# MEDICAL POLICY

| MEDICAL POLICY DETAILS | |
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| **Medical Policy Title** | **JAK2, MPL, and CALR Testing for Myeloproliferative Neoplasms** |
| **Policy Number** | **2.02.53** |
| **Category** | **Technology Assessment** |
| **Original Effective Date** | **06/17/21** |
| **Committee Approval Date** | **06/17/21, 04/21/22, 03/23/23, 03/21/24** |
| **Current Effective Date** | **03/21/24** |
| **Archived Date** | **N/A** |
| **Archive Review Date** | **N/A** |
| **Product Disclaimer** | • *Services are contract dependent; if a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.*<br>• *If a commercial product (including an Essential Plan or Child Health Plus product), medical policy criteria apply to the benefit.*<br>• *If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.*<br>• *If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.*<br>• *If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.* |

## POLICY STATEMENT

Primary Myelofibrosis (PMF) and Essential Thrombocythemia (ET)

I. Based upon our criteria and assessment of the peer-reviewed literature including the National Comprehensive Cancer Network (NCCN) clinical guidelines, molecular testing of bone marrow or blood is considered **medically necessary** in the diagnosis of patients presenting with clinical, laboratory, or pathologic findings suggesting primary myelofibrosis (PMF) and Essential Thrombocythemia (ET) for ANY of the following after evaluation for secondary causes:
   A. Janus kinase 2 (JAK2);
   B. Myeloproliferative Leukemia (MPL);
   C. Calreticulin (CALR);

Polycythemia Vera (PV)

II. Based upon our criteria and assessment of the peer-reviewed literature, Janus kinase 2 (JAK2) testing is considered **medically necessary** in the diagnosis of patients presenting with clinical, laboratory, or pathologic findings suggesting Polycythemia Vera (PV) after evaluation for secondary causes.

III. Based upon our criteria and assessment of the peer-reviewed literature, JAK2, MPL, and CALR testing is considered **investigational** in all other circumstances including, but not limited to, the following situations:
   A. Diagnosis of nonclassic forms of myeloproliferative neoplasms (MPNs);
   B. Molecular phenotyping of patients with MPNs.

*Refer to Corporate Medical Policy #11.01.03 Experimental and Investigational Services*

## POLICY GUIDELINES

I. The Health Plan and its employees adhere to all State and Federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom

such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test or in compliance with applicable law.

II. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.

III. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

IV. Patients suspected to have polycythemia vera (PV) should first be tested for JAK2 V617F. If the testing is negative, further testing to detect other JAK2 tyrosine kinase variants (e.g., in exon 12) is warranted.

V. Patients suspected to have essential thrombocythemia (ET) or primary myelofibrosis (PMF) should first be tested for JAK2 V617F mutation. If testing is negative, further testing to detect MPL and CALR variants is warranted.

VI. Based on criteria from the World Health Organization and the International Consensus Classification for diagnosis of PV, documentation of a serum erythropoietin level below the reference range for normal is recommended before JAK2 testing.

VII. It is recommended by NCCN to use highly sensitive assays for JAK2 V617F (sensitivity level <1%) and CALR and MPL (sensitivity level 1%–3%) in negative cases, consider searching for non-standard or atypical JAK2 mutations.

VIII. Multigene NGS may be useful to establish clonality in selected circumstances (e.g., triple-negative non-mutated JAK2, MPL, and CALR) and to detect high-molecular-risk mutations associated with myeloid neoplasms (e.g., ASXL1, EZH2, IDH1, IDH2, SF3B1, SRSF2, and TET2 mutations).

## DESCRIPTION

Myeloproliferative neoplasms (MPNs) are hematologic malignancies classified as myeloid vs lymphoid and then further subdivided into acute and chronic. Myeloproliferative neoplasms are a subsect of chronic myeloid disorders that usually exhibit terminal expansion in the peripheral blood as opposed to the bone marrow. MPNs cause thrombocytosis and erythrocytosis in the peripheral blood. The four main types of MPNs are PV (Polycythemia Vera), ET (Essential Thrombocythemia), PMF (primary myelofibrosis), and CML (chronic myeloid leukemia).

MPN, unclassifiable is an appropriate diagnosis for cases presenting with clinical, morphologic, and molecular features that prevent a clear diagnosis of a specific MPN subtype. In addition, this category is appropriate for patients presenting in very early phase disease in which the required diagnostic features are not yet fully developed and relevant diagnostic thresholds not met (Arber, 2022).

