.

Documentation Requirements

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage, but do not guarantee coverage of the service requested.

HCPCS Codes*	Required Clinical Information
Remicade[®], Renflexis[®], Ixifi[™]	
J1745 Q5104 Q5109	<p>For initial and continuation of therapy requests, medical notes documenting all of the following:</p> <ul style="list-style-type: none"> ● One of the following: <ul style="list-style-type: none"> ○ Both of the following: <ul style="list-style-type: none"> ▪ History of a trial of at least 14 weeks of Inflectra or Avsola resulting in minimal clinical response to therapy and residual disease activity; and ▪ Physician attests that in their clinical opinion, the clinical response would be expected to be superior with Remicade, Renflexis, or other infliximab biosimilar product, than experienced with Inflectra and Avsola. or ○ Both of the following: <ul style="list-style-type: none"> ▪ Documentation of intolerance, contraindication, or adverse event to Inflectra or Avsola; and ▪ Physician attests that in their clinical opinion, the same intolerance, contraindication, or adverse event would not be expected to occur with Remicade, Renflexis, or other infliximab biosimilar product.

*For code descriptions, refer to the [Applicable Codes](#) section.

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J1745	Injection, infliximab, excludes biosimilar, 10 mg
Q5103	Injection, infliximab-dyyb, biosimilar, (Inflectra), 10 mg
Q5104	Injection, infliximab-abda, biosimilar, (Renflexis), 10 mg
Q5109	Injection, infliximab-qbtx, biosimilar, (Ixifi), 10 mg
Q5121	Injection, infliximab-axxq, biosimilar, (Avsola), 10 mg

Diagnosis Code	Description
D86.0	Sarcoidosis of lung
D86.1	Sarcoidosis of lymph nodes
D86.2	Sarcoidosis of lung with sarcoidosis of lymph nodes
D86.3	Sarcoidosis of skin
D86.81	Sarcoid meningitis
D86.82	Multiple cranial nerve palsies in sarcoidosis
D86.83	Sarcoid iridocyclitis
D86.84	Sarcoid pyelonephritis
D86.85	Sarcoid myocarditis
D86.86	Sarcoid arthropathy
D86.87	Sarcoid myositis
D86.89	Sarcoidosis of other sites
D86.9	Sarcoidosis, unspecified
D89.810	Acute graft-versus-host disease
H20.041	Secondary noninfectious iridocyclitis, right eye
H20.042	Secondary noninfectious iridocyclitis, left eye
H20.043	Secondary noninfectious iridocyclitis, bilateral
H20.049	Secondary noninfectious iridocyclitis, unspecified eye
H20.10	Chronic iridocyclitis, unspecified eye
H20.11	Chronic iridocyclitis, right eye
H20.12	Chronic iridocyclitis, left eye
H20.13	Chronic iridocyclitis, bilateral
H20.821	Vogt-Koyanagi syndrome, right eye
H20.822	Vogt-Koyanagi syndrome, left eye
H20.823	Vogt-Koyanagi syndrome, bilateral
H20.829	Vogt-Koyanagi syndrome, unspecified eye
H30.001	Unspecified focal chorioretinal inflammation, right eye
H30.002	Unspecified focal chorioretinal inflammation, left eye
H30.003	Unspecified focal chorioretinal inflammation, bilateral

Diagnosis Code	Description
H30.009	Unspecified focal chorioretinal inflammation, unspecified eye
H30.011	Focal chorioretinal inflammation, juxtapapillary, right eye
H30.012	Focal chorioretinal inflammation, juxtapapillary, left eye
H30.013	Focal chorioretinal inflammation, juxtapapillary, bilateral
H30.019	Focal chorioretinal inflammation, juxtapapillary, unspecified eye
H30.021	Focal chorioretinal inflammation of posterior pole, right eye
H30.022	Focal chorioretinal inflammation of posterior pole, left eye
H30.023	Focal chorioretinal inflammation of posterior pole, bilateral
H30.029	Focal chorioretinal inflammation of posterior pole, unspecified eye
H30.031	Focal chorioretinal inflammation, peripheral, right eye
H30.032	Focal chorioretinal inflammation, peripheral, left eye
H30.033	Focal chorioretinal inflammation, peripheral, bilateral
H30.039	Focal chorioretinal inflammation, peripheral, unspecified eye
H30.041	Focal chorioretinal inflammation, macular or paramacular, right eye
H30.042	Focal chorioretinal inflammation, macular or paramacular, left eye
H30.043	Focal chorioretinal inflammation, macular or paramacular, bilateral
H30.049	Focal chorioretinal inflammation, macular or paramacular, unspecified eye
H30.101	Unspecified disseminated chorioretinal inflammation (chorioretinitis/choroiditis), right eye
H30.102	Unspecified disseminated chorioretinal inflammation (chorioretinitis/choroiditis), left eye
H30.103	Unspecified disseminated chorioretinal inflammation (chorioretinitis/choroiditis), bilateral
H30.109	Unspecified disseminated chorioretinal inflammation (chorioretinitis/choroiditis), unspecified eye
H30.111	Disseminated chorioretinal inflammation (choroiditis/chorioretinitis) posterior pole, right eye
H30.112	Disseminated chorioretinal inflammation (choroiditis/chorioretinitis) posterior pole, left eye
H30.113	Disseminated chorioretinal inflammation (choroiditis/chorioretinitis) posterior pole, bilateral
H30.119	Disseminated chorioretinal inflammation (choroiditis/chorioretinitis) posterior pole, unspecified eye
H30.121	Disseminated chorioretinal inflammation (chorioretinitis/choroiditis) peripheral, right eye
H30.122	Disseminated chorioretinal inflammation (chorioretinitis/choroiditis) peripheral, left eye
H30.123	Disseminated chorioretinal inflammation (chorioretinitis/choroiditis) peripheral, bilateral
H30.129	Disseminated chorioretinal inflammation (chorioretinitis/choroiditis) peripheral, unspecified eye
H30.131	Disseminated chorioretinal inflammation, generalized, right eye
H30.132	Disseminated chorioretinal inflammation, generalized, left eye
H30.133	Disseminated chorioretinal inflammation, generalized, bilateral
H30.139	Disseminated chorioretinal inflammation, generalized, unspecified eye
H30.20	Posterior cyclitis, unspecified eye
H30.21	Posterior cyclitis, right eye
H30.22	Posterior cyclitis, left eye
H30.23	Posterior cyclitis, bilateral
H30.811	Harada's disease, right eye
H30.812	Harada's disease, left eye
H30.813	Harada's disease, bilateral
H30.819	Harada's disease, unspecified eye
H30.891	Other chorioretinal inflammations, right eye

Diagnosis Code	Description
H30.892	Other chorioretinal inflammations, left eye
H30.893	Other chorioretinal inflammations, bilateral
H30.899	Other chorioretinal inflammations, unspecified eye
H30.90	Unspecified chorioretinal inflammation, unspecified eye
H30.91	Unspecified chorioretinal inflammation, right eye
H30.92	Unspecified chorioretinal inflammation, left eye
H30.93	Unspecified chorioretinal inflammation, bilateral
H35.021	Exudative retinopathy, right eye
H35.022	Exudative retinopathy, left eye
H35.023	Exudative retinopathy, bilateral
H35.029	Exudative retinopathy, unspecified eye
H35.061	Retinal vasculitis, right eye
H35.062	Retinal vasculitis, left eye
H35.063	Retinal vasculitis, bilateral
H35.069	Retinal vasculitis, unspecified eye
H44.111	Panuveitis, right eye
H44.112	Panuveitis, left eye
H44.113	Panuveitis, bilateral
H44.119	Panuveitis, unspecified eye
H44.131	Sympathetic uveitis, right eye
H44.132	Sympathetic uveitis, left eye
H44.133	Sympathetic uveitis, bilateral
H44.139	Sympathetic uveitis, unspecified eye
I30.8	Other forms of acute pericarditis
I30.9	Acute pericarditis, unspecified
I40.8	Other acute myocarditis
I40.9	Acute myocarditis, unspecified
I50.9	Heart failure, unspecified
J70.2	Acute drug-induced interstitial lung disorders
J70.4	Drug-induced interstitial lung disorders, unspecified
K31.6	Fistula of stomach and duodenum
K50.00	Crohn's disease of small intestine without complications
K50.011	Crohn's disease of small intestine with rectal bleeding
K50.012	Crohn's disease of small intestine with intestinal obstruction
K50.013	Crohn's disease of small intestine with fistula
K50.014	Crohn's disease of small intestine with abscess
K50.018	Crohn's disease of small intestine with other complication
K50.019	Crohn's disease of small intestine with unspecified complications
K50.10	Crohn's disease of large intestine without complications
K50.111	Crohn's disease of large intestine with rectal bleeding
K50.112	Crohn's disease of large intestine with intestinal obstruction
K50.113	Crohn's disease of large intestine with fistula

Diagnosis Code	Description
K50.114	Crohn's disease of large intestine with abscess
K50.118	Crohn's disease of large intestine with other complication
K50.119	Crohn's disease of large intestine with unspecified complications
K50.80	Crohn's disease of both small and large intestine without complications
K50.811	Crohn's disease of both small and large intestine with rectal bleeding
K50.812	Crohn's disease of both small and large intestine with intestinal obstruction
K50.813	Crohn's disease of both small and large intestine with fistula
K50.814	Crohn's disease of both small and large intestine with abscess
K50.818	Crohn's disease of both small and large intestine with other complication
K50.819	Crohn's disease of both small and large intestine with unspecified complications
K50.90	Crohn's disease, unspecified, without complications
K50.911	Crohn's disease, unspecified, with rectal bleeding
K50.912	Crohn's disease, unspecified, with intestinal obstruction
K50.913	Crohn's disease, unspecified, with fistula
K50.914	Crohn's disease, unspecified, with abscess
K50.918	Crohn's disease, unspecified, with other complication
K50.919	Crohn's disease, unspecified, with unspecified complications
K51.00	Ulcerative (chronic) pancolitis without complications
K51.011	Ulcerative (chronic) pancolitis with rectal bleeding
K51.012	Ulcerative (chronic) pancolitis with intestinal obstruction
K51.013	Ulcerative (chronic) pancolitis with fistula
K51.014	Ulcerative (chronic) pancolitis with abscess
K51.018	Ulcerative (chronic) pancolitis with other complication
K51.019	Ulcerative (chronic) pancolitis with unspecified complications
K51.20	Ulcerative (chronic) proctitis without complications
K51.211	Ulcerative (chronic) proctitis with rectal bleeding
K51.212	Ulcerative (chronic) proctitis with intestinal obstruction
K51.213	Ulcerative (chronic) proctitis with fistula
K51.214	Ulcerative (chronic) proctitis with abscess
K51.218	Ulcerative (chronic) proctitis with other complication
K51.219	Ulcerative (chronic) proctitis with unspecified complications
K51.30	Ulcerative (chronic) rectosigmoiditis without complications
K51.311	Ulcerative (chronic) rectosigmoiditis with rectal bleeding
K51.312	Ulcerative (chronic) rectosigmoiditis with intestinal obstruction
K51.313	Ulcerative (chronic) rectosigmoiditis with fistula
K51.314	Ulcerative (chronic) rectosigmoiditis with abscess
K51.318	Ulcerative (chronic) rectosigmoiditis with other complication
K51.319	Ulcerative (chronic) rectosigmoiditis with unspecified complications
K51.40	Inflammatory polyps of colon without complications
K51.411	Inflammatory polyps of colon with rectal bleeding
K51.412	Inflammatory polyps of colon with intestinal obstruction
K51.413	Inflammatory polyps of colon with fistula

