Qualified Health Plans offered in North Carolina by CareSource North Carolina Co., d/b/a CareSource

General Inflammation Testing

Policy Number: AHS – G2155 – General Inflammation Testing	Prior Policy Name and Number, as applicable:
Effective Date: 12/01/2023	

I. Policy Description

Inflammatory response can occur due to tissue injury and/or various disorders, including arthritis, lupus, and infection. Acute phase reactants, such as serum C-reactive protein (CRP), are released in the acute phase response during inflammation and can be used to monitor inflammation. Inflammation may also be measured using the simple laboratory technique of erythrocyte sedimentation rate (ESR) (Kushner, 2023).

For guidance on the use of CRP as a cardiac biomarker, please see policy AHS-G2150-Biomarkers for Myocardial Infarction and Chronic Heart Failure. For guidance on the use of CRP as a marker for acute pancreatitis, please see AHS-G2153-Pancreatic Enzyme Testing for Acute Pancreatitis.

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request.

1) Measurement of C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR) **MEETS COVERAGE CRITERIA** for inflammatory conditions as specified in Note 1.

2) For individuals without a diagnosed inflammatory condition, measurement of ESR **DOES NOT MEET COVERAGE CRITERIA.**

3) Measurement of CRP and/or ESR during general exam without abnormal findings **DOES NOT MEET COVERAGE CRITERIA**.

NOTES:

Note 1: Coverage of ESR, CRP (conventional or high-sensitivity), or both CRP and ESR is designated based on the diagnosed or suspected inflammatory condition.

Condition	Test Preference	Frequency of Testing
Acute and Chronic Urticaria	CRP or ESR	Not specified (NS)
Acute Hematogenous Osteomyelitis (AHO)	CRP	To confirm diagnosis; 2 to 3 days during the early therapeutic course; weekly until normalization (or a clear trend toward normalization is evident)
Acute Phase Inflammation	CRP	NS
Ankylosing Spondylitis	CRP or ESR	Regular interval use in patients with active symptoms
Arthritis	CRP and ESR	1-3 months initially; 6-12 months later
Castleman's Disease	CRP or ESR	NS
General Inflammation	CRP	NS
Giant Cell Arteritis	CRP and ESR	To confirm diagnosis; during follow-up visits
Hodgkin Lymphoma	ESR	Every 3 to 6 months for 1 to 2 years; every 6 to 12 months for the next 3 years; annually thereafter
Irritable Bowel Syndrome	CRP and ESR	During initial assessment to exclude other diagnoses
Large Vessel Vasculitis	CRP or ESR	NS
Nonradiographic axial sponyloarthritis	CRP or ESR	Regular interval use in patients with active symptoms
Polymyalgia Rheumatica	CRP or ESR	At initial diagnosis; every 3 months during long-term steroid therapy
Periprosthetic Joint Infections (PJI)	CRP and ESR	NS
Rheumatoid Arthritis	CRP or ESR	Prior to treatment; every 1-3 months during active disease; annually when disease is inactive
Systemic Lupus Erythematosus	CRP or ESR	At initial assessment; every 1-3 months during active disease; every 6-12 months during stable disease; during pregnancy
T-cell lymphomas	ESR	NS

III. Table of Terminology

Term	Definition
AAAAI	Academy of Allergy, Asthma & Immunology
AAFP	American Academy of Family Physicians
AAOS	American Association of Orthopaedic Surgeons
AAOS	American Academy of Orthopaedic Surgeons
ABIM	American Board of Internal Medicine
ABVD	Adriamycin, bleomycin, vinblastine, dacarbazine
ACAAI	American College of Allergy, Asthma & Immunology
aCL	Anticardiolipin
ACPA	Anti-cyclic citrullinated peptide antibodies
ACR	American College of Rheumatology

Term	Definition
ACR	American College of Radiology
ANA	Antinuclear antibodies
Anti-CCP	Anti-cyclic citrullinated peptides
Anti-dsDNA	Anti-double stranded DNA
Anti-β2-GPI	Anti-β2-glycoprotein I
aPL	Antiphospholipid antibodies
AS	Ankylosing spondylitis
ASCP	American Society for Clinical Pathology
ASCP	Anti-cyclic citrullinated peptide antibodies
AUC	Area under the curve
BHPR	British Health Professionals in Rheumatology
BSR	British Society for Rheumatology
CBC	Complete blood count
cCRP	Cardiac C-reactive protein
CDAI	Clinical disease activity index
CHL	Classic Hodgkin lymphoma
CLIA	Clinical laboratory improvement act
CRA	Canadian Rheumatology Association
CRP	C-reactive protein
CTD	Connective tissue diseases
CVD	Cardiovascular disease
DAS	Disease activity score
DAS28	28-Joint disease activity score
DAS28-CRP	Disease activity score 28 C-reactive protein
DAS28-ESR	Disease activity score with 28-joint counts - erythrocyte sedimentation rate
EDL	Essential In Vitro Diagnostics
EDTA	Ethylenediamine tetraacetic acid
eGFR	Estimated glomerular filtration rate
EIA	Enzyme immunoassay
ENA	Extractable nuclear antigens
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
GCA	Giant cell arteritis
HCSC	Health care service corporation
HL	Hodgkin lymphoma
hsCRP	High-sensitivity C-reactive protein
IBS	Irritable bowel syndrome

Term	Definition
ICSH	International Council for Standardization in Hematology
ISRT	Involved-site radiation therapy
IVD	In vitro diagnostics
JTFPP	Joint Task Force on Practice Parameters
LAC	Lupus anticoagulant
LDH	Lactate dehydrogenase
MCD	Multicentric Castleman Disease
MSIS	Musculoskeletal Infection Society
NA	Not applicable
NASH	Nonalcoholic steatohepatitis
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NPV	Negative predictive value
NS	Not specified
NSAID	Non-steroidal anti-inflammatory drugs
PAS	Patient activity scale
PJI	Periprosthetic joint infections
PMR	Polymyalgia rheumatica
PPV	Positive predictive value
RA	Rheumatoid arthritis
RACGP	Rheumatoid Arthritis Working Group of The Royal Australian College of General Practitioners
RAPID3	Routine assessment of patient index data 3
RD	Rheumatic disease
RDT	Rapid diagnostic test
RF	Rheumatoid factor
SAA	Spondylitis Association of America
SDAI	Simplified disease activity index
SIRS	Systemic inflammatory response syndrome
SLE	Systemic lupus erythematosus
TSH	Thyroid-stimulating hormone
VASDA	Visual analog scale disease activity
VASQOL	VAS quality of life
WHO	World Health Organization