The Janus kinase 2 (JAK2) tyrosine kinase protein is part of the JAK/signal transduction pathway and activators of transcript (STAT) proteins that are important for the controlled production of blood cells from hematopoietic cells. Mutation of JAK2 causes an always on mutation that leads to cell proliferation myeloid cells. This leads to a subsequent uncontrolled cell proliferation in hematocrit, red blood cells, and platelets, and subsequent decrease in epo level. Somatic (acquired) variants in the JAK2 gene are found in patients with MPNs such as PV, ET, and PMF. There are two JAK2 variants associated with MPN disorders, the JAK2 V617F variant and JAK2 Exon 12 Variants (4 different variants). The JAK2 V617F gene is found in 95% of patients with PV, 60% to 65% of patients with ET, and 60 to 65% of patients with PMF. JAK2 exon 12 variants are also found in 5% of PV cases.

The MPL gene, located on chromosome 1, contains the genetic code for making the thrombopoietin receptor, a cell surface protein, which stimulates the JAK/STAT signal transduction pathway. The thrombopoietin receptor is critical for the cell growth and division of megakaryocytes, which produce platelets involved in blood clotting. Somatic variants in the MPL gene are associated with ET and PMF.

The CALR (gene, located on chromosome 19, contains the genetic code for making the calreticulin protein, a multifunctional protein located in the endoplasmic reticulum, cytoplasm, and cell surface. The calreticulin protein is thought to play a role in cell growth and division and regulation of gene activity. Somatic variants in the CALR gene are associated with ET and PMF.

The International Consensus Classification and World Health Organization Diagnostic Criteria for:

| Polycythemia Vera |
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| Major criteria:<br>1. Elevated hemoglobin concentration or elevated hematocrit or increased red blood cell mass.<br>2. Bone marrow biopsy showing age-adjusted hypercellularity with trilineage proliferation (panmyelosis), including prominent erythroid, granulocytic, and increase in pleomorphic, mature megakaryocytes without atypia.<br>3. Presence of JAK2 V617F or JAK2 exon 12 mutation.<br>Minor criteria:<br>1. Subnormal serum erythropoietin level. |
| The diagnosis of PV requires either all three (3) major criteria or the first two (2) major criteria plus the minor criterion. |

| Primary Myelofibrosis |
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| Major criteria:<br>1. Bone marrow biopsy showing megakaryocytic proliferation and atypia, bone marrow fibrosis grade <2, increased age-adjusted bone marrow cellularity, granulocytic proliferation, and (often) decreased. erythropoiesis<br>2. JAK2, CALR, or MPL mutation or presence of another clonal marker or absence of reactive bone marrow reticulin fibrosis.<br>3. Diagnostic criteria for BCR: ABL1-positive CML, PV, ET, Myelodysplastic syndromes, or other myeloid neoplasms are not met.<br>Minor criteria:<br>1. Anemia not attributed to a comorbid condition.<br>2. Leukocytosis ≥11 x 109/L.<br>3. Palpable splenomegaly.<br>4. Lactate Dehydrogenase (LDH) level above the above reference range. |
| The diagnosis of pre-PMF or overt PMF requires all three (3) major criteria and at least one (1) minor criterion confirmed in two (2) consecutive determinations. |

| Essential Thrombocythemia |
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| Major criteria:<br>1. Platelet count ≥450 × 109/L.<br>2. Bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated staghorn-like nuclei, infrequently dense clusters; no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis; no relevant bone marrow fibrosis.<br>3. Diagnostic criteria for BCR::ABL1-positive CML, PV, PMF, or other myeloid neoplasms are not met.<br>4. JAK2, CALR, or MPL mutation.<br>Minor criteria:<br>1. Presence of a clonal marker or absence of evidence of reactive thrombocytosis |
| The diagnosis of ET requires either all major criteria or the first three (3) major criteria plus the minor criteria. |

## RATIONALE

National Comprehensive Cancer Network (NCCN) Version 1.2024 for Myeloproliferative Neoplasms:

NCCN follows the recommendations of the World Health Organization and The International Consensus Classification of Myeloid Neoplasm and Acute Leukemias.

Molecular testing (blood or bone marrow) for JAK2 V617F mutation; if negative, test for CALR and MPL mutations (for patients with essential thrombocythemia [ET] and myelofibrosis [MF]) and JAK2 exon 12 mutations (for patients with polycythemia vera [PV]); or molecular testing using multigene next generation sequencing (NGS) panel that includes JAK2, CALR, and MPL. Prognostic models incorporating other mutations have been proposed to identify patients with MF as well as PV and ET to better estimate overall survival (OS), MF-free survival (PV and ET), and rates of leukemic transformation. NGS may be useful to establish clonality in selected circumstances (e.g., triple-negative non-mutated JAK2, MPL, and CALR).