Diagnosis Code	Description
K51.414	Inflammatory polyps of colon with abscess
K51.418	Inflammatory polyps of colon with other complication
K51.419	Inflammatory polyps of colon with unspecified complications
K51.50	Left sided colitis without complications
K51.511	Left sided colitis with rectal bleeding
K51.512	Left sided colitis with intestinal obstruction
K51.513	Left sided colitis with fistula
K51.514	Left sided colitis with abscess
K51.518	Left sided colitis with other complication
K51.519	Left sided colitis with unspecified complications
K51.80	Other ulcerative colitis without complications
K51.811	Other ulcerative colitis with rectal bleeding
K51.812	Other ulcerative colitis with intestinal obstruction
K51.813	Other ulcerative colitis with fistula
K51.814	Other ulcerative colitis with abscess
K51.818	Other ulcerative colitis with other complication
K51.819	Other ulcerative colitis with unspecified complications
K51.90	Ulcerative colitis, unspecified, without complications
K51.911	Ulcerative colitis, unspecified with rectal bleeding
K51.912	Ulcerative colitis, unspecified with intestinal obstruction
K51.913	Ulcerative colitis, unspecified with fistula
K51.914	Ulcerative colitis, unspecified with abscess
K51.918	Ulcerative colitis, unspecified with other complication
K51.919	Ulcerative colitis, unspecified with unspecified complications
K52.1	Toxic gastroenteritis and colitis
K60.3	Anal fistula
K60.4	Rectal fistula
K60.5	Anorectal fistula
K63.2	Fistula of intestine
L40.0	Psoriasis vulgaris
L40.1	Generalized pustular psoriasis
L40.2	Acrodermatitis continua
L40.3	Pustulosis palmaris et plantaris
L40.4	Guttate psoriasis
L40.50	Arthropathic psoriasis, unspecified
L40.51	Distal interphalangeal psoriatic arthropathy
L40.52	Psoriatic arthritis mutilans
L40.53	Psoriatic spondylitis
L40.54	Psoriatic juvenile arthropathy
L40.59	Other psoriatic arthropathy
L40.8	Other psoriasis
L40.9	Psoriasis, unspecified

Diagnosis Code	Description
M05.00	Felty's syndrome, unspecified site
M05.011	Felty's syndrome, right shoulder
M05.012	Felty's syndrome, left shoulder
M05.019	Felty's syndrome, unspecified shoulder
M05.021	Felty's syndrome, right elbow
M05.022	Felty's syndrome, left elbow
M05.029	Felty's syndrome, unspecified elbow
M05.031	Felty's syndrome, right wrist
M05.032	Felty's syndrome, left wrist
M05.039	Felty's syndrome, unspecified wrist
M05.041	Felty's syndrome, right hand
M05.042	Felty's syndrome, left hand
M05.049	Felty's syndrome, unspecified hand
M05.051	Felty's syndrome, right hip
M05.052	Felty's syndrome, left hip
M05.059	Felty's syndrome, unspecified hip
M05.061	Felty's syndrome, right knee
M05.062	Felty's syndrome, left knee
M05.069	Felty's syndrome, unspecified knee
M05.071	Felty's syndrome, right ankle and foot
M05.072	Felty's syndrome, left ankle and foot
M05.079	Felty's syndrome, unspecified ankle and foot
M05.09	Felty's syndrome, multiple sites
M05.20	Rheumatoid vasculitis with rheumatoid arthritis of unspecified site
M05.211	Rheumatoid vasculitis with rheumatoid arthritis of right shoulder
M05.212	Rheumatoid vasculitis with rheumatoid arthritis of left shoulder
M05.219	Rheumatoid vasculitis with rheumatoid arthritis of unspecified shoulder
M05.221	Rheumatoid vasculitis with rheumatoid arthritis of right elbow
M05.222	Rheumatoid vasculitis with rheumatoid arthritis of left elbow
M05.229	Rheumatoid vasculitis with rheumatoid arthritis of unspecified elbow
M05.231	Rheumatoid vasculitis with rheumatoid arthritis of right wrist
M05.232	Rheumatoid vasculitis with rheumatoid arthritis of left wrist
M05.239	Rheumatoid vasculitis with rheumatoid arthritis of unspecified wrist
M05.241	Rheumatoid vasculitis with rheumatoid arthritis of right hand
M05.242	Rheumatoid vasculitis with rheumatoid arthritis of left hand
M05.249	Rheumatoid vasculitis with rheumatoid arthritis of unspecified hand
M05.251	Rheumatoid vasculitis with rheumatoid arthritis of right hip
M05.252	Rheumatoid vasculitis with rheumatoid arthritis of left hip
M05.259	Rheumatoid vasculitis with rheumatoid arthritis of unspecified hip
M05.261	Rheumatoid vasculitis with rheumatoid arthritis of right knee
M05.262	Rheumatoid vasculitis with rheumatoid arthritis of left knee
M05.269	Rheumatoid vasculitis with rheumatoid arthritis of unspecified knee

Diagnosis Code	Description
M05.271	Rheumatoid vasculitis with rheumatoid arthritis of right ankle and foot
M05.272	Rheumatoid vasculitis with rheumatoid arthritis of left ankle and foot
M05.279	Rheumatoid vasculitis with rheumatoid arthritis of unspecified ankle and foot
M05.29	Rheumatoid vasculitis with rheumatoid arthritis of multiple sites
M05.30	Rheumatoid heart disease with rheumatoid arthritis of unspecified site
M05.311	Rheumatoid heart disease with rheumatoid arthritis of right shoulder
M05.312	Rheumatoid heart disease with rheumatoid arthritis of left shoulder
M05.319	Rheumatoid heart disease with rheumatoid arthritis of unspecified shoulder
M05.321	Rheumatoid heart disease with rheumatoid arthritis of right elbow
M05.322	Rheumatoid heart disease with rheumatoid arthritis of left elbow
M05.329	Rheumatoid heart disease with rheumatoid arthritis of unspecified elbow
M05.331	Rheumatoid heart disease with rheumatoid arthritis of right wrist
M05.332	Rheumatoid heart disease with rheumatoid arthritis of left wrist
M05.339	Rheumatoid heart disease with rheumatoid arthritis of unspecified wrist
M05.341	Rheumatoid heart disease with rheumatoid arthritis of right hand
M05.342	Rheumatoid heart disease with rheumatoid arthritis of left hand
M05.349	Rheumatoid heart disease with rheumatoid arthritis of unspecified hand
M05.351	Rheumatoid heart disease with rheumatoid arthritis of right hip
M05.352	Rheumatoid heart disease with rheumatoid arthritis of left hip
M05.359	Rheumatoid heart disease with rheumatoid arthritis of unspecified hip
M05.361	Rheumatoid heart disease with rheumatoid arthritis of right knee
M05.362	Rheumatoid heart disease with rheumatoid arthritis of left knee
M05.369	Rheumatoid heart disease with rheumatoid arthritis of unspecified knee
M05.371	Rheumatoid heart disease with rheumatoid arthritis of right ankle and foot
M05.372	Rheumatoid heart disease with rheumatoid arthritis of left ankle and foot
M05.379	Rheumatoid heart disease with rheumatoid arthritis of unspecified ankle and foot
M05.39	Rheumatoid heart disease with rheumatoid arthritis of multiple sites
M05.40	Rheumatoid myopathy with rheumatoid arthritis of unspecified site
M05.411	Rheumatoid myopathy with rheumatoid arthritis of right shoulder
M05.412	Rheumatoid myopathy with rheumatoid arthritis of left shoulder
M05.419	Rheumatoid myopathy with rheumatoid arthritis of unspecified shoulder
M05.421	Rheumatoid myopathy with rheumatoid arthritis of right elbow
M05.422	Rheumatoid myopathy with rheumatoid arthritis of left elbow
M05.429	Rheumatoid myopathy with rheumatoid arthritis of unspecified elbow
M05.431	Rheumatoid myopathy with rheumatoid arthritis of right wrist
M05.432	Rheumatoid myopathy with rheumatoid arthritis of left wrist
M05.439	Rheumatoid myopathy with rheumatoid arthritis of unspecified wrist
M05.441	Rheumatoid myopathy with rheumatoid arthritis of right hand
M05.442	Rheumatoid myopathy with rheumatoid arthritis of left hand
M05.449	Rheumatoid myopathy with rheumatoid arthritis of unspecified hand
M05.451	Rheumatoid myopathy with rheumatoid arthritis of right hip
M05.452	Rheumatoid myopathy with rheumatoid arthritis of left hip

Diagnosis Code	Description
M05.459	Rheumatoid myopathy with rheumatoid arthritis of unspecified hip
M05.461	Rheumatoid myopathy with rheumatoid arthritis of right knee
M05.462	Rheumatoid myopathy with rheumatoid arthritis of left knee
M05.469	Rheumatoid myopathy with rheumatoid arthritis of unspecified knee
M05.471	Rheumatoid myopathy with rheumatoid arthritis of right ankle and foot
M05.472	Rheumatoid myopathy with rheumatoid arthritis of left ankle and foot
M05.479	Rheumatoid myopathy with rheumatoid arthritis of unspecified ankle and foot
M05.49	Rheumatoid myopathy with rheumatoid arthritis of multiple sites
M05.50	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified site
M05.511	Rheumatoid polyneuropathy with rheumatoid arthritis of right shoulder
M05.512	Rheumatoid polyneuropathy with rheumatoid arthritis of left shoulder
M05.519	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified shoulder
M05.521	Rheumatoid polyneuropathy with rheumatoid arthritis of right elbow
M05.522	Rheumatoid polyneuropathy with rheumatoid arthritis of left elbow
M05.529	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified elbow
M05.531	Rheumatoid polyneuropathy with rheumatoid arthritis of right wrist
M05.532	Rheumatoid polyneuropathy with rheumatoid arthritis of left wrist
M05.539	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified wrist
M05.541	Rheumatoid polyneuropathy with rheumatoid arthritis of right hand
M05.542	Rheumatoid polyneuropathy with rheumatoid arthritis of left hand
M05.549	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified hand
M05.551	Rheumatoid polyneuropathy with rheumatoid arthritis of right hip
M05.552	Rheumatoid polyneuropathy with rheumatoid arthritis of left hip
M05.559	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified hip
M05.561	Rheumatoid polyneuropathy with rheumatoid arthritis of right knee
M05.562	Rheumatoid polyneuropathy with rheumatoid arthritis of left knee
M05.569	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified knee
M05.571	Rheumatoid polyneuropathy with rheumatoid arthritis of right ankle and foot
M05.572	Rheumatoid polyneuropathy with rheumatoid arthritis of left ankle and foot
M05.579	Rheumatoid polyneuropathy with rheumatoid arthritis of unspecified ankle and foot
M05.59	Rheumatoid polyneuropathy with rheumatoid arthritis of multiple sites
M05.60	Rheumatoid arthritis of unspecified site with involvement of other organs and systems
M05.611	Rheumatoid arthritis of right shoulder with involvement of other organs and systems
M05.612	Rheumatoid arthritis of left shoulder with involvement of other organs and systems
M05.619	Rheumatoid arthritis of unspecified shoulder with involvement of other organs and systems
M05.621	Rheumatoid arthritis of right elbow with involvement of other organs and systems
M05.622	Rheumatoid arthritis of left elbow with involvement of other organs and systems
M05.629	Rheumatoid arthritis of unspecified elbow with involvement of other organs and systems
M05.631	Rheumatoid arthritis of right wrist with involvement of other organs and systems
M05.632	Rheumatoid arthritis of left wrist with involvement of other organs and systems
M05.639	Rheumatoid arthritis of unspecified wrist with involvement of other organs and systems
M05.641	Rheumatoid arthritis of right hand with involvement of other organs and systems