IV. Scientific Background

Conditions Associated with Acute Inflammatory Responses

Diseases most associated with an acute inflammatory response measured by C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR) include arthritis, especially rheumatoid arthritis (RA), polymyalgia rheumatica (PMR), giant cell arteritis (GCA), systemic lupus erythematosus (SLE), cardiovascular disease (CVD) (Kushner, 2023), and Hodgkin lymphoma (HL) (NCCN, 2022). RA is a systemic polyarthritis that can lead to joint loss as well as tendon and ligament deformation to the point of affecting day-to-day living. The diagnosis of RA can be made in a patient "with inflammatory arthritis involving three or more joints, positive RF [rheumatoid factor] and/or anti-citrullinated peptide/protein antibody, disease duration of more than six weeks, and elevated CRP or ESR, but without evidence of diseases with similar clinical features" (Baker, 2023). PMR "is an inflammatory rheumatic condition characterized clinically by aching and morning stiffness about the shoulders, hip girdle, and neck" (C. Salvarani & F. Muratore, 2023). PMR is frequently associated with GCA (also known as Horton disease), which is vasculitis of medium-to-large blood vessels and can include the aorta and cranial arteries. Cranial arteritis can lead to permanent vision loss. An estimated 40-50% of patients with GCA also suffer from PMR whereas 15% of all PMR patients are also diagnosed with GCA. Due to inflammation of the aorta and aortic branches, aortic aneurysm and aortic dissection can occur in patients with GCA (C. Salvarani & F. Muratore, 2023). In both PMR and GCA, ESR and CRP levels are typically elevated. SLE "is a complex autoimmune disease with chronic relapsing-remitting course and variable manifestations leading a spectrum from mild mucocutaneous to devastating, life-threatening illness… Epigenetic modifications mediate the effect of the environment on immunologic responses, eventually leading to an inflammatory, autoimmune, multi-systemic disease characterized by autoantibody production and tissue injury" (Gergianaki & Bertsias, 2018). Since patients with SLE can be prone to infection, ESR and CRP may be used in monitoring inflammation (Kushner, 2023). CVD is a very common inflammatory disorder in the United States. Although serum CRP is a non-specific inflammatory marker and is not a causative agent of CVD, serum CRP can be used as a biomarker for CVD (Black et al., 2004; Kushner, 2023). Hodgkin lymphoma accounts for 10% of lymphomas and is characterized as a B-cell lymphoma "containing a minority of neoplastic cells (Reed-Sternberg cells and their variants) in an inflammatory background" (Aster & Pozdnyakova, 2023). ESR is elevated in HL, and an ESR ≥50 is considered as an "early-stage unfavorable factor" (NCCN, 2022).

Erythrocyte Sedimentation Rate (ESR)

Erythrocyte sedimentation rate (ESR) is a common laboratory method used to monitor general inflammation. ESR is used to analyze many different conditions, including RA, SLE, arteritis, PMR (Kushner, 2023; Wu et al., 2010). The simple Westergren method of ESR consists of measuring the distance a blood sample travels in a tube within one hour. The International Council for Standardization in Hematology (ICSH) established a calibration reference to this method using citrate-diluted samples. Automated ESR methods have been established; however, some of these analyzers use different dilution solutions, such as EDTA, rather than citrate. EDTA is commonly used as an anticoagulant in hematology measurements whereas the use of citrate is less prevalent. Horsti et al. (2010) compared blood samples from 200 patients using the traditional Westergren method versus an EDTA-based method. Their data has an R^2 value of only 0.72 and 55 subjects had a difference of over 30%, clearly indicating that ESR is significantly affected by sample preparation methods (Horsti et al., 2010). ESR can also be

affected by red blood cell morphology, ambient conditions (such as high room temperature or tilting of the ESR tube), anemia, renal disease, obesity, heart failure, and hypofibrinogenemia (Kushner, 2023; Taylor & Deleuran, 2023).

More, ESR may be affected by noninflammatory factors, thus reducing its specificity for inflammatory processes. Noninflammatory biological factors and environmental conditions can increase a sample's observed ESR. If the serum sample contains elevated concentrations of ions or charged proteins, an elevated ESR may occur; for example, an increase in positively charged plasma proteins could result in agglutination of erythrocytes within a sample for rapid sedimentation (Hale et al., 2019).

The ICSH established a Working Group to investigate the ESR methodology used in laboratories; the findings of this working group were published in 2017. Data from over 6000 laboratories on four different continents was examined. Of the laboratories included in the study, only 28% used the "gold standard" Westergren method exclusively (i.e. the method with the established validation by the ICSH) "while 72% of sites used modified or alternate methods." The data obtained from the new methodologies could deviate from the Westergren method by up to 142% and could differ "from each other of up to 42%." The ICSH released recommendations based up the results of these studies. One such recommendation for labs using the non-Westergren method of ESR is to "consider adding an interpretative comment to every result stating that 'This result was obtained with an ESR instrument that is not based on the standard Westergren method. The sensitivity and specificity of this method for various disease states may be different from the standard Westergren method'" (Kratz et al., 2017).

Besides the Westergren method, other methods have been developed to measure ESR including the Zeta sedimentation ratio, Wintrobe's method, and micro-ESR. In a validation study, Shaikh discussed the use of the Ves-Matic Cube 30 analyzer to address the drawbacks of the Westergren method such as contamination risk, the significant blood volume required, and increased duration of analysis. A strong positive correlation was observed between Westergren and Ves-Matic methods with Spearman's coefficient of 0.97. The study concluded that Ves-Matic Cube 30 analyzer can be used in high workload clinical settings for ESR measurement as the generated results were in concordance with those from the Westergren method.

C-reactive Protein (CRP)

C-reactive protein (CRP) was first discovered in the early twentieth century when it was isolated in a co-precipitation reaction with the pneumococcal C polysaccharide. The polysaccharide component bound by CRP later was identified to be phosphocholine. Since then, studies have shown that CRP can bind ligands other than bacterial cell wall components. During an acute inflammatory response, hepatocytes can upregulate CRP synthesis more than 1000-fold. The increase in serum CRP "after tissue injury or infection suggests that it contributes to host defense and that it is part of the innate immune response" (Black et al., 2004). Determining CRP concentration and fluctuations in plasma CRP can be useful in monitoring inflammatory response; however, what dictates "normal" CRP levels is of debate since CRP concentrations can

vary considerably between individuals, people groups, and laboratory testing methodology. The units used to denote CRP concentrations also vary between laboratories (Kushner, 2023).