Diagnosis Code	Description
M05.642	Rheumatoid arthritis of left hand with involvement of other organs and systems
M05.649	Rheumatoid arthritis of unspecified hand with involvement of other organs and systems
M05.651	Rheumatoid arthritis of right hip with involvement of other organs and systems
M05.652	Rheumatoid arthritis of left hip with involvement of other organs and systems
M05.659	Rheumatoid arthritis of unspecified hip with involvement of other organs and systems
M05.661	Rheumatoid arthritis of right knee with involvement of other organs and systems
M05.662	Rheumatoid arthritis of left knee with involvement of other organs and systems
M05.669	Rheumatoid arthritis of unspecified knee with involvement of other organs and systems
M05.671	Rheumatoid arthritis of right ankle and foot with involvement of other organs and systems
M05.672	Rheumatoid arthritis of left ankle and foot with involvement of other organs and systems
M05.679	Rheumatoid arthritis of unspecified ankle and foot with involvement of other organs and systems
M05.69	Rheumatoid arthritis of multiple sites with involvement of other organs and systems
M05.7A	Rheumatoid arthritis with rheumatoid factor of other specified site without organ or systems involvement
M05.70	Rheumatoid arthritis with rheumatoid factor of unspecified site without organ or systems involvement
M05.711	Rheumatoid arthritis with rheumatoid factor of right shoulder without organ or systems involvement
M05.712	Rheumatoid arthritis with rheumatoid factor of left shoulder without organ or systems involvement
M05.719	Rheumatoid arthritis with rheumatoid factor of unspecified shoulder without organ or systems involvement
M05.721	Rheumatoid arthritis with rheumatoid factor of right elbow without organ or systems involvement
M05.722	Rheumatoid arthritis with rheumatoid factor of left elbow without organ or systems involvement
M05.729	Rheumatoid arthritis with rheumatoid factor of unspecified elbow without organ or systems involvement
M05.731	Rheumatoid arthritis with rheumatoid factor of right wrist without organ or systems involvement
M05.732	Rheumatoid arthritis with rheumatoid factor of left wrist without organ or systems involvement
M05.739	Rheumatoid arthritis with rheumatoid factor of unspecified wrist without organ or systems involvement
M05.741	Rheumatoid arthritis with rheumatoid factor of right hand without organ or systems involvement
M05.742	Rheumatoid arthritis with rheumatoid factor of left hand without organ or systems involvement
M05.749	Rheumatoid arthritis with rheumatoid factor of unspecified hand without organ or systems involvement
M05.751	Rheumatoid arthritis with rheumatoid factor of right hip without organ or systems involvement
M05.752	Rheumatoid arthritis with rheumatoid factor of left hip without organ or systems involvement
M05.759	Rheumatoid arthritis with rheumatoid factor of unspecified hip without organ or systems involvement
M05.761	Rheumatoid arthritis with rheumatoid factor of right knee without organ or systems involvement
M05.762	Rheumatoid arthritis with rheumatoid factor of left knee without organ or systems involvement
M05.769	Rheumatoid arthritis with rheumatoid factor of unspecified knee without organ or systems involvement
M05.771	Rheumatoid arthritis with rheumatoid factor of right ankle and foot without organ or systems involvement
M05.772	Rheumatoid arthritis with rheumatoid factor of left ankle and foot without organ or systems involvement
M05.779	Rheumatoid arthritis with rheumatoid factor of unspecified ankle and foot without organ or systems involvement
M05.79	Rheumatoid arthritis with rheumatoid factor of multiple sites without organ or systems involvement
M05.8A	Other rheumatoid arthritis with rheumatoid factor of other specified site
M05.80	Other rheumatoid arthritis with rheumatoid factor of unspecified site
M05.811	Other rheumatoid arthritis with rheumatoid factor of right shoulder
M05.812	Other rheumatoid arthritis with rheumatoid factor of left shoulder

Diagnosis Code	Description
M05.819	Other rheumatoid arthritis with rheumatoid factor of unspecified shoulder
M05.821	Other rheumatoid arthritis with rheumatoid factor of right elbow
M05.822	Other rheumatoid arthritis with rheumatoid factor of left elbow
M05.829	Other rheumatoid arthritis with rheumatoid factor of unspecified elbow
M05.831	Other rheumatoid arthritis with rheumatoid factor of right wrist
M05.832	Other rheumatoid arthritis with rheumatoid factor of left wrist
M05.839	Other rheumatoid arthritis with rheumatoid factor of unspecified wrist
M05.841	Other rheumatoid arthritis with rheumatoid factor of right hand
M05.842	Other rheumatoid arthritis with rheumatoid factor of left hand
M05.849	Other rheumatoid arthritis with rheumatoid factor of unspecified hand
M05.851	Other rheumatoid arthritis with rheumatoid factor of right hip
M05.852	Other rheumatoid arthritis with rheumatoid factor of left hip
M05.859	Other rheumatoid arthritis with rheumatoid factor of unspecified hip
M05.861	Other rheumatoid arthritis with rheumatoid factor of right knee
M05.862	Other rheumatoid arthritis with rheumatoid factor of left knee
M05.869	Other rheumatoid arthritis with rheumatoid factor of unspecified knee
M05.871	Other rheumatoid arthritis with rheumatoid factor of right ankle and foot
M05.872	Other rheumatoid arthritis with rheumatoid factor of left ankle and foot
M05.879	Other rheumatoid arthritis with rheumatoid factor of unspecified ankle and foot
M05.89	Other rheumatoid arthritis with rheumatoid factor of multiple sites
M05.9	Rheumatoid arthritis with rheumatoid factor, unspecified
M06.0A	Rheumatoid arthritis without rheumatoid factor, other specified site
M06.00	Rheumatoid arthritis without rheumatoid factor, unspecified site
M06.011	Rheumatoid arthritis without rheumatoid factor, right shoulder
M06.012	Rheumatoid arthritis without rheumatoid factor, left shoulder
M06.019	Rheumatoid arthritis without rheumatoid factor, unspecified shoulder
M06.021	Rheumatoid arthritis without rheumatoid factor, right elbow
M06.022	Rheumatoid arthritis without rheumatoid factor, left elbow
M06.029	Rheumatoid arthritis without rheumatoid factor, unspecified elbow
M06.031	Rheumatoid arthritis without rheumatoid factor, right wrist
M06.032	Rheumatoid arthritis without rheumatoid factor, left wrist
M06.039	Rheumatoid arthritis without rheumatoid factor, unspecified wrist
M06.041	Rheumatoid arthritis without rheumatoid factor, right hand
M06.042	Rheumatoid arthritis without rheumatoid factor, left hand
M06.049	Rheumatoid arthritis without rheumatoid factor, unspecified hand
M06.051	Rheumatoid arthritis without rheumatoid factor, right hip
M06.052	Rheumatoid arthritis without rheumatoid factor, left hip
M06.059	Rheumatoid arthritis without rheumatoid factor, unspecified hip
M06.061	Rheumatoid arthritis without rheumatoid factor, right knee
M06.062	Rheumatoid arthritis without rheumatoid factor, left knee
M06.069	Rheumatoid arthritis without rheumatoid factor, unspecified knee
M06.071	Rheumatoid arthritis without rheumatoid factor, right ankle and foot

Diagnosis Code	Description
M06.072	Rheumatoid arthritis without rheumatoid factor, left ankle and foot
M06.079	Rheumatoid arthritis without rheumatoid factor, unspecified ankle and foot
M06.08	Rheumatoid arthritis without rheumatoid factor, vertebrae
M06.09	Rheumatoid arthritis without rheumatoid factor, multiple sites
M06.1	Adult-onset Still's disease
M06.20	Rheumatoid bursitis, unspecified site
M06.211	Rheumatoid bursitis, right shoulder
M06.212	Rheumatoid bursitis, left shoulder
M06.219	Rheumatoid bursitis, unspecified shoulder
M06.221	Rheumatoid bursitis, right elbow
M06.222	Rheumatoid bursitis, left elbow
M06.229	Rheumatoid bursitis, unspecified elbow
M06.231	Rheumatoid bursitis, right wrist
M06.232	Rheumatoid bursitis, left wrist
M06.239	Rheumatoid bursitis, unspecified wrist
M06.241	Rheumatoid bursitis, right hand
M06.242	Rheumatoid bursitis, left hand
M06.249	Rheumatoid bursitis, unspecified hand
M06.251	Rheumatoid bursitis, right hip
M06.252	Rheumatoid bursitis, left hip
M06.259	Rheumatoid bursitis, unspecified hip
M06.261	Rheumatoid bursitis, right knee
M06.262	Rheumatoid bursitis, left knee
M06.269	Rheumatoid bursitis, unspecified knee
M06.271	Rheumatoid bursitis, right ankle and foot
M06.272	Rheumatoid bursitis, left ankle and foot
M06.279	Rheumatoid bursitis, unspecified ankle and foot
M06.28	Rheumatoid bursitis, vertebrae
M06.29	Rheumatoid bursitis, multiple sites
M06.30	Rheumatoid nodule, unspecified site
M06.311	Rheumatoid nodule, right shoulder
M06.312	Rheumatoid nodule, left shoulder
M06.319	Rheumatoid nodule, unspecified shoulder
M06.321	Rheumatoid nodule, right elbow
M06.322	Rheumatoid nodule, left elbow
M06.329	Rheumatoid nodule, unspecified elbow
M06.331	Rheumatoid nodule, right wrist
M06.332	Rheumatoid nodule, left wrist
M06.339	Rheumatoid nodule, unspecified wrist
M06.341	Rheumatoid nodule, right hand
M06.342	Rheumatoid nodule, left hand
M06.349	Rheumatoid nodule, unspecified hand

Diagnosis Code	Description
M06.351	Rheumatoid nodule, right hip
M06.352	Rheumatoid nodule, left hip
M06.359	Rheumatoid nodule, unspecified hip
M06.361	Rheumatoid nodule, right knee
M06.362	Rheumatoid nodule, left knee
M06.369	Rheumatoid nodule, unspecified knee
M06.371	Rheumatoid nodule, right ankle and foot
M06.372	Rheumatoid nodule, left ankle and foot
M06.379	Rheumatoid nodule, unspecified ankle and foot
M06.38	Rheumatoid nodule, vertebrae
M06.39	Rheumatoid nodule, multiple sites
M06.4	Inflammatory polyarthropathy
M06.8A	Other specified rheumatoid arthritis, other specified site
M06.80	Other specified rheumatoid arthritis, unspecified site
M06.811	Other specified rheumatoid arthritis, right shoulder
M06.812	Other specified rheumatoid arthritis, left shoulder
M06.819	Other specified rheumatoid arthritis, unspecified shoulder
M06.821	Other specified rheumatoid arthritis, right elbow
M06.822	Other specified rheumatoid arthritis, left elbow
M06.829	Other specified rheumatoid arthritis, unspecified elbow
M06.831	Other specified rheumatoid arthritis, right wrist
M06.832	Other specified rheumatoid arthritis, left wrist
M06.839	Other specified rheumatoid arthritis, unspecified wrist
M06.841	Other specified rheumatoid arthritis, right hand
M06.842	Other specified rheumatoid arthritis, left hand
M06.849	Other specified rheumatoid arthritis, unspecified hand
M06.851	Other specified rheumatoid arthritis, right hip
M06.852	Other specified rheumatoid arthritis, left hip
M06.859	Other specified rheumatoid arthritis, unspecified hip
M06.861	Other specified rheumatoid arthritis, right knee
M06.862	Other specified rheumatoid arthritis, left knee
M06.869	Other specified rheumatoid arthritis, unspecified knee
M06.871	Other specified rheumatoid arthritis, right ankle and foot
M06.872	Other specified rheumatoid arthritis, left ankle and foot
M06.879	Other specified rheumatoid arthritis, unspecified ankle and foot
M06.88	Other specified rheumatoid arthritis, vertebrae
M06.89	Other specified rheumatoid arthritis, multiple sites
M06.9	Rheumatoid arthritis, unspecified
M08.1	Juvenile ankylosing spondylitis
M45.0	Ankylosing spondylitis of multiple sites in spine
M45.1	Ankylosing spondylitis of occipito-atlanto-axial region
M45.2	Ankylosing spondylitis of cervical region

Diagnosis Code	Description
M45.3	Ankylosing spondylitis of cervicothoracic region
M45.4	Ankylosing spondylitis of thoracic region
M45.5	Ankylosing spondylitis of thoracolumbar region
M45.6	Ankylosing spondylitis lumbar region
M45.7	Ankylosing spondylitis of lumbosacral region
M45.8	Ankylosing spondylitis sacral and sacrococcygeal region
M45.9	Ankylosing spondylitis of unspecified sites in spine
M48.8X1	Other specified spondylopathies, occipito-atlanto-axial region
M48.8X2	Other specified spondylopathies, cervical region
M48.8X3	Other specified spondylopathies, cervicothoracic region
M48.8X4	Other specified spondylopathies, thoracic region
M48.8X5	Other specified spondylopathies, thoracolumbar region
M48.8X6	Other specified spondylopathies, lumbar region
M48.8X7	Other specified spondylopathies, lumbosacral region
M48.8X8	Other specified spondylopathies, sacral and sacrococcygeal region
M48.8X9	Other specified spondylopathies, site unspecified
N17.8	Other acute kidney failure
N17.9	Acute kidney failure, unspecified
N82.2	Fistula of vagina to small intestine
N82.3	Fistula of vagina to large intestine
N82.4	Other female intestinal-genital tract fistulae
R19.7	Diarrhea, unspecified
T45.1X5A	Adverse effect of antineoplastic and immunosuppressive drugs, initial encounter
T45.1X5D	Adverse effect of antineoplastic and immunosuppressive drugs, subsequent encounter
T45.1X5S	Adverse effect of antineoplastic and immunosuppressive drugs, sequela

Background

Infliximab is a genetically engineered chimeric human/mouse monoclonal antibody (cA2) against tumor necrosis factor alfa (TNF-alfa), a key mediator of mucosal inflammation. Increased levels of TNF-alfa are found in the intestinal mucosa and stool of patients with active Crohn's disease and in the joints of rheumatoid arthritis patients. Elevated TNF-alfa concentrations are also involved in ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. TNF-alfa activity is neutralized by cA2 antibody binding to the soluble and transmembrane forms which blocks the binding of TNF-alfa with its receptors. Activities inhibited by anti-TNF-alfa antibodies include induction of interleukins, enhancement of leukocyte migration, and expression of adhesion molecules. In vitro studies have demonstrated that cells expressing transmembrane TNF-alfa bound by infliximab are lysed by complement or effector cells. In animal models, antibodies to TNF-alfa were shown to prevent or reduce inflammation.¹

Clinical Evidence

Proven

Sarcoidosis

The use of infliximab in patients with chronic pulmonary sarcoidosis was assessed in a multicenter, randomized, double-blind, placebo-controlled study.⁵² Patients must have been treated with at least 10 mg/d of prednisone or equivalent or one or more immunosuppressants for ≥ 3 months before screening. They received infliximab 3 mg/kg (n = 46), 5 mg/kg (n = 47), or placebo

(n = 45) at weeks 0, 2, 6, 12, 18, and 24. They were followed through 52 weeks. The primary endpoint was the change at week 24 from baseline in percent of predicted forced vital capacity (FVC). Patients receiving infliximab 3 or 5 mg/kg had a mean increase of 2.5% compared with no change for those receiving placebo (p = 0.038).

Infliximab has also been studied for use in sarcoidosis in small clinical trials, small, published studies and reports that also conclude that clinical evidence supports the use of infliximab for treatment-resistant sarcoidosis.^{6,25,39,40,46}

Noninfectious Uveitis

Long-term safety and efficacy of treatment with infliximab in uveitis for more than 1 year in patients (n = 164) with Behçet's disease (BD) was evaluated via questionnaire in a retrospective multicenter study.¹² Primary outcome measures assessed were best-corrected VA (BCVA) determined by the Landolt ring, proportion of subjects without relapse of uveitis, frequency of ocular inflammatory attacks per year, and adverse effects of the therapy. The mean age at initiation of infliximab treatment was 42.6 ±11.7 years, and the mean treatment duration was 32.9 ±14.4 months. Data before and at the last visit during infliximab treatment were analyzed in 4 groups divided by duration of treatment: group A (n = 43, 12- < 24 months), group B (n = 62, 24- < 36 months), group C (n = 42, 36- < 48 months), and group D (n = 17, ≥ 48 months). The frequency of ocular attacks decreased in all groups (from 5.3 ±3.0 to 1.0 ±0.3 in group A, 4.8 ±4.6 to 1.4 ±0.3 in group B, 4.1 ±2.9 to 0.9 ±0.3 in group C, and 9.5 ±5.8 to 1.6 ±0.5 in group D; all p < 0.05). The BCVA was improved in approximately 55% of the eyes after treatment. Mean BCVA was improved after treatment with infliximab in groups A to C (from 0.79 ±1.04 to 0.59 ±0.94 in group A, 0.59 ±1.07 to 0.41 ±1.04 in group B, and 1.15 ±1.77 to 0.92 ±1.73 in group C; all p < 0.05) but not in group D. Uveitis relapsed in 59.1% of all patients after infliximab treatment, and no difference in duration until relapse was observed between individual groups. Approximately 80% of relapses occurred within 1 year after the initiation of infliximab treatment in all groups, 90% of which were controlled by increasing doses of topical corticosteroids and shortening the interval of infliximab infusion. Adverse effects were observed in 65 cases or 35% of all subjects. Infliximab treatment was continued in 85% of the patients, but 15% of the patients discontinued infliximab treatment because of adverse effects or insufficient efficacy. Researchers concluded that this study demonstrated that infliximab reduced the frequency of ocular attacks and improved VA in patients with BD-related uveitis refractory to conventional therapies and was generally well tolerated, with few serious adverse events.

Kruh et al conducted a retrospective, interventional, noncomparative cohort study which evaluated the safety and efficacy of infliximab for the treatment of refractory noninfectious uveitis. Patients (n = 88) with chronic, recalcitrant uveitis treated with infliximab were identified through an electronic medical record database.¹³ All charts were reviewed for sex, diagnosis, location of inflammation, presence of vasculitis, prior immunomodulatory treatments, duration of infliximab treatment, dose received, secondary side effects, and other medications continued while receiving treatment with infliximab. The primary outcome measures assessed were the rate of remission, time to remission, relapse rate, failure rate, and patient tolerance. Additional analysis was aimed to identify risk factors that would predict a higher success rate of infliximab to treat various types of noninfectious uveitis. Of the 72 patients (81.8%) who achieved clinical remission while being treated with infliximab, 42 (58.3%) required additional immunomodulatory medications. At 7, 18.1, and 44.7 weeks, 25%, 50%, and 75% of patients, respectively, achieved clinical remission off all corticosteroids. Thirty-two patients (36.4%) experienced at least 1 side effect while on infliximab therapy, and 17 patients (19.3%) discontinued treatment secondary to 1 or more intolerable side effects. The most common adverse effects were skin rash (9.1%) and fatigue (8%). Factors associated with a higher chance to achieve clinical remission were non-idiopathic uveitis (p < 0.001), intermediate or panuveitis (p < 0.001), absence of vasculitis (p < 0.001), and a starting dose ≥ 5 mg/kg (p < 0.011). Researchers concluded that infliximab treatment induced a high rate of complete clinical remission in recalcitrant uveitis and is well tolerated by most patients.

NCCN Recommended Uses

According to the NCCN Drugs & Biologics Compendium, NCCN recommends (2A) infliximab for the treatment of:

- Acute graft-versus-host disease (GVHD) as additional therapy in conjunction with systemic corticosteroids following no response (steroid-refractory disease) to first-line therapy options:
 - Therapy for steroid-refractory acute GVHD is often used in conjunction with the original immunosuppressive agent.
- Immune Checkpoint Inhibitor-Related Toxicities – Consider adding infliximab for the management of immunotherapy-related:
 - Myocarditis as a further intervention if no improvement within 24-48 hours of starting pulse-dose methylprednisolone.
 - Moderate (G2) and strongly consider for severe (G3-4) diarrhea or colitis if no response after 2 days of systemic corticosteroids.

- Moderate (G2) pneumonitis if no improvement after 2 to 3 days of corticosteroids or severe (G3-4) pneumonitis if no improvement after 2 days of systemic corticosteroids.
- Severe (G3) or life-threatening (G4) acute renal failure/elevated serum creatinine if toxicity remains > G2 after 4-6 weeks of systemic corticosteroids.
- G1-4 uveitis that is refractory to high-dose systemic corticosteroids.
- Severe inflammatory arthritis as additional disease modifying anti-rheumatic therapy if symptoms do not improve after 7 days of starting high-dose corticosteroids or if unable to taper corticosteroids by week 2.
- Moderate, severe, or life-threatening steroid-refractory myalgias or myositis if refractory to steroids.

Unproven

Juvenile Idiopathic Arthritis (Juvenile Rheumatoid Arthritis)

In an international, multicenter, randomized, placebo-controlled, double-blind study, 122 children with polyarticular juvenile rheumatoid arthritis (JRA) and persistent symptoms despite at least 3 months prior MTX were randomized to receive infliximab 3 mg/kg + MTX or placebo + MTX at weeks 0, 2, and 6.²⁴ At week 14, the placebo group was switched to infliximab 6 mg/kg + placebo. Responses were measured according to American College of Rheumatology Pediatric 30 (Pedi 30) criteria. Although a higher percentage of patients in the 3 mg/kg group achieved responses at week 14 (63.8% vs. 49.2% in placebo group), the study failed to show the efficacy of infliximab for JRA as the difference was not statistically significant. By week 16, similar percentage response was achieved in both groups. At week 52, the percentages reaching ACR Pedi 50 and ACR Pedi 70 were 69.6% and 51.8%, respectively. The safety profile of infliximab 3 mg/kg was generally less favorable than that of infliximab 6 mg/kg, with more serious adverse events, infusion reactions, antibodies to infliximab, and newly induced antinuclear antibodies and antibodies to double-stranded DNA. Patients who completed the study also continued to receive open-label treatment for up to 2 years.

Infliximab has also been studied for use in JIA in smaller, open-label trials.^{24,31-34,36,43-45} Further large-scale studies are required to characterize the efficacy and safety of infliximab in JIA.