Clinical Validity and Utility of CRP and ESR in Measuring Inflammatory Processes

Both CRP and ESR have been used to monitor RA. Elevated CRP and ESR does correlate to observed radiologic damage in RA. Unlike ESR, CRP can be evaluated in stored serum. This could be advantageous due to the time constraints of ESR testing (Taylor & Deleuran, 2023). A 2009 study by Crowson et al. (2009) show that the use of both ESR and CRP testing in the case of RA is not warranted. Data from three randomized trials of 1247 RA patients was examined. "Where available, the CRP alone may be preferred for disease activity assessment as a simple, validated, reproducible, non age-dependent test" (Crowson et al., 2009). Since both ESR and CRP have been incorporated into composite scoring for RA, the elimination of one or the other will not hinder the quantitative evaluation of the patient using a composite scoring system such as DAS (Disease Activity Score) or SDAI (Simplified Disease Activity Index). A 2015 Danish study clearly shows that the data obtained in DAS using either ESR or CRP "are interchangeable when assessing RA patients and the two versions of DAS28 are comparable" (Nielung et al., 2015). This study compared the baseline data and one-year follow-up of 109 different patients with RA using the DAS28-ESR and DAS28-CRP. Using the EULAR (European League Against Rheumatism) response criteria, only 14 patients show a divergence between using the ESR and CRP methods. Of those 14, "12 showed a better response (in terms of responder category) using DAS28-CRP, while two patients showed a better response using DAS28-ESR." However, a 2006 study by Fransen and van Riel (2006) show that it is still possible for a patient to have a high number of swollen joints and yet receive a low DAS28-ESR score within the remission range due to a low ESR value since ESR has a significant weight on the DAS28-ESR algorithm (Fransen & van Riel, 2006). This study did not include CRP measurements to compare its validity to that of the DAS28-ESR. Another study released in 2010 (Hensor et al., 2010) shows that the DAS28-CRP could also underestimate RA remission rates since those values are usually lower than the corresponding DAS28-ESR values, but the discrepancy is not significant if age and gender are added as factors into the DAS28-CRP methodology. To confound issues, "newer biologic agents that target specific inflammatory cytokines are differentially reflected in the ESR and CRP and may therefore disproportionately deflate the composite score" (Anderson et al., 2012).

Erythrocyte sedimentation rate cannot be used to predict RA as a screening method. Suarez-Almazor and colleagues investigated the predictive value of ESR for connective tissue diseases (CTD) and RA. Their review of 711 records by more than 300 different primary care physicians in Alberta show that ESR positively predicted 35% for CTD and only 17% for cases of RA. For SLE, the positive predictive value for ESR was even lower at only 3%. CRP testing was not included in this study. The authors note that "most tests were negative, and were often requested in patients without CTD, resulting in low positive predictive values and questionable clinical utility" (Suarez-Almazor et al., 1998). A study by Keenan et al. (2008) compared the utilization of ESR and CRP in RA, SLE, and osteoarthritis. The data showed that for the 188 patients with RA, the number of patients with both ESR and CRP elevated were statistically the same as those with normal test levels or those with only one test elevated. Conclusions stated "that another look

at the role of ESR and CRP as markers of inflammation in RA patients seen in routine care may be in order" (Keenan et al., 2008).

Bitik et al. (2015) researched the use of elevated ESR and CRP levels in distinguishing the definitive diagnosis of a rheumatic disorder from patients with nonspecific inflammation. In their study of 112 patients, 47 had a previously diagnosed rheumatic disorder and 65 had no history of a rheumatism. Of the 65 patients with no history of a rheumatic disorder, 52.3% were diagnosed with a new rheumatic disorder with PMR/GCA comprising 38.2%, while 47.7% had a non-rheumatic diagnosis. Within this latter group, only the "CRP levels were significantly higher in infections when compared with new onset RD (rheumatic disease) or malignancies ($p < 0.05$)" (Bitik et al., 2015). The ESR levels between the three groups were statistically insignificant. This indicates that CRP is more sensitive to acute infections than ESR. The authors state that "although ESR and CRP levels have a very low specificity in differentiating between these conditions, in cases of unusually high levels of CRP (especially above 200), more consideration should be given to infections or malignancies."

A 2014 study of 60 different PMR patients compared the efficacy of ESR and CRP in assessing disease activity versus patient-reported outcomes and plasma fibrinogen. In this study, the VASDA (Visual analog scale disease activity) and VASQOL (VAS quality of life), two patient-reported outcome methods, were the most responsive to changes in disease activity. Of the serum biomarkers, fibrinogen, ESR, and CRP, fibrinogen was the most accurate with a correlation coefficient of 1.63 whereas 1.2 and 1.05 were the correlation coefficients of ESR and CRP, respectively. These data suggest that plasma fibrinogen would be a more sensitive measure of PMR disease activity as compared to either ESR or CRP (McCarthy et al., 2014).

A two-year retrospective study released in 2010 (Ernst et al., 2010) researched the validity of using either ESR and/or CRP in assessing septic joints. This study consisted of 163 patients and included both genders as well as patients with alcohol or drug histories. The mean ESR value for the 119 control non-septic joints was 46 while the septic joint mean ESR value was 57, which was however, the mean CRP value was 13 in the septic joints and 8.5 in the non-septic joints. The conclusion of the authors is that "CRP is helpful in determining the presence of a septic joint; ESR is not" (Ernst et al., 2010).

Erythrocyte sedimentation rate is used in determining the algorithm to follow in the treatment of Hodgkin lymphoma (CHL). For example, in stage 1A CHL, a patient with an ESR <50 would follow either the NCCN HODG-3 or HODG-4 algorithm with an initial 2-3 cycles of ABVD (Adriamycin, bleomycin, vinblastine, dacarbazine) most likely whereas a stage 1A patient with an ESR ≥50 would follow the NCCN HODG-6 algorithm with a possible involved-site radiation therapy (ISRT) initially along with the chemotherapy since an ESR ≥50 is considered an "unfavorable factor" (NCCN, 2022).

CRP elevation is associated with a number of inflammatory disorders (including RA), tissue damage (such as after a myocardial infarction), as well as bacterial infections; however, CRP levels in SLE do not mirror disease progression (Kushner, 2023). Even during cases of severe disease phenotypes, CRP levels can be normal to modestly increased. One possible reason is

CRP suppression by type I interferons, which are increased in SLE. Another possibility is that low concentrations of wildtype CRP play a role in lupus. "Three lines of investigation have raised the possibility that low plasma levels of CRP may be related to the pathogenesis of SLE: 1) an association between SLE and several CRP genetic polymorphisms, at least one of which is associated with low CRP levels, 2) the possibility that low CRP levels may contribute to defective clearance of autoantigens during apoptosis, and 3) the therapeutic efficacy of CRP in mouse models of SLE" (Gaitonde et al., 2008). Also, CRP and anti-CRP may form large complexes in patients with SLE, which could also decrease the serum concentrations of free CRP (Gordon et al., 2018). A study by O'Neill and colleagues in 2010 show that anti-CRP levels are directly proportional in an increase to disease activity (32.6, 24.8, and 16.8 AU, respectively, for high activity, low activity, and control groups) and that anti-CRP levels were above the upper limit of normal in 26.3% of the high activity cases versus only 12.8% for the low activity cases (O'Neill et al., 2010). Patients with SLE usually have elevated ESR, but this elevation may be due to persistent polyclonal hypergammaglobulinemia (increased production of several different immunoglobulins) (Gordon et al., 2018).

Periprosthetic joint infections (PJI) may also benefit from testing of CRP and ESR. Joint arthroplasties (replacements) are typically performed in response to joint damage or destruction and commonly involve areas such as the hip, knee, or shoulder. Up to 2% of total knee replacements may become infected. Common signs of infection are present in PJI such as joint pain or warmth at the incision site, and microbiological cultures may be performed to confirm the diagnosis. CRP and ESR have been suggested as supportive biomarkers in cases where a definitive diagnosis cannot be made. CRP and ESR are considered minor clinical diagnostic criteria in some definitions of PJI, but due to the ubiquity of these markers, their levels are usually interpreted cautiously (Baddour & Chen, 2023).