Miscellaneous

The medical literature contains a number of small open-label studies and case reports of infliximab therapy for the treatment of adult-onset Still's disease,^{26,27} Sjogren's syndrome,^{22,28} graft-vs-host disease,²⁹⁻³⁰ myelodysplastic syndromes,³⁷ undifferentiated spondyloarthritis,³⁵ Reiter's syndrome,¹⁹ hidradenitis suppurativa,^{21,49-51} and Wegener's granulomatosis.^{38,47-48} While these studies and reports showed infliximab to have a positive effect on the manifestations of these diseases, the use of infliximab for these conditions has not been evaluated in large, controlled trials.

Professional Societies

Ulcerative Colitis

In 2020, the American Gastroenterological Association (AGA) published a clinical practice guideline on the management of moderate to severe ulcerative colitis. In regard to infliximab, the guidelines recommend:

- In adult outpatients with moderate-severe ulcerative colitis, the AGA recommends using infliximab, adalimumab, golimumab, vedolizumab, tofacitinib or ustekinumab over no treatment. (Strong recommendation, moderate quality evidence).
- In adult outpatients with moderate-severe ulcerative colitis who are naïve to biologic agents, the AGA suggests using infliximab or vedolizumab rather than adalimumab, for induction of remission. (Conditional recommendation, moderate quality evidence).
- In adult outpatients with moderate-severe ulcerative colitis who have previously been exposed to infliximab, particularly those with primary non-response, the AGA suggests using ustekinumab or tofacitinib, rather than vedolizumab or adalimumab for induction of remission. (Conditional recommendation, low quality evidence).
- In adult outpatients with active moderate-severe ulcerative colitis, the AGA suggests using biologic monotherapy (TNF α antagonists, vedolizumab, ustekinumab) rather than thiopurine monotherapy for INDUCTION of remission. (Conditional recommendation, low quality evidence).
- In adult outpatients with moderate-severe ulcerative colitis in remission, the AGA makes no recommendation in favor of, or against, using biologic monotherapy (TNF α antagonists, vedolizumab or ustekinumab), rather than thiopurine monotherapy for maintenance of remission. (No recommendation, knowledge gap).

- In adult outpatients with moderate-severe ulcerative colitis, the AGA suggests combining TNF α antagonists, vedolizumab or ustekinumab with thiopurines or methotrexate, rather than biologic monotherapy. (Conditional recommendation, low quality evidence).
- In adult outpatients with moderate-severe ulcerative colitis, the AGA suggests combining TNF α antagonists, vedolizumab or ustekinumab with thiopurines or methotrexate, rather than thiopurine monotherapy. (Conditional recommendation, low quality evidence).
- In adult outpatients with moderate-severe ulcerative colitis, the AGA suggests early use of biologic agents with or without immunomodulator therapy, rather than gradual step up after failure of 5-aminosalicylates. (Conditional recommendation, very low-quality evidence).
- In adult outpatients with moderate-severe ulcerative colitis who have achieved remission with biologic agents and/or immunomodulators, or tofacitinib, the AGA suggests against continuing 5-aminosalicylates for induction and maintenance of remission. (Conditional recommendation, very low-quality evidence).
- In hospitalized adult patients with acute severe ulcerative colitis refractory to intravenous corticosteroids, the AGA suggests using infliximab or cyclosporine. (Conditional recommendation, low quality evidence).
- In hospitalized adult patients with acute severe ulcerative colitis, refractory to intravenous corticosteroids, being treated with infliximab, the AGA makes no recommendation on routine use of intensive vs. standard infliximab dosing. (No recommendation, knowledge gap).

The American College of Gastroenterology (ACG) published their guidelines for the management of adults with ulcerative colitis in 2019. In regard to infliximab or anti-TNF therapy, the guidelines recommend:

Summary and strength of graded recommendations for the management of ulcerative colitis:

- Induction of remission in moderately to severely active ulcerative colitis:
 - In patients with moderately to severely active UC, the ACG recommends anti-TNF therapy using adalimumab, golimumab, or infliximab for induction of remission (strong recommendation, high quality of evidence).
 - In patients with moderately to severely active UC who have failed 5-ASA therapy and in whom anti-TNF therapy is used for induction of remission, the ACG suggests against using 5-ASA for added clinical efficacy (conditional recommendation, low quality of evidence).
 - When infliximab is used as induction therapy for patients with moderately to severely active UC, the ACG recommends combination therapy with a thiopurine (strong recommendation, moderate quality of evidence for azathioprine).
 - In patients with moderately to severely active UC who are responders to anti-TNF therapy and now losing response, the ACG suggests 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).
- Maintenance of remission in patients with previously moderately to severely active ulcerative colitis:
 - In patients with previously moderately to severely active UC who have achieved remission but previously failed 5-ASA therapy and are now on anti-TNF therapy, the ACG recommends against using concomitant 5-ASA for efficacy of maintenance of remission (conditional recommendation, low quality of evidence).
 - The ACG recommends continuing anti-TNF therapy using adalimumab, golimumab, or infliximab to maintain remission after anti-TNF induction in patients with previously moderately to severely active UC (strong recommendation, moderate quality of evidence).
- Management of the hospitalized patient with acute severe ulcerative colitis (ASUC):
 - In patients with ASUC failing to adequately respond to intravenous corticosteroids by 3–5 days the ACG recommends medical rescue therapy with infliximab or cyclosporine (strong recommendation, moderate quality of evidence).
 - In patients with ASUC who achieve remission with infliximab treatment, the ACG recommends maintenance of remission with the same agent (strong recommendation, moderate quality of evidence).

Summary of key concept statements for the management of ulcerative colitis:

- Induction of remission in moderately to severely active ulcerative colitis:
 - Robust data on combination anti-TNF and immunomodulator therapy in moderately to severely active UC exist only for infliximab and thiopurines.
 - Patients who are primary nonresponders to an anti-TNF (defined as lack of therapeutic benefit after induction despite adequate drug levels) should be evaluated and considered for alternative mechanisms of disease control (e.g., in a different class of therapy) rather than cycling to another drug within the anti-TNF class.

- In patients with moderately to severely active UC who had an initial response but subsequently lost efficacy to one anti-TNF therapy, the ACG recommends alternative anti-TNF therapy (but not the biosimilar to the original brand) compared with no treatment for induction of remission.

Plaque Psoriasis

In 2019, the American Academy of Dermatology and the National Psoriasis Foundation published updated treatment guidelines for the management and treatment of psoriasis with biologic therapies. In regard to ustekinumab, the guidelines state:

- Infliximab is recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis.
- The recommended starting dose of infliximab is an infusion of 5 mg/kg administered at wk 0, wk 2, and wk 6, and thereafter it is administered every 8 wks.
- Infliximab is recommended to be administered at a more frequent interval (less than every 8 weeks and as frequently as every 4 weeks during the maintenance phase) and/or at a higher dose up to 10 mg/kg for better disease control in some adult patients.
- Infliximab can be recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the palms and soles (plaque-type palmoplantar psoriasis).
- Infliximab can be recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the nails.
- Infliximab can be recommended as a monotherapy treatment option in adult patients with moderate-to-severe plaque psoriasis affecting the scalp.
- Infliximab may be recommended as a monotherapy treatment option in adult patients with other subtypes (pustular or erythrodermic) of moderate-to-severe plaque psoriasis.
- Infliximab is recommended as a monotherapy treatment option in adult patients with plaque psoriasis of any severity when associated with significant psoriatic arthritis. Infliximab also inhibits radiographically detected damage of joints in patients with psoriatic arthritis.
- Combination of infliximab and topicals such as high-potency corticosteroids with or without a vitamin D analogue can be recommended as a treatment option to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults.
- Infliximab may be combined with acitretin to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults.
- Infliximab may be combined with methotrexate to possibly augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults.
- Infliximab may be combined with apremilast to augment efficacy for the treatment of moderate-to-severe plaque psoriasis in adults when clinically indicated.

Psoriatic Arthritis

In 2018, the American College of Rheumatology and the National Psoriasis Foundation published treatment guidelines for the treatment of psoriatic arthritis. In regard to psoriatic arthritis (PsA) and TNFi's, the guidelines state:

- Recommendations for the initial treatment of patients with active psoriatic arthritis who are oral small molecule (OSM)-and other treatment-naïve patients:
 - Treat with a TNFi biologic over an OSM1
 - Conditional recommendation based on low-quality evidence; may consider an OSM if the patient does not have severe PsA, does not have severe psoriasis,§ prefers oral therapy, has concern over starting a biologic as the first therapy, or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.
 - Treat with a TNFi biologic over an IL-17i biologic
 - Conditional recommendation based on very-low-quality evidence; may consider an IL-17i biologic if the patient has severe psoriasis or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.
 - Treat with a TNFi biologic over an IL-12/23i biologic
 - Conditional recommendation based on very-low-quality evidence; may consider an IL-12/23i biologic if the patient has severe psoriasis, prefers less frequent drug administration, or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.
- Recommendations for treatment of patients with active psoriatic arthritis despite treatment with an OSM:
 - Switch to a TNFi biologic over a different OSM

- Conditional recommendation based on moderate-quality evidence; may consider switching to a different OSM if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, if the patient prefers an oral versus parenteral therapy, or in patients without evidence of severe PsA or severe psoriasis.
 - Switch to a TNFi biologic over an IL-17i biologic
 - Conditional recommendation based on moderate-quality evidence; may consider an IL-17i if the patient has severe psoriasis and/or has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, and/or a family history of demyelinating disease such as multiple sclerosis.
 - Switch to a TNFi biologic over an IL-12/23i biologic
 - Conditional recommendation based on moderate-quality evidence; may consider an IL-12/23i if the patient has severe psoriasis and/or contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or prefers less frequent drug administration.
 - Switch to a TNFi biologic over abatacept
 - Conditional recommendation based on low-quality evidence; may consider abatacept if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease.
 - Switch to a TNFi biologic over tofacitinib
 - Conditional recommendation based on low-quality evidence; may consider tofacitinib if the patient has contraindications to TNFi biologics, including congestive heart failure, previous serious infections, recurrent infections, or demyelinating disease, or prefers oral medication.
 - Switch to a TNFi biologic monotherapy over MTX and a TNFi biologic combination therapy
 - Conditional recommendation based on low-quality evidence; may consider MTX and TNFi biologic combination therapy if the patient has severe skin manifestations, has had a partial response to current MTX therapy, has concomitant uveitis (since uveitis may respond to MTX therapy), and if the current TNFi biologic is infliximab or adalimumab.
- Recommendations for treatment of patients with active psoriatic arthritis despite treatment with a TNFi biologic, as monotherapy or in combination with MTX:
 - Switch to a different TNFi biologic over switching to an IL-17i biologic
 - Conditional recommendation based on low-quality evidence; may consider an IL-17i if the patient had a primary TNFi biologic efficacy failure or a TNFi biologic–associated serious adverse event or severe psoriasis.
 - Switch to a different TNFi biologic over switching to an IL-12/23i biologic
 - Conditional recommendation based on low-quality evidence; may consider an IL-12/23i if the patient had a primary TNFi biologic efficacy failure or a TNFi biologic–associated serious adverse effect or prefers less frequent drug administration.
 - Switch to a different TNFi biologic over switching to abatacept
 - Conditional recommendation based on low-quality evidence; may consider abatacept if the patient had a primary TNFi biologic efficacy failure or TNFi biologic–associated serious adverse effect.
 - Switch to a different TNFi biologic over switching to tofacitinib
 - Conditional recommendation based on low-quality evidence; may consider tofacitinib if the patient prefers an oral therapy or had a primary TNFi biologic efficacy failure or a TNFi biologic–associated serious adverse effect.
 - Switch to a different TNFi biologic (with or without MTX) over adding MTX to the same TNFi biologic monotherapy
 - Conditional recommendation based on very-low-quality evidence; may consider adding MTX when patients have demonstrated partial response to the current TNFi biologic therapy, especially if the TNFi biologic is a monoclonal antibody.
 - Switch to a different TNFi biologic monotherapy over switching to a different TNFi biologic and MTX combination therapy
 - Conditional recommendation based on very-low-quality evidence; may consider switching to a TNFi biologic and MTX combination therapy if the current TNFi biologic is infliximab.
- In adult patients with active PsA despite treatment with a TNFi biologic and MTX combination therapy:
 - Switch to a different TNFi biologic + MTX over switching to a different TNFi biologic monotherapy.
 - Conditional recommendation based on very-low-quality evidence; may consider switching to a different TNFi biologic monotherapy if the patient has demonstrated MTX-associated adverse events, prefers to receive fewer medications, or perceives MTX as a burden.

Ankylosing Spondylitis

In 2017, the British Society for Rheumatology (BSR) and the British Health Professionals in Rheumatology published a revision to their 2005 BSR guidelines to provide guidance for clinicians in the United Kingdom prescribing biologic drugs for the treatment of axial spondyloarthritis (axSpA), including ankylosing spondylitis. This includes the criteria for starting treatment, choice of drug, and assessing response. In regard to tumor necrosis factor inhibitors (TNFi), the guidelines recommend:

- The effectiveness of biologics in axSpA:
 - Anti-TNF therapy is effective at reducing disease activity and spinal pain in axSpA. While short-term MRI data support the efficacy of anti-TNF therapy in treating inflammatory SIJ and spinal lesions in axSpA, evidence for anti-TNF therapy on radiographic disease progression is currently limited.
 - Currently there is insufficient evidence to recommend the use of other biologic agents in axSpA.
- Initiating treatment:
 - Patients should be considered for anti-TNF therapy if they have active axSpA.
- Choice of drug:
 - Extra-articular manifestations and patient choice should be considered when selecting an anti-TNF agent. In the absence of head-to-head studies, systematic reviews have shown no statistical difference in efficacy between infliximab, golimumab, etanercept and adalimumab in the treatment of AS (certolizumab data were not included in these comparative reviews, but its efficacy has been established in clinical trials).
 - There are insufficient data to comment on relative efficacy in nr-axSpA. However, not all biologics are licensed for or effective in the treatment of extra-articular disease, so drug choice should take into account co-morbidities and the preferred route and frequency of administration.
- Assessing response:
 - Initial efficacy response should be assessed following 3–6 months of therapy and responders should then be reassessed every 6 months.
- Withdrawal of therapy:
 - In the absence of an initial clinical response by 6 months, or failure to maintain response at two consecutive assessments, withdrawal of that anti-TNF agent should be considered.
 - There is no evidence to support the withdrawal of anti-TNF therapy in treatment responders.
- Switching:
 - In the event of anti-TNF failure due to inefficacy or adverse events, an alternative anti-TNF agent should be offered if clinically appropriate.
- Safety:
 - The safety of anti-TNF therapies in axSpA is comparable to other inflammatory joint diseases such as RA. There is little evidence to suggest that safety issues differ hugely with different disease groups, and the 2010 British Society for Rheumatology (BSR) guidelines on the safety of anti-TNF therapies in RA are applicable in axSpA.

In 2016, the Assessment of Spondyloarthritis international Society (ASAS) and European League Against Rheumatism (EULAR) updated and integrated the recommendations for ankylosing spondylitis (AS) and the recommendations for the use of tumour necrosis factor inhibitors (TNFi) in axial spondyloarthritis (axSpA) into one guideline applicable to the full spectrum of patients with axSpA. The recommendations describe all aspects of the management of patients with a diagnosis of axSpA. The recommendations related to biologic DMARDs (bDMARDs) are:

- bDMARDs should be considered in patients with persistently high disease activity despite conventional treatments (e.g., non-biologic DMARDs); current practice is to start with TNFi therapy.
- If TNFi therapy fails, switching to another TNFi or IL-17i therapy should be considered.
- If a patient is in sustained remission, tapering of a bDMARD can be considered.

In 2019, the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network published an update of their recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis.⁷⁷ The recommendations related to bDMARDs are:

- TNFi are recommended over secukinumab or ixekizumab as the first biologic to be used.
- Secukinumab or ixekizumab is recommended over the use of a second TNFi in patients with primary nonresponse to the first TNFi.
- TNFi, secukinumab, and ixekizumab are favored over tofacitinib.
- Co-administration of low-dose methotrexate with TNFi is not recommended, nor is a strict treat-to-target strategy or discontinuation or tapering of biologics in patients with stable disease.
- Sulfasalazine is recommended only for persistent peripheral arthritis when TNFi are contraindicated.

- For patients with unclear disease activity, spine or pelvis magnetic resonance imaging could aid assessment.
- Routine monitoring of radiographic changes with serial spine radiographs is not recommended.

Crohn's Disease

According to the American College of Gastroenterology Practice Guidelines for the Management of Crohn's Disease in Adults (ACG Practice Guidelines) published in February 2009, patients with moderate-severe disease usually have a Crohn's Disease Activity Index (CDAI) of 220-450. They have failed to respond to treatment for mild-moderate disease, or have more prominent symptoms of fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia.³

The CDAI⁵² is the sum of the following clinical or laboratory variables after multiplying by their weighting factor given in parentheses:

- Number of liquid or soft stools each day for seven days (2).
- Abdominal pain graded from 0-3 in severity each day for seven days (5).
- General well-being, subjectively assessed from 0 (well) to 4 (terrible) each day for seven days (7).
- Presence of complications where 1 point is added for each complication (20). Complications include:
 - The presence of joint pains (arthralgia) or frank arthritis.
 - Inflammation of the iris or uveitis.
 - Presence of erythema nodosum, pyoderma gangrenosum, or aphthous ulcers.
 - Anal fissures, fistulae or abscesses.
 - Other fistulae (e.g. Enterocutaneous, vesicle, vaginal).
 - Fever (> 37.8 C) during the previous week.
- Taking diphenoxylate/atropine [Lomotil[®]] or opiates for diarrhea (30).
- Presence of an abdominal mass where 0 = none, 2 = questionable, 5 = definite (10);
- Absolute deviation of hematocrit from 47% in males and 42% in females (6).
- Percentage deviation from standard body weight (1).

The 2018 ACG Practice Guidelines support the use of infliximab for treatment and maintenance of patients with moderate to severely active Crohn's disease which is resistant or refractory to corticosteroids, thiopurines or methotrexate. In addition, they state anti-TNF agents can be considered to treat severely active Crohn's disease.⁶⁴

Rheumatoid Arthritis

The 2015 American College of Rheumatology (ACR) RA treatment guideline addresses the use of DMARDs, biologics, tofacitinib, and glucocorticoids in early (< 6 months) and established (≥ 6 months) RA and the use of various treatment approaches in frequently encountered clinical scenarios, including treat-to-target, switching between therapies, tapering of therapy, the use of biologics and DMARDs in high-risk RA patients, vaccination in patients with RA receiving DMARDs or biologics, TB screening with biologics or tofacitinib, and laboratory monitoring with DMARDs.² The guideline recommendations apply to common clinical situations, since the panel considered issues common to most patients, not exceptions. Recommendations are classified as either strong or conditional. A strong recommendation means that the panel was confident that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to most patients, and only a small proportion would not want to follow the recommendation. A conditional recommendation means that the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of patients, but some may not want to follow the recommendation. As a result, conditional recommendations are preference sensitive and warrant a shared decision-making approach.

Supplementary Appendix 5, of the 2015 ACR RA guideline, summarizes recommendations for patients with early RA, established RA, and high-risk comorbidities:²

Recommendations for Early RA Patients

- The panel strongly recommends using a treat-to-target strategy rather than a non-targeted approach, regardless of disease activity level. The ideal target should be low disease activity or remission, as determined by the clinician and the patient. In some cases, another target may be chosen because risk tolerance by patients or comorbidities may mitigate the usual choices.

- For DMARD-naïve patients with early, symptomatic RA, the panel strongly recommends DMARD monotherapy over double or triple DMARD therapy in patients with low disease activity and conditionally recommends DMARD monotherapy over double or triple DMARD therapy in patients with moderate or high disease activity. Methotrexate should be the preferred initial therapy for most patients with early RA with active disease.
- For patients with moderate or high disease activity despite DMARD therapy (with or without glucocorticoids), the panel strongly recommends treatment with a combination of DMARDs or a TNFi or a non-TNF biologic, with or without methotrexate (MTX) in no particular order of preference, rather than continuing DMARD monotherapy alone. Biologic therapy should be used in combination with MTX over biologic monotherapy, when possible, due to superior efficacy.
- For patients with moderate or high disease activity despite any of the above DMARD or biologic therapies, the panel conditionally recommends adding low-dose glucocorticoids (defined as ≤ 10 mg/day of prednisone or equivalent). Low-dose glucocorticoids may also be used in patients who need a bridge until realizing the benefits of DMARD therapy. The risk/benefit ratio of glucocorticoid therapy is favorable as long as the dose is low and the duration of therapy is short.
- For patients experiencing a flare of RA, the panel conditionally recommends adding short-term glucocorticoids (< 3 months of treatment) at the lowest possible dose for the shortest possible duration, to provide a favorable benefit-risk ratio for the patient.

Recommendations for Established RA Patients

- The panel strongly recommends using a treat-to-target strategy rather than a non-targeted approach, regardless of disease activity level. The ideal target should be low disease activity or remission, as determined by the clinician and the patient. In some cases, however, another target may be chosen because tolerance by patients or comorbidities may mitigate the usual choices.
- For DMARD-naïve patients with low disease activity, the panel strongly recommends using DMARD monotherapy over a TNFi. For DMARD-naïve patients with moderate or high disease activity, the panel conditionally recommends DMARD monotherapy over double or triple DMARD therapy and DMARD monotherapy over tofacitinib. In general, MTX should be the preferred initial therapy for most patients with established RA with active disease.
- For patients with moderate or high disease activity despite DMARD monotherapy including methotrexate, the panel strongly recommends using combination DMARDs or adding a TNFi or a non-TNF biologic or tofacitinib (all choices with or without methotrexate) in no particular order of preference, rather than continuing DMARD monotherapy alone. Biologic therapy should be used in combination with MTX over biologic monotherapy, when possible, due to its superior efficacy.