Berbari et al. (2010) performed a meta-analysis of inflammatory markers in prosthetic joint infection. A total of 30 studies including 3909 revision total hip or knee replacements were assessed, and of the 3909 operations, 1270 infections occurred. CRP was included in 23 of 30 studies, and its diagnostic odds ratio was found to be 13.1. ESR was included in 25 of 30 studies, and its diagnostic odds ratio was calculated to be 7.2. Interleukin-6 was found to be the best marker of all markers addressed, albeit with only three studies (Berbari et al., 2010).

Perez-Prieto et al. (2017) examined the performance of CRP and ESR for PJI diagnosis. A total of 73 patients were included in the study. Preoperative CRP levels were found to be normal in 23 patients, and of those 23 patients, 17 patients also had normal ESR levels. Further, 16 patients with normal CRP levels were found to have "low-virulence" organisms (such as *Propionibacterium acnes* and coagulase-negative staphylococci) present. Overall, the authors found that 23% of the patients included in this study would not have been diagnosed with PJI according to the American Association of Orthopaedic Surgeons (AAOS) guidelines or the Musculoskeletal Infection Society definition (Perez-Prieto et al., 2017).

Kheir et al. (2018) evaluated the accuracy of inflammatory markers in diagnosis periprosthetic joint infections (PJI). A total of "549 periprosthetic joint infection cases and 653 aseptic total joint arthroplasty revisions" were reviewed. The sensitivity of ESR to diagnose PJI was 0.85 and

0.88 for CRP. ESR was also elevated in antibiotic-resistant strains of bacteria compared to culture-negative cases. For CRP, gram-negative species had higher levels of CRP than culture-negative cases. Overall, the authors concluded that both ESR and CRP had higher false-negative levels than previously reported (Kheir et al., 2018).

Hamann et al. (2019) compared the DAS28-ESR and DAS28-CRP to determine the impact on disease activity stratification in RA. A total of 31,074 paired data sets were included in this study and were obtained from the British Society for Rheumatology Biologics Register for RA. Results showed that "DAS28-CRP scores were ~0.3 lower than DAS28-ESR overall, with greatest differences for women (-0.35) and patients over 50 years old (-0.34). Mean male DAS28-CRP scores were 0.15 less than corresponding DAS28-ESR scores" (Hamann et al., 2019). When DAS28-CRP data is adjusted by gender, significant agreement ($P<0.001$) is seen with DAS28-CRP and DAS28-ESR scores.

Bingham et al. (2019) measured the specificity and sensitivity of ESR and CRP when screening for a PJI infection using the standard MSIS cutoff of 30 mm/h and 10 mg/L, respectively. The researchers also hoped to determine the optimal CRP and ESR cutoff to achieve a ≥95% sensitivity. Data from a total of 81 PJI patients and 83 noninfected arthroplasty patients was analyzed for this study. Results showed that "The ESR cutoff that resulted in a sensitivity ≥ to 95% (95% CI: 85.2-97.6%) was 10 mm/h, and the CRP cutoff that resulted in a sensitivity ≥ to 95% (95% CI: 87.1-98.4%) was 5 mg/L. The sensitivity and specificity with a combined ESR and CRP of 10 mm/h and 5 mg/L was 100%" (Bingham et al., 2019). The authors note that the accepted cutoff of 30 mm/h and 10 mg/L leads to a high number of false positives and low sensitivity; these thresholds therefore need to be reevaluated.

In a prospective cohort study, Watson et al. (2019) compared the diagnostic value of CRP and ESR and evaluated whether measuring two inflammatory markers increases accuracy. For each test, sensitivity, specificity, PPV, NPV, and AUC were calculated. 136,961 patients with inflammatory testing were measured of which 61.2% had a single marker measured and 38.8% had multiple markers measured. CRP and ESR were broadly similar in terms of sensitivity, specificity, PPV, and NPV. However, CRP had the highest overall AUC of 0.682 while the AUC for ESR was 0.589. Adding a second test did little improvement in AUC. When CRP and ESR were both tested for, the AUC increased from 0.682 to 0.688. Overall, the authors conclude that "Testing multiple inflammatory markers simultaneously does not increase ability to rule out disease and should generally be avoided. CRP has marginally superior diagnostic accuracy for infections, and is equivalent for autoimmune conditions and cancers, so should generally be the first-line test" (Watson et al., 2019).

In a cross-sectional study, Sherkatolabbasieh et al. (2020) investigated platelet count, ESR, and CRP levels in pediatric patients with inflammatory disease. A total of 150 children (75 male and 75 female) with diagnosis of infectious and inflammatory diseases were included in the study. Platelet count, ESR, and CRP levels were measured at the time of hospitalization and at discharge. At time of hospitalization, all 150 children had abnormal ESR levels, 73.3% had abnormal CRP levels, and 8% had abnormal platelet levels. At time of discharge, only one patient recovered to normal ESR levels, 88% had normal CRP, and 93.3% had normal platelet count.

The Fisher exact test showed a significant relationship between platelet count and CRP levels at the time of discharge ($p < 0.0002$) and admission ($p < 0.007$), especially in the female patients. CRP levels were significantly higher in the female patients and changes in platelet count were more prevalent. No relation between platelet count and ESR was observed at admission and discharge. This study found that there are differences in inflammatory markers between the two sexes. The authors conclude that this study showed significant correlation between CRP and platelet levels in girls and CRP level measurement is useful in treatment follow up (Sherkatolabbasieh et al., 2020).

Alende-Castro et al. (2021) studied the use of CRP vs ESR in 1472 patients with no inflammatory conditions. All participants were measured for ESR, CRP and IL-6 concentrations. 74.9% of participants showed normal CRP and ESR values, 4.6% showed high ESR and CRP values, and 13.8% showed high CRP but normal ESR values. Participants with high ESR/CRP values also were of older age, and reported high alcohol consumption, low physical activity, high BMI, and the presence of metabolic syndrome. In those patients who had high CRP but normal ESR, BMI seemed to be the main determinant of CRP concentrations. The authors concluded that "In this general adult population with no overt inflammatory disease, the discordant pattern of high ESR and normal CRP was associated with greater age, whereas the pattern of high CRP and normal ESR was associated with higher BMI" (Alende-Castro et al., 2021).

In a retrospective study, Christopher studied the use of ESR/CRP ratio to differentiate acute vs chronic periprosthetic joint infections. A total of 147 patients (81 acute and 66 chronic) were measured for ESR and CRP concentrations. The mean ESR / CRP ratio in acute patients was 0.48 compared to 2.87 in chronic patients. The ideal cutoff value was 0.96 for ESR / CRP to predict a chronic (>0.96) vs. acute (<0.96) PJI. The sensitivity at this value was 0.74 and the specificity was 0.90. The authors conclude that "The ESR / CRP ratio may help determine the duration of PJI in uncertain cases. This metric may give arthroplasty surgeons more confidence in defining the duration of the PJI and therefore aid in treatment selection" (Christopher et al., 2021).

Dhudasia et al. (2022) conducted a retrospective cohort study to determine the clinical utility of CRP in diagnosing early-onset sepsis and assessing patient outcomes. The patient sample included over 10,000 infants admitted to the neonatal intensive care units from 2009-2014, when CRP was used routinely. The cutoff utilized as ≥10mg/L for diagnosis of "culture-confirmed early-onset sepsis." Based on when the CRP was obtained from the blood culture, which was taken at 3 days of birth, the results yielded varying specificities and sensitivities. If the CRP was obtained at ±4 hours, the sensitivity was 41.7%, specificity 89.9%, and positive likelihood ratio was 4.12. When obtained 24-72 hours later, the sensitivity became 89.5%, but specificity decreased to 55.7% and positive likelihood ratio to 2.02. During this time of routine CRP testing, there were higher rates of early-onset sepsis evaluation, antibiotic initiation, and antibiotic prolongation "in the absence of early-onset sepsis," but no difference in time to detection and in-hospital mortality with a period of non-routine CRP testing. The researchers ultimately concluded that the diagnostic performance of CRP in diagnosing early-onset sepsis was insufficient to warrant routine testing, as patient outcomes were not significantly affected with the elimination of routine CRP testing. Other factors with higher sensitivities, specificities, and positive likelihood ratios need to be included in the evaluation (Dhudasia et al., 2022).

V. Guidelines and Recommendations

World Health Organization (WHO)

On May 16, 2018, the WHO released their first edition of the *Model List of Essential In Vitro Diagnostics* (EDL) "to advance universal health coverage, address health emergencies, and promote healthier populations." This list of in vitro diagnostics (IVD) is to be used as a reference of the essential diagnostic tools for laboratories to complement their Model List of Essential Medicines. With respect to the diagnostic tool "to detect inflammation as an indicator of various conditions," the WHO recommends CRP either in an EIA (enzyme immunoassay) or RDT (rapid diagnostic test) assay format. The specimen type can be venous whole blood, serum, or plasma.

In 2019, the WHO released the *Second WHO Model List of Essential In Vitro Diagnostics.* In a table titled *General IVDs for Use in Clinical Laboratories*, CRP is once again listed. The WHO now recommends CRP in an RDT, latex agglutination assay or immunoassay format (WHO, 2019).

In 2020, the WHO released *The selection and use of essential in vitro diagnostics*, which included the third WHO model list. In the section on "General IVDs for community settings and health facilities without laboratories," the WHO performed an evaluation of utilizing ESR "to aid diagnosis and monitoring of certain infections and immune diseases; and as an alternative to a C-reactive protein (CRP) test where this is not available." In their table, they recommend using the Westergren assay format with sampling from venous whole blood. The WHO ultimately concluded that despite several guidelines recommending ESR to aid in diagnosing several inflammatory diseases, "there is no strong evidence supporting ESR as an essential test" since there are also high rates of false positives and false negatives. They conclude that CRP "should remain the preferred choice of test," except in cases of systemic lupus erythematosus and low-grade bone and joint infections since "there is evidence that the condition elevates ESR without causing a raise in CRP." As of this meeting, CRP now has the purpose "to monitor response to treatment" in addition to "detect inflammation as an indicator of various response conditions," and can be assayed as RDT, latex agglutination assay, and immunoassay with sampling venous whole blood, serum, and plasma (WHO, 2020).

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines concerning Hodgkin Lymphoma uses ESR as a diagnostic tool in characterizing the stage/risk classification of Classic Hodgkin Lymphoma (CHL) as well as the primary treatment of the disease. In the diagnosis/workup of Hodgkin Lymphoma in adults (age ≥18 years) (recommendation 2A), they list erythrocyte sedimentation rate (ESR) as "essential" and that ESR should be tested within 6 months of diagnosis.

In the guidelines concerning follow-up after completion of treatment up to five years, the NCCN (2022) recommends obtaining an interim history and physical "every 3-6 [months] for 1-2 [years], then every 6-12 [months] until year 3, then annually," as well as laboratory studies, which included a "[complete blood count], platelets, ESR if elevated at time of initial diagnosis, chemistry profile, as clinically indicated" with the same timeline. ESR is also used in determining

the dosage of involved-site radiation therapy (ISRT). "A dose of 20 Gy following ABVD X 2 is sufficient if the patient has non-bulky stage I-IIA disease with an ESR <50, no extralymphatic lesions, and only one or two lymph node regions involved." An ESR ≥50 is considered as an "unfavorable risk factor" for stages I and II Hodgkin Lymphoma along with B symptoms. Please note that the NCCN guidelines concerning Hodgkin Lymphoma do not contain any information concerning the use of CRP as a diagnostic or prognostic tool (NCCN, 2022).

In the NCCN guidelines concerning the B-cell lymphomas under the section concerning Castleman Disease, the NCCN recommends (category 2A) as "essential" laboratory tests "LDH, CRP, [and] ESR." Within the discussion of the text, it does not mention if all three are required or if only a minimum of one of the three tests are essential in the workup. The guidelines for B-cell lymphomas do not list either CRP or ESR for follow-up testing post-treatment.

Regarding diagnostic criteria for idiopathic MCD (Multicentric Castleman Disease), minor diagnostic criteria include elevated CRP (>10 mg/L) or ESR (>15 mm/h) where an "Evaluation of CRP is mandatory and tracking CRP levels is highly recommended, but ESR will be accepted if CRP is not available" (NCCN, 2023b).

In the NCCN guidelines concerning the T-cell lymphomas, they state that the "evaluation of serological markers such as rheumatoid factor (RF), antinuclear antibodies (ANA), and erythrocyte sedimentation rate (ESR) is useful in patients with autoimmune disease"(NCCN, 2023a). The guidelines concerning T-cell lymphomas do not mention the diagnostic or prognostic use of CRP.

American Society for Clinical Pathology (ASCP)

In the Choosing Wisely site of the ABIM Foundation, the ASCP released the recommendation to not "order an erythrocyte sedimentation rate (ESR) to look for inflammation in patients with undiagnosed conditions. Order a C-reactive protein (CRP) to detect acute phase inflammation" due to the higher sensitivity and specificity of CRP for acute phase of inflammation. "In the first 24 hours of a disease process, the CRP will be elevated, while the ESR may be normal. If the source of inflammation is removed, the CRP will return to normal within a day or so, while the ESR will remain elevated for several days until excess fibrinogen is removed from the serum" (ASCP, 2015).

European League Against Rheumatism (EULAR)

In 2009, EULAR issued their recommendations concerning the management of large vessel vasculitis. With a "Level of Evidence 3, Strength of recommendation C", they recommend "monitoring of therapy for large vessel vasculitis should be clinical and supported by measurement of inflammatory markers…. For patients with giant cell arteritis, a relapse is usually associated with a rise in ESR and CRP" (Mukhtyar et al., 2009). In this paper, no mention of the frequency of ESR and/or CRP testing is mentioned.

In 2013 in *EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis* (Colebatch et al., 2013), they state that "baseline

inflammatory disease measured by scintigraphy appears to be associated with radiographic progression. In addition, multiple regression analysis has demonstrated that progression of radiographic joint destruction was primarily predicted by ^{99m}Tc-IgG scintigraphy; joint swelling, ESR and IgM RF (Rheumatoid Factor) were not predictive. This suggests that scintigraphy may be superior to conventional clinical and laboratory measurements in the prediction of joint destruction." This set of guidelines did not include any mention concerning CRP or the frequency of ESR testing.