For All Scenarios for Established RA Below, Treatment May Be With or Without MTX

- For moderate or high disease activity despite TNFi therapy in patients currently not on a DMARD, the panel strongly recommends that one or two DMARDs be added to TNFi therapy rather than continuing TNFi therapy alone.
- If disease activity is moderate or high despite single TNFi biologic therapy, the panel conditionally recommends using a non-TNF biologic.
- If disease activity is moderate or high despite non-TNF biologic therapy, the panel conditionally recommends using another non-TNF biologic. However, if a patient has failed multiple non-TNF biologics and they are TNFi-naïve with moderate or high disease activity, the panel conditionally recommends treatment with a TNFi.
- For patients with moderate or high disease activity despite prior treatment with at least one TNFi and at least one non-TNF-biologic (sequentially, not combined), the panel conditionally recommends first treating with another non-TNF biologic. However, when a non-TNF biologic is not an option (e.g., patient declines non-TNF biologic therapy due to inefficacy or side effects), the panel conditionally recommends treatment with tofacitinib.
- If disease activity is moderate or high despite the use of multiple (2+) TNFi therapies (in sequence, not concurrently), the panel conditionally recommends non-TNF biologic therapy and then conditionally treating with tofacitinib when a non-TNF biologic is not an option.
- If disease activity is moderate or high despite any of the above DMARD or biologic therapies, the panel conditionally recommends adding low-dose glucocorticoids.
- If patients with established RA experience an RA flare while on DMARD, TNFi, or non-TNF biologic therapy, the panel conditionally recommends adding short-term glucocorticoids (< 3 months of treatment) at the lowest possible dose and for shortest possible duration to provide the best benefit-risk ratio for the patient.
- In patients with established RA and low disease activity but not remission, the panel strongly recommends continuing DMARD therapy, TNFi, non-TNF biologic or tofacitinib rather than discontinuing respective medication.
- In patients with established RA currently in remission, the panel conditionally recommends tapering DMARD therapy, TNFi, non-TNF biologic, or tofacitinib.

- The panel strongly recommends not discontinuing all therapies in patients with established RA in disease remission.

Recommendations for RA Patients with High-Risk Comorbidities

Congestive Heart Failure

- In patients with established RA with moderate or high disease activity and New York Heart Association (NYHA) class III or IV congestive heart failure (CHF), the panel conditionally recommends using combination DMARD therapy, a non-TNF biologic, or tofacitinib rather than a TNFi.
- If patients in this population are treated with a TNFi and their CHF worsens while on the TNFi, the panel conditionally recommends switching to combination DMARD therapy, a non-TNF biologic, or tofacitinib rather than a different TNFi.

Hepatitis B

- In patients with established RA with moderate or high disease activity and evidence of active hepatitis B infection (hepatitis surface antigen positive > 6 months), who are receiving or have received effective antiviral treatment, the panel strongly recommends treating them the same as patients without this condition.
- For a patient with natural immunity from prior exposure to hepatitis B (i.e., HB core antibody and HBS antibody positive and normal liver function tests), the panel recommends the same therapies as those without such findings as long as the patient's viral load is monitored.
- For patients with chronic hepatitis B who are untreated, referral for antiviral therapy is appropriate prior to immunosuppressive therapy.

Hepatitis C

- In patients with established RA with moderate or high disease activity and evidence of chronic hepatitis C virus (HCV) infection, who are receiving or have received effective antiviral treatment, the panel conditionally recommends treating them the same as the patients without this condition.
- The panel recommends that rheumatologists work with gastroenterologists and/or hepatologists who would monitor patients and reassess the appropriateness of antiviral therapy. This is important considering the recent availability of highly effective therapy for HCV, which may lead to a greater number of HCV patients being treated successfully.
- If the same patient is not requiring or receiving antiviral treatment for their hepatitis C, the panel conditionally recommends using DMARD therapy rather than TNFi.

Malignancy

- Previous Melanoma and Non-Melanoma Skin Cancer:
 - In patients with established RA and moderate or high disease activity and a history of previously treated or untreated skin cancer (melanoma or non-melanoma), the panel conditionally recommends the use of DMARD therapy over biologics or tofacitinib.
- Previous Lymphoproliferative Disorders:
 - In patients with established RA with moderate or high disease activity and a history of a previously treated lymphoproliferative disorder, the panel strongly recommends using rituximab rather than a TNFi and conditionally recommends using combination DMARD therapy, abatacept or tocilizumab rather than TNFi.
- Previous Solid Organ Cancer:
 - In patients with established RA with moderate or high disease activity and previously treated solid organ cancer, the panel conditionally recommends that they be treated for RA just as one would treat an RA patient without a history of solid organ cancer.

Serious Infections

- In patients with established RA with moderate or high disease activity and previous serious infection(s), the panel conditionally recommends using combination DMARD therapy or abatacept rather than TNFi.

In 2021, the American College of Rheumatology published an update to their guideline for the treatment of rheumatoid arthritis and included several new topics, including recommendations for administration of methotrexate, use of methotrexate in patients with subcutaneous nodules, pulmonary disease, and NAFLD, use of rituximab in patients with hypogammaglobulinemia, and treatment of RA in patients with NTM lung disease.⁷⁸ Areas covered in the 2015 guidelines that are not covered in this update include recommendations for patients with hepatitis C and solid malignancies.

The recommendations related to bDMARDs [TNF inhibitors (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), T cell costimulatory inhibitor (abatacept), IL-6 receptor inhibitors (tocilizumab, sarilumab), anti-CD20 antibody (rituximab)] are:

- Methotrexate monotherapy is strongly recommended over bDMARD or tsDMARD monotherapy for DMARD-naive patients with moderate-to-high disease activity.
- Methotrexate monotherapy is strongly recommended over methotrexate plus a non-TNF inhibitor bDMARD or tsDMARD for DMARD-naive patients with moderate-to-high disease activity.
- Methotrexate monotherapy is conditionally recommended over the combination of methotrexate plus a bDMARD or tsDMARD.
- A treat-to-target approach is strongly recommended over usual care for patients who have not been previously treated with bDMARDs or tsDMARDs.
- A treat-to-target approach is conditionally recommended over usual care for patients who have had an inadequate response to bDMARDs or tsDMARDs.
- Addition of a bDMARD or tsDMARD is conditionally recommended over triple therapy (i.e., addition of sulfasalazine and hydroxychloroquine) for patients taking maximally tolerated doses of methotrexate who are not at target.
- Switching to a bDMARD or tsDMARD of a different class is conditionally recommended over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target.
- Gradual discontinuation of methotrexate is conditionally recommended over gradual discontinuation of the bDMARD or tsDMARD for patients taking methotrexate plus a bDMARD or tsDMARD who wish to discontinue a DMARD.

Heart Failure

- Addition of a non-TNF inhibitor bDMARD or tsDMARD is conditionally recommended over addition of a TNF inhibitor for patients with New York Heart Association (NYHA) class III or IV heart failure and an inadequate response to csDMARDs. Switching to a non-TNF inhibitor bDMARD or tsDMARD is conditionally recommended over continuation of a TNF inhibitor for patients taking a TNF inhibitor who develop heart failure.

Hepatitis B Infection

- Prophylactic antiviral therapy is strongly recommended over frequent monitoring of viral load and liver enzymes alone for patients initiating rituximab who are hepatitis B core antibody positive (regardless of hepatitis B surface antigen status). Prophylactic antiviral therapy is strongly recommended over frequent monitoring alone for patients initiating any bDMARD or tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen positive.
- Frequent monitoring alone of viral load and liver enzymes is conditionally recommended over prophylactic antiviral therapy for patients initiating a bDMARD other than rituximab or a tsDMARD who are hepatitis B core antibody positive and hepatitis B surface antigen negative.

Persistent Hypogammaglobulinemia Without Infection

- In the setting of persistent hypogammaglobulinemia without infection, continuation of rituximab therapy for patients at target is conditionally recommended over switching to a different bDMARD or tsDMARD.

Previous Serious Infection

- Addition of csDMARDs is conditionally recommended over addition of a bDMARD or tsDMARD for patients with a serious infection within the previous 12 months who have moderate-to-high disease activity despite csDMARD monotherapy.

Nontuberculous Mycobacterial (NTM) Lung Disease

- Addition of csDMARDs is conditionally recommended over addition of a bDMARD or tsDMARD for patients with NTM lung disease who have moderate-to-high disease activity despite csDMARD monotherapy.
- Abatacept is conditionally recommended over other bDMARDs and tsDMARDs for patients with NTM lung disease who have moderate-to high disease activity despite csDMARDs.

Juvenile Idiopathic Arthritis

The 2011 American College of Rheumatology (ACR) recommendations for the Treatment of Juvenile Idiopathic Arthritis include the tumor necrosis factor (TNF) inhibitors adalimumab, etanercept, infliximab and do not differentiate between the agents.^{34,66}

For JIA patients with history of arthritis of 4 or fewer joints:

- Initiation of a TNF inhibitor was recommended for patients who have received glucocorticoids joint injections and 3 months of methotrexate at the maximum tolerated typical dose and have moderate or high disease activity and features of poor prognosis (level C).
- Initiation of a TNF inhibitor was also recommended for patients who have received glucocorticoids joint injections and 6 months of methotrexate and have high disease activity without features of poor prognosis (level C).
- Initiation of a TNF inhibitor was recommended for patients specifically with the enthesitis-related arthritis category of JIA who have received glucocorticoids joint injections and an adequate trial of sulfasalazine (without prior methotrexate) and have moderate or high disease activity, irrespective of prognostic features (level C).

For JIA patients with history of arthritis of 5 or more joints:

- Initiation of a TNF inhibitor was recommended for patients who have received methotrexate or leflunomide for 3 months at the maximum tolerated typical dose and have moderate or high disease activity, irrespective of poor prognostic features (level B).
- Initiation of a TNF inhibitor was also recommended for patients who have received methotrexate or leflunomide for 6 months and have low disease activity, irrespective of poor prognostic features (level B).
- Switching from one TNF inhibitor to another was recommended as one treatment approach for patients who have received the current TNF inhibitor for 4 months and have moderate or high disease activity, irrespective of poor prognostic features (level C).
- Switching to a TNF inhibitor was recommended as one treatment approach for patients who have received abatacept for 3 months and have high disease activity and features of poor prognosis and for patients who have received abatacept for 6 months and have moderate or high disease activity, irrespective of prognostic features (level D).

Level of evidence “B” was assigned when the recommendation was supported by nonrandomized controlled studies (e.g., cohort and case-control studies) or extrapolations from randomized clinical trials.

Level of evidence “C” was assigned when the recommendation was supported by uncontrolled studies (case series), extrapolations from nonrandomized controlled studies, or marked extrapolations from randomized clinical trials (e.g., studies of adult arthritis patients applied to juvenile arthritis or studies of polyarthritis phenotype applied to oligoarthritis).

In 2019, the ACR published additional guidelines for the treatment of juvenile idiopathic arthritis manifesting as non-systemic polyarthritis, sacroiliitis, or enthesitis.⁷⁹ Recommendations including the use of TNF inhibitors (adalimumab, etanercept, infliximab, golimumab) and non-TNF inhibitors (abatacept, tocilizumab, rituximab) are summarized below:

Polyarthritis

- In children and adolescents with JIA and polyarthritis initiating treatment with a biologic (etanercept, adalimumab, golimumab, abatacept, or tocilizumab) combination therapy with a DMARD is conditionally recommended over biologic monotherapy (Very low level of evidence).
- Combination therapy with a DMARD is strongly recommended for infliximab (Low level of evidence).
- Initial therapy
 - In patients without risk factors, a DMARD is conditionally recommended over a biologic (Low level of evidence).
 - In patients with risk factors, a DMARD is conditionally recommended over a biologic, recognizing that there are situations where initial therapy that includes a biologic may be preferred (Low level of evidence).
 - Initial biologic therapy may be considered for patients with risk factors and involvement of high-risk joints (e.g., cervical spine, wrist, or hip), high disease activity, and/or those judged by their physician to be at high risk of disabling joint damage.
- Subsequent therapy: Low disease activity (cJADAS-10 \leq 2.5 and \geq 1 active joint)
 - For children receiving a DMARD and/or biologic, escalating therapy is conditionally recommended over no escalation of therapy. Escalation of therapy may include: Intraarticular glucocorticoid injection(s), optimization of DMARD dose, trial of methotrexate if not done, and adding or changing biologic. (Very low level of evidence).
- Subsequent therapy: Moderate/high disease activity (cJADAS-10 $>$ 2.5)
 - If patient is receiving DMARD monotherapy:
 - Adding a biologic to original DMARD is conditionally recommended over changing to a second DMARD (Low level of evidence).
 - Adding a biologic is conditionally recommended over changing to triple DMARD therapy (Low level of evidence).