In 2015, EULAR and the American College of Rheumatology (ACR) issued joint recommendations concerning the management of polymyalgia rheumatica (PMR) (Dejaco et al., 2015). Within their recommendations, they list assessments that "every case of PMR should have…prior to the prescription of therapy (primary or secondary care)." They include a basic laboratory workup "to exclude mimicking conditions and establish a baseline for monitoring of therapy", and they state that this includes "rheumatoid factor and/or anti-cyclic citrullinated peptide antibodies (ACPA), C-reactive protein and/or erythrocyte sedimentation rate (ESR), blood count, glucose, creatinine, liver function tests, bone profile (including calcium, alkaline phosphatase) and dipstick urinalysis." They do not state a specific preference of either CRP or ESR nor do they state the frequency of testing.

EULAR in 2016 updated their 2007 recommendations concerning the management of early arthritis (Combe et al., 2017). The 2016 updates included the following recommendation: "Monitoring of disease activity should include tender and swollen joint counts, patient and physician global assessments, ESR and CRP, usually by applying a composite measure. Arthritis activity should be assessed at 1-month to 3-month intervals until the treatment target has been reached." The recommendation concerning including both ESR and CRP did not change between the 2016 and 2007 recommendations. Within the discussion of the recommendations, they state, "In every patient with active arthritis, closely monitoring disease activity is now considered of particular importance in the therapeutic strategy to provide a good outcome. . . Monitoring disease activity should be as frequent as the level of disease activity mandates, usually every 1-3 months, then potentially less frequently (such as every 6-12 months) once the treatment target has been achieved. Nevertheless, three changes were proposed to this item…. First, a composite measure was recommended as the method of choice to monitor disease activity; second, a specific time frame for monitoring structural damage was deliberately left out and third, patient-reported outcomes were expanded beyond functional assessments" (Combe et al., 2017).

In 2018, EULAR issued *EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice* (Dejaco et al., 2018). They make no recommendation concerning the preference of ESR or CRP nor do they state the frequency of testing; they do state "in patients with a high clinical suspicion of GCA (>50%), for example, in case of new-onset headache, visual symptoms, jaw claudication and elevated erythrocyte sedimentation rate (ESR) and C reactive protein, a positive ultrasound would result in a post-test probability of >95%."

American College of Rheumatology (ACR)

In 2012, ACR released their recommendations concerning the clinical practice of using disease activity measures of rheumatoid arthritis (RA) (Anderson et al., 2012). The recommend using the Disease Activity Score with 28-joint counts (DAS28), the Clinical Disease Activity Index, the Patient Activity Scale (PAS), the PAS-II, the Simplified Disease Activity Index (SDAI), and Routine Assessment of Patient Index Data with 3 measures. The DAS28 is a composite test that can use either CRP or ESR data. The ACR states that both the CRP or ESR used in the DAS28 have been validated in RA. Of the six activity measures recommended by the ACR, only DAS28 received "excellent" recommendations for all three psychometric properties—reliability, validity, and responsiveness. Within the guidelines, the ACR also issued the scores corresponding to remission, low/minimal, moderate, and high/severe RA for all the disease activity measures, including the DAS28, as well as the mathematical formula using either CRP or ESR data to determine the DAS28. CRP is also used in the SDAI; however, the SDAI is rated as "good" for reliability because they state that "test-retest reliability for composite has not been evaluated" for the SDAI. No mention of frequency of testing is made. They do note that the "inclusion of acute-phase reactants in the DAS28 and SDAI complicates the logistics and timing using these measures in point-of-care clinical decision making. Although these measures have traditionally been used in clinical trials, academic medical centers, and large multispecialty clinics, logistical barriers have likely delayed their widespread adoption in smaller practice settings" (Anderson et al., 2012).

The ACR in 2015 (Singh et al., 2015) issued guidelines for the treatment of RA. While not specifying a preference of either CRP or ESR in diagnosing or predicting the prognosis of RA, they do state in their "Key provisos and principles" that "functional status assessment using a standardized, validated measure should be performed routinely for RA patients, at least once per year, but more frequently if disease is active." They also state that disease activity be measured using ACR-validated scales, including the DAS28 and/or SDAI. Moreover, they define RA remission as "a tender joint count, swollen joint count, C-reactive protein level (mg/dl), and patient global assessment of ≤1 each or a Simplified DAS of ≤3.3, 1 of 6 ACR-endorsed disease activity measures".

Also, in 2015 (but published in 2016), the ACR and the Spondylitis Association of America (SAA) issued their joint recommendations concerning the treatment of ankylosing spondylitis (AS) and nonradiographic axial spondyloarthritis (Ward et al., 2016). Regarding "the treatment of patients with either active or stable AS…we conditionally recommend regular-interval use and monitoring of the CRP concentrations or erythrocyte sedimentation rate (ESR) over usual care without regular CRP or ESR monitoring." This received a "very low-quality evidence; vote 100% agreement" rating. They do make note that as of the time of publication "no studies addressed the effect of routine monitoring of a disease activity measure" but that "the panel thought that monitoring would be most helpful in patients with active symptoms as a guide to treatment." Testing is not required for every clinic visit. The two organizations reaffirm the same recommendations in their 2019 update (Ward et al., 2019).

In 2019, updated recommendations by the RA disease activity measures working group were published by England et al. (2019). Recommended tests include the Clinical Disease Activity Index (CDAI), the Simplified Disease Activity Index (SDAI), the Routine Assessment of Patient

Index Data 3 (RAPID3), and the 28-Joint Disease Activity Score (DAS28). As noted above, the DAS28 is a composite test that can use either CRP or ESR data. The ACR states that both the CRP or ESR used in the DAS28 have been validated in RA. Updates to the management of rheumatoid arthritis were released by the ACR in 2022, but no mention of CRP or ESR were made (Arnold, 2022).

In 2021, the ACR published a guideline to provide evidence-based recommendations and expert guidance for the management of giant cell arteritis (GCA). They present 22 recommendations and 2 ungraded position statements for GCA and note that all but 1 of the recommendations are conditional due to very low- to low-quality evidence. They break these recommendations down into categories, including diagnostic testing, medical management, surgical intervention, and clinical/laboratory monitoring. All diagnostic recommendations involve biopsy or imaging- they do not recommend the use of CRP or ESR for diagnosis of GCA. However, they do recommend inflammation marker monitoring as part of clinical/laboratory monitoring. They define clinical monitoring as "assessing for clinical signs and symptoms of active disease, obtaining 4 extremity blood pressures, and obtaining clinical laboratory results, including inflammation marker levels", with inflammation markers further defined as being CRP and ESR:

"Recommendation: For patients with GCA in apparent clinical remission, we strongly recommend long-term clinical monitoring over no clinical monitoring: The optimal frequency and length of monitoring are not well established and depend on factors including the duration of remission, site of involvement, risk of disease progression, whether the patient is receiving immunosuppressive therapy, and reliability of the patient to report new signs or symptoms. Clinical monitoring may include history taking, examinations, and laboratory and imaging studies. This is a strong recommendation given the minimal risks and potential catastrophic outcomes if monitoring is not performed.

Recommendation: For patients with GCA who have an increase in levels of inflammation markers alone, we conditionally recommend clinical observation and monitoring without escalation of immunosuppressive therapy. Increases in levels of inflammation markers such as erythrocyte sedimentation rate and C-reactive protein can be nonspecific (69). Therefore, increasing immunosuppressive therapy is not warranted in the setting of increased levels of inflammation markers in the absence of other signs of disease activity. However, these increased levels may warrant more frequent clinical and/or radiographic assessments for active disease" (Maz et al., 2021)

American Academy of Family Physicians (AAFP)

In 2013, the AAFP released *Recognition and Management of Polymyalgia Rheumatica and Giant Cell Arteritis*. For polymyalgia rheumatica (PMR), they note that "a normal ESR is found in 6% to 20% of persons with [PMR], although in those cases C-reactive protein level is elevated. ESR predicts relapse more reliably, but C-reactive protein is more sensitive, and is less affected by age and other factors." For giant cell arteritis (GCA), ESR is elevated in up to 89% of patients, but the sensitivity and specificity increase to 99% and 97%, respectively, if both ESR and CRP are tested. Regardless of using either ESR or CRP testing, the AAFP recommends that either

ESR or CRP is tested at each clinic visit for patients with either PMR or GCA (Caylor & Perkins, 2013).

American College of Radiology (ACR)

The ACR released their updated guidelines concerning the follow-up of Hodgkin lymphoma in 2014. They state that "limited data are available on the role of routine blood work in detecting relapses." ESR is listed as one of the tests conducted as routine blood work in follow-up of Hodgkin lymphoma. They summarize their findings as the following: "In general a majority of recurrences can be detected initially by history and physical examination rather than by routine imaging studies or blood tests such as ESR, CBC, and chemistry" (Ha et al., 2014). Four of the five variants they reviewed had ESR tests conducted 1 – 2 times per year, and the ACR rated the use of ESR as a 3, 5, 5, and 7 in these four variants where a "3" indicates "usually not appropriate," a "5" is "may be appropriate", and a "7" falls in the "usually appropriate" category.

The ACR released guidelines concerning management of multi-system inflammatory syndrome in children and devised a two-tier algorithm for diagnosis. ACR recommends routine lab tests as tier 1 testing, including complete blood count with manual differential, comprehensive metabolic panel, erythrocyte sedimentation rate [ESR], CRP measurement, and testing for SARS-CoV-2 by polymerase chain reaction or serology. If tier 1 lab results include CRP ≥5 or ESR≥40 and one suggestive lab feature such as neutrophilia, lymphopenia, thrombocytopenia, hyponatremia, or hypoalbuminemia, the child should undergo tier 2 testing, which involves EKG and echocardiogram (Henderson et al., 2020; Henderson et al., 2021).

The British Society for Rheumatology (BSR) & British Health Professionals in Rheumatology (BHPR)

In 2010, BSR and BHPR issued joint guidelines concerning the management of giant cell arteritis (GCA) (Dasgupta, 2010; Dasgupta, Borg, Hassan, Alexander, et al., 2010). They recommend "early recognition and diagnosis of GCA is paramount. Particular attention should be paid to the predictive features of ischaemic neuro-ophthalmic complications." As part of this diagnostic recommendation, they specifically list laboratory tests that should be included— "full blood count, urea and electrolytes, liver function tests, CRP, ESR." They note that, although elevated ESR and CRP levels are hallmarks of GCA, "GCA can occur in the face of lower levels of inflammatory markers, if the clinical picture is typical." Another specific recommendation states, "Monitoring of therapy should be clinical and supported by the measurement of inflammatory markers (C; this is a consensus statement)" and that at each visit "full blood count, ESR/CRP, urea and electrolytes, [and] glucose" lab tests be performed.

Also, in 2010, BSR and BHPR issued joint guidelines concerning the management of polymyalgia rheumatica (PMR) (Dasgupta, Borg, Hassan, Barraclough, et al., 2010). For PMR, they recommend initial lab testing for diagnosis to include either ESR and/or CRP prior to initiating long-term steroid therapy. Also, during such therapy, they recommend monitoring either ESR or CRP every three months. This is a portion of the recommendation (B) of "vigilant monitoring of patients for response to treatment and disease activity."

The British Society for Rheumatology (BSR)

The BSR alone issued their guidelines for the management of systemic lupus erythematosus (SLE) in 2018 (Gordon et al., 2018). For the statement "CRP low or normal unless infection," the BSR gives an overall level of evidence of 2++ with a B grade of recommendation whereas they grade the statement "ESR correlates with active lupus" a 2+ and only a C grade of recommendation. "ESR is often raised in active SLE, but can also reflect persistent polyclonal hypergammaglobulinaemia, and is not a reliable marker of disease activity…. A significantly raised CRP is more likely to indicate infection, and patients with raised CRP will need therefore to be thoroughly screened for infection, given that infection is the commonest cause of death in lupus patients. In contrast, a raised ESR does not discriminate between active lupus and infection." They recommend that CRP is tested at initial diagnosis and then every 1-3 months during active disease states. Once stabilized, then testing frequency can be every 6-12 months. They also state that CRP testing should be conducted on mothers with SLE during pregnancy, but they do not state the frequency of the testing during pregnancy. This guideline is currently in revision.

The BSR has also published guidelines on the diagnosis and treatment of giant cell arteritis (GCA). Regarding which evaluations should be performed when starting treatment, the BSR states that "When starting glucocorticoids for suspected GCA, diagnostically relevant symptoms and signs should be documented. Blood should be taken for full blood count, CRP and ESR before or immediately after commencing high-dose glucocorticoids. If GCA is strongly suspected, the first dose of glucocorticoid can be given without waiting for laboratory results" (Mackie et al., 2020). Further, the BSR provides a list of clinical assessments which should be carried out at or near a GCA diagnosis. These lists include "Measures of activity of GCA: laboratory markers of inflammation (CRP for all patients, plus either ESR or plasma viscosity) and full blood count (platelet count may be elevated in GCA)." Finally, regarding follow-up visits, "Each follow-up visit should include at least a full history, targeted physical examination and measurement of at least a full blood count, ESR and/or CRP, plus follow-up of any abnormalities relevant to the individual patient as well as drug-specific screening for toxicity" (Mackie et al., 2020). Revision for this guideline will be considered in 2024.

Canadian Rheumatology Association (CRA)

The 2012 guidelines by the CRA titled "Canadian Rheumatology Association Recommendations for Pharmacological Management of Rheumatoid Arthritis with Traditional and Biologic Disease-modifying Antirheumatic Drugs" recommends (with Level II and Strength B) "the presence of the following poor prognostic features should be assessed at baseline and considered when making treatment decisions: RF positivity, anti-CCP positivity, functional limitation, high number of swollen and tender joints, early erosions, extraarticular features, high ESR or CRP." They also recommend (with Level I and Strength A) "RA care providers should monitor disease activity as frequently as every 1 to 3 months in patients with active RA." The disease activity should be monitored by a validated method, such as DAS28 or SDAI. The most recent updated "living guidelines" for this statement does not include prognostic features or make recommendations for factors included in treatment decisions (Hazlewood et al., 2022).