- If patient is receiving first TNFi (±DMARD):
 - Switching to a non-TNFi biologic (tocilizumab or abatacept) is conditionally recommended over switching to a second TNFi.
 - A second TNFi may be appropriate for patients with good initial response to their first TNFi (Very low level of evidence).
- If patient is receiving second biologic:
 - Using TNFi, abatacept, or tocilizumab (depending on prior biologics received) is conditionally recommended over rituximab (Very low level of evidence).

Sacroiliitis

- In children and adolescents with active sacroiliitis despite treatment with NSAIDs:
 - Adding TNFi is strongly recommended over continued NSAID monotherapy (Low level of evidence).

Enthesitis

- In children and adolescents with active enthesitis despite treatment with NSAIDs:
 - Using a TNFi is conditionally recommended over methotrexate or sulfasalazine (Low level of evidence).

A strong recommendation means that the Voting Panel was confident that the desirable effects of following the recommendation outweigh the undesirable effects (or vice versa), so the course of action would apply to all or almost all patients, and only a small proportion would not want to follow the recommendation. In some cases, strong recommendations were made even in the absence of moderate- or high-quality evidence based on Voting Panel experience and data from adult studies.

A conditional recommendation means that the Voting Panel believed that the desirable effects of following the recommendation probably outweigh the undesirable effects, so the course of action would apply to the majority of the patients, but some may not want to follow the recommendation. Because of this, conditional recommendations are particularly preference-sensitive and warrant a shared decision-making approach. Conditional recommendations were generally based on low- to very low-quality evidence.

In 2021, the ACR published additional guidelines for the treatment of juvenile idiopathic arthritis manifesting as oligoarthritis, TMJ arthritis, and systemic JIA with and without macrophage activation syndrome (MAS).⁸⁰ Recommendations including the use of TNF inhibitors (adalimumab, etanercept, infliximab, golimumab, certolizumab pegol) and other biologic response modifiers (abatacept, tocilizumab, anakinra, canakinumab) are summarized below:

Oligoarticular JIA

- Biologic DMARDs are strongly recommended if there is inadequate response to or intolerance of NSAIDs and/or intraarticular glucocorticoids (IAGCs) and at least 1 conventional synthetic DMARD (Very low certainty of evidence).

TMJ Arthritis

- Biologic DMARDs are conditionally recommended if there is inadequate response to or intolerance of NSAIDs and/or intraarticular glucocorticoids (IAGCs) and at least 1 conventional synthetic DMARD (Very low certainty of evidence).

Systemic JIA without Macrophage Activation Syndrome (MAS)

- Biologic DMARDs (IL-1 and IL-6 inhibitors) are conditionally recommended as initial monotherapy (Very low certainty of evidence).
- IL-1 and IL-6 inhibitors are strongly recommended over a single or combination of conventional synthetic DMARDs for inadequate response to or intolerance of NSAIDs and/or glucocorticoids (Very low certainty of evidence).
- Biologic DMARDs or conventional synthetic DMARDs are strongly recommended over long-term glucocorticoids for residual arthritis and incomplete response to IL-1 and/or IL-6 inhibitors (Very low certainty of evidence).

Systemic JIA with MAS

- IL-1 and IL-6 inhibitors are conditionally recommended over calcineurin inhibitors alone to achieve inactive disease and resolution of MAS. (Very low certainty of evidence).

- Biologic DMARDs or conventional synthetic DMARDs are strongly recommended over long-term glucocorticoids for residual arthritis and incomplete response to IL-1 and/or IL-6 inhibitors (Very low certainty of evidence).

Noninfectious Uveitis

In 2014, a subcommittee of the Executive Committee of the American Uveitis Society conducted a systematic review of published literature and developed a guideline for the use of anti-tumor necrosis factor α (TNF- α) biologic agents in patients with ocular inflammatory disorders. Their recommendations are as follows:

- Strong recommendation. Anti-TNF therapy with infliximab (good-quality evidence) or adalimumab (moderate-quality evidence) should be considered early in management of patients with vision-threatening ocular manifestations of Behçet's disease.
- Strong recommendation. Anti-TNF therapy with infliximab (good-quality evidence) or adalimumab (good-quality evidence) should be considered as second-line immunomodulatory therapy for children with vision-threatening uveitis secondary to JIA in whom methotrexate therapy is insufficiently effective or not tolerated. Methotrexate therapy, if tolerated, may be combined with infliximab therapy.
- Strong recommendation. Anti-TNF therapy with infliximab or potentially adalimumab should be considered as second-line immunomodulatory therapy in patients with vision-threatening chronic uveitis from seronegative spondyloarthritis (good- to moderate-quality evidence).
- Discretionary recommendation. Anti-TNF therapy with infliximab or adalimumab for other forms of ocular inflammation, including sarcoidosis, scleritis, and panuveitis, may be considered in patients with vision-threatening, corticosteroid-dependent disease who have failed first-line immunomodulatory therapies such as antimetabolites or calcineurin inhibitors (moderate-quality evidence). The literature for adalimumab is less developed than for infliximab, but these agents seem to show similar efficacy in most studies. Until more comparative data are available, no recommendation can be made as to preferred agent, although numerous studies have suggested that adalimumab may be effective in patients who have become intolerant to or have developed reduced clinical responsiveness to infliximab.
- Strong recommendation. Use of infliximab or adalimumab should be considered before etanercept therapy for treatment of ocular inflammatory disease. Etanercept may have efficacy for treatment of some forms of ocular inflammatory disease such as mucocutaneous Behçet's disease, but it has been associated with development of uveitis in JIA patients and development of sarcoid-like disease in others. Patients presently taking etanercept for other indications with existing, incompletely controlled uveitis or new ocular inflammatory disease should consider switching to infliximab or adalimumab if possible.

Technology Assessments

A 2020 Cochrane review was published to compare the efficacy and safety of conventional systemic agents, small molecules, and biologics for patients with moderate to severe psoriasis.²⁴ The technical assessment also sought to provide a ranking of these treatments according to their efficacy and safety. The assessment included 140 studies (31 new studies for the update) in the review (51,749 randomised participants, 68% men, mainly recruited from hospitals). Nineteen treatments were assessed. At class level, in terms of reaching PASI 90, the biologic treatments anti-IL17, anti-IL12/23, anti-IL23, and anti-TNF alpha were significantly more effective than the small molecules and the conventional systemic agents. At drug level, in terms of reaching PASI 90, infliximab, all of the anti-IL17 drugs (ixekizumab, secukinumab, bimekizumab and brodalumab) and the anti-IL23 drugs (risankizumab and guselkumab, but not tildrakizumab) were significantly more effective in reaching PASI 90 than ustekinumab and 3 anti-TNF alpha agents: adalimumab, certolizumab and etanercept. Adalimumab and ustekinumab were significantly more effective in reaching PASI 90 than certolizumab and etanercept. There was no significant difference between tofacitinib or apremilast and between two conventional drugs: ciclosporin and methotrexate. The network meta-analysis also showed that infliximab, ixekizumab, risankizumab, bimekizumab, guselkumab, secukinumab and brodalumab outperformed other drugs when compared to placebo in reaching PASI 90. The authors review showed that compared to placebo, the biologics infliximab, ixekizumab, risankizumab, bimekizumab, guselkumab, secukinumab and brodalumab were the best choices for achieving PASI 90 in people with moderate-to-severe psoriasis on the basis of moderate- to high-certainty evidence (low-certainty evidence for bimekizumab).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Remicade is a tumor necrosis factor (TNF) blocker indicated for¹:

Infliximab (Avsola[®], Inflectra[®], Remicade[®], & Renflexis[™]) (for Mississippi Only)
 UnitedHealthcare Community Plan Medical Benefit Drug Policy

- **Crohn's Disease:**
 - Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy
 - Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease
- **Pediatric Crohn's Disease:**
 - Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy
- **Ulcerative Colitis:**
 - Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy
- **Pediatric Ulcerative Colitis:**
 - Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy
- **Rheumatoid Arthritis in combination with methotrexate:**
 - Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active disease
- **Plaque Psoriasis:**
 - Treatment of adult patients with chronic severe (i.e., extensive and /or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate
- **Psoriatic Arthritis:**
 - Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in adult patients with psoriatic arthritis
- **Ankylosing Spondylitis:**
 - Reducing signs and symptoms in adult patients with active disease

Avsola (infliximab-axxq), Inflectra (infliximab-dyyb), and Renflexis (infliximab-abda) are biosimilar* to Remicade (infliximab). Avsola, Inflectra and Renflexis are a tumor necrosis factor (TNF) blocker indicated for^{57-60, 62}:

- **Crohn's Disease:**
 - Reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy
 - Reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease
- **Pediatric Crohn's Disease:**
 - Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy
- **Ulcerative Colitis:**
 - Reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy
- **Pediatric Ulcerative Colitis:**
 - Reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy
- **Rheumatoid Arthritis in combination with methotrexate:**
 - Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active disease
- **Ankylosing Spondylitis:**
 - Reducing signs and symptoms in adult patients with active disease
- **Psoriatic Arthritis:**
 - Reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in adult patients with psoriatic arthritis
- **Plaque Psoriasis:**
 - Treatment of adult patients with chronic severe (i.e., extensive and /or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate

*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product.

Reference Product	Biosimilar Product
Remicade	Avsola, Inflectra, Ixifi, Renflexis

The FDA issued an alert dated September 7, 2011, to inform healthcare professionals that the Boxed Warning for the entire class of Tumor Necrosis Factor-alpha (TNF α) blockers has been updated to include the risk of infection from two bacterial pathogens, Legionella and Listeria. In addition, the Boxed Warning and Warnings and Precautions sections of the labels for all of the TNF α blockers have been revised so that they contain consistent information about the risk for serious infections and the associated disease-causing pathogens.¹¹

The FDA issued an update on November 3, 2011 regarding their ongoing safety review of Tumor Necrosis Factor (TNF) blockers and malignancy in children, adolescents, and young adults (30 years of age or younger). This issue was previously communicated in June 2008, August 2009, and April 2011. The FDA is requiring the manufacturers of TNF blockers to perform enhanced safety surveillance for these products. The manufacturers will also provide FDA with annual summaries and assessments of malignancies and TNF blocker utilization data. Healthcare professionals should remain vigilant for cases of malignancy in patients treated with TNF blockers.¹⁰

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Policy History/Revision Information

Date	Summary of Changes
05/01/2024	<p>Coverage Rationale</p> <ul style="list-style-type: none"> ● Revised coverage criteria for initial therapy for Crohn's disease; added criterion requiring the patient has a history of failure to one of the following conventional therapies up to maximally indicated doses within the last 3 months, unless contraindicated or clinically significant adverse effects are experienced: <ul style="list-style-type: none"> ○ Corticosteroids (e.g., prednisone, methylprednisolone, budesonide) ○ 6-mercaptopurine (Purinethol) ○ Azathioprine (Imuran) ○ Methotrexate (Rheumatrex, Trexall) <p>Supporting Information</p> <ul style="list-style-type: none"> ● Archived previous policy version CSMS2024D0004AN

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.