In 2018, CRA released guidelines on assessment and monitoring of Systemic Lupus Erythematosus. Regarding diagnosis, CRA recommends that best clinical practice includes a complete history and physical examination at baseline with laboratory monitoring which could possibly include (but is not limited to) the following tests: "complete blood count (CBC), liver enzymes, creatine kinase, creatinine and estimated glomerular filtration rate (eGFR), urine routine/microscopic (urinalysis), urine protein-creatinine ratio, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), complements (C3, C4), anti-dsDNA, antinuclear antibodies, antibodies to extractable nuclear antigens, antiphospholipid antibodies (aPL), lupus anticoagulant (LAC), anticardiolipin (aCL), anti-β2-glycoprotein I (anti-β2-GPI), and lipid profile. Follow up laboratory monitoring will depend on the patient's clinical status and may include CBC, eGFR, urinalysis, urine protein-creatinine ratio, CRP, and/or ESR, C3, C4, and anti-dsDNA antibodies" (Keeling et al., 2018).

Joint Task Force on Practice Parameters (JTFPP) of the Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology

The JTFPP within their guidelines concerning the diagnosis and management of acute and chronic urticaria state, "Targeted laboratory testing based on history or physical examination findings is appropriate, and limited laboratory testing can be obtained. Limited laboratory testing includes a CBC with differential, sedimentation rate, and/or C-reactive protein, liver enzyme, and thyroid-stimulating hormone (TSH) measurement… Targeted laboratory testing based on history and/or physical examination (eg, obtaining TSH in a patient with weight gain, heat/cold intolerance, and thyromegaly) is recommended" (Bernstein et al., 2014).

National Institute for Health and Care Excellence (NICE)

The NICE first issued the guidelines concerning irritable bowel syndrome (IBS) in 2008 with updates in 2015 and 2017. In individuals who meet the IBS diagnostic criteria, they recommend ESR and CRP along with full blood count and antibody testing for celiac disease or tissue transglutaminase to exclude other possible diagnoses. They do not state anything concerning follow-up testing of either ESR or CRP (NICE, 2017).

In 2020, NICE issues guidelines concerning management of rheumatoid arthritis (RA). In adults with active RA, they recommend measuring CRP and disease activity monthly in specialist care until remission or low disease activity is achieved (NICE, 2020).

American Academy of Orthopaedic Surgeons (AAOS)

The AAOS notes that "Strong evidence supports the use of [ESR and CRP] to aid in the preoperative diagnosis of prosthetic joint infection (PJI)." However, the AAOS remarks that neither biomarker is perfectly accurate for PJI diagnosis and should not be used as sole tests for diagnosis. Critically, neither marker informs clinicians of the microbiology of the PJI.

These guidelines were endorsed by IDSA, the American College of Radiology, and the Society of Nuclear Medicine and Molecular Imaging (AAOS, 2019).

Pediatric Infectious Diseases Society and the Infectious Diseases Society of America

In 2021, a guideline was released on the diagnosis and management of Acute Hematogenous Osteomyelitis (AHO) in pediatrics. In children with suspected AHO, they recommend performing a serum C-reactive protein (CRP) on initial evaluation. "Serum CRP has a low accuracy to establish the diagnosis of AHO, but in situations where AHO is confirmed, the serum CRP performed on initial evaluation can serve as the baseline value for sequential monitoring." They recommend against using serum PCT. In terms of ESR, they comment that the ESR is no longer used routinely to diagnose AHO in children. "ESR combined with CRP may slightly improve sensitivity and negative predictive value for the diagnosis of AHO, but specific thresholds and the overall clinical utility of using both CRP and ESR for diagnostic purposes remain uncertain" (Woods et al., 2021).

"There are no data to support a particular frequency of CRP monitoring during the course of AHO in children. Measurement every 2 to 3 days during the early therapeutic course, rather than daily, followed by weekly or other periodic measurement until normalization (or a clear trend toward normalization is evident) is an acceptable approach" (Woods et al., 2021).

VI. Applicable State and Federal Regulations

Food and Drug Administration

Testing of serum acute phase reactants and ESR is performed in laboratories meeting Clinical Laboratory Improvement Act (CLIA) quality standards. The FDA has approved multiple tests for human CRP, including assays for conventional CRP, high-sensitivity CRP (hsCRP), and cardiac CRP (cCRP). On September 22, 2005, the FDA issued guidelines concerning the assessment of CRP (FDA, 2005). A search of the FDA Medical Devices database (FDA, 2018) on April 20, 2021, shows that the FDA has approved ESR systems from multiple companies, including the ESR Control -M Hematology Erythrocyte Sedimentation system (K972172) and the ESR Control -HC Hematology Erythrocyte Sedimentation system (K972170) by R & D Systems, the Seditainer Erythrocyte Sedimentation Rate System (K953994) from Becton Dickinson Vacutainer Systems, the Westergren Dispette for ESR (K831195) by Ulster Scientific, and the Dade ESR Kit (K823368) from American Dade.

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VII. Applicable CPT/HCPCS Procedure Codes

Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all inclusive and is subject to updates. In addition, codes listed are not a

guarantee of payment.

CPT	Code Description
85651	Sedimentation rate, erythrocyte; non-automated
85652	Sedimentation rate, erythrocyte; automated
86140	C-reactive protein

VIII. Evidence-based Scientific References

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IX. Revision History

Revision Date	Summary of Changes
01/01/2023	Initial Effective Date
04/04/2023	Reviewed with minimal changes: Fixed typographical error in Table 1- "Irritable Bowel Disorders" changed to "Irritable Bowel Syndrome" and the frequency for IBS changed from "NS" to "During initial assessment to exclude other diagnoses" Committee approved 4/4/2023
08/15/2023	Reviewed and Updated: Updated background, guidelines, and evidence-based scientific references. Literature review necessitated the following changes in coverage criteria: In CC1, reordered so that CRP is first due to preference for CRP over ESR. Addition of new CC2: "2) For individuals without a diagnosed inflammatory condition, measurement of ESR DOES NOT MEET COVERAGE CRITERIA." Addition of "(conventional or high sensitivity)" to Note 1: "Coverage of ESR, CRP (conventional or high-sensitivity), or both CRP and ESR is designated based on the diagnosed or suspected inflammatory condition." In Note 1, changed some of the "and"s to "or"s for these conditions: Acute and Chronic Urticaria, Polymyalgia Rheumatica, Systemic Lupus Erythematosus. In Note 1, "Frequency of Testing" changed for AHO (from NS to "To confirm diagnosis; 2 to 3 days during the early therapeutic course; weekly until normalization (or a clear trend toward normalization is evident)), GCA (from at or near diagnosis to "to confirm diagnosis"), and RA (addition of "annually when disease is inactive"). Added CPT code 86141. Committee approved: 08/15/2023