The World Health Organization (WHO) Published the 5th edition of Hematolymphoid Tumors 2022 5th edition:

In individuals with suspected MPN, a positive genetic test for JAK2 satisfies a major criterion the WHO classification for Ph-negative MPNs and eliminates secondary or reactive causes of erythrocytosis and thrombocythemia from the differential diagnosis. The presence of a documented JAK2 variant may aid in the selection of ruxolitinib, a JAK2 inhibitor; however, ruxolitinib is classified as second-line therapy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

In individuals with suspected MPN, a positive genetic test for CALR or MPL satisfies a major criterion for the International Consensus Classification (2022) and the World Health Organization (2022, 5th edition) classification for ET and PMF and eliminates secondary or reactive causes of thrombocythemia from the differential diagnosis. The goal of ET treatment is to alleviate symptoms and minimize thrombotic events and bleeding irrespective of MPL or CALR variant status. For PMF, hematopoietic cell transplantation is the only treatment with curative potential while most other treatment options focus on symptom alleviation. However, in both ET and PMF, establishing the diagnosis through MPL or CALR genetic testing does not result in changes in management that would be expected to improve the net health outcome. Thus, the clinical utility has not been established.

Major diagnostic criteria for the diagnosis of PV include elevated hemoglobin concentration and/or hematocrit, accompanied by trilineage hyperplasia (panmyelosis), with pleomorphic mature megakaryocytes in the bone marrow, and NM_004972: JAK2 p.V617F or JAK2 exon 12 mutations. As the determination of increased red cell mass with Cr-labeled red cells has become uncommon in routine clinical practice, it has been removed as a diagnostic criterion.

While JAK2, CALR, and MPL mutations are considered driver events, mutations in other genes – particularly TET2, ASXL1, and DNMT3A–are found in over half of patients with MPN. Mutations affecting splicing regulators (SRSF2, SF3B1, U2AF1, ZRSR2) and other regulators of chromatin structure, epigenetic functions and cellular signaling (e.g., EZH2, IDH1, IDH2, CBL, KRAS, NRAS, STAG2, TP53) are less common. These additional mutations are more frequent in Primary myelofibrosis (PMF) and advanced disease compared to PV and ET, and some are known to correlate with a poorer prognostic risk (e.g., EZH2, IDH1, IDH2, SRSF2, U2AF1, and ASXL1 mutations in PMF).

The International Consensus Classification of Myeloid Neoplasm and Acute Leukemias 2022:

Accurate identification of MPN-associated driver mutations, JAK2 V617F, JAK2 exon 12, MPL W515L/K, and calreticulin (CALR) by highly sensitive single target (quantitative reverse transcriptase-polymerase chain reaction [RT-qPCR], digital droplet PCR [ddPCR]) or multitarget panel/next generation sequencing (NGS) assays with a minimal sensitivity of variant allele frequency (VAF) 1%, is important to support a diagnosis of PV, ET, or PMF and to separate wild-type or triple-negative cases. In triple-negative cases, the search for noncanonical JAK2 and MPL mutations (the latter for suspected ET and PMF) is encouraged, whereas a JAK2 V617F VAF of <1% should prompt the search for coexisting standard CALR (and MPL) mutations. In PV, high VAF for JAK2 V617F is associated with older age, higher hemoglobin level, leukocytosis, and lower platelet count. JAK2 exon 12 mutated cases are prognostically similar to JAK2 V617F mutated cases, although they may occur at a younger age. Because a proportion of these cases may be characterized by isolated erythrocytosis associated with erythroid preponderance in the BM, the diagnostic criterion of panmyelosis may not be applicable to this patient subset (Arber, 2022).

## CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

**CPT Codes**

| Code | Description |
|---|---|
| 81219 | CALR (calreticulin) (e.g., myeloproliferative disorders), gene analysis, common variants in exon 9 |
| 81270 | JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant |
| 81279 | JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) targeted sequence analysis (e.g., exons 12 and 13) |
| 81338 | MPL (MPL proto-oncogene, thrombopoietin receptor) (e.g., myeloproliferative disorder) gene analysis; common variants (e.g., W515A, W515K, W515L, W515R) |
| 81339 | MPL (MPL proto-oncogene, thrombopoietin receptor) (e.g., myeloproliferative disorder) gene analysis; sequence analysis, exon 10 |
| 81450 | Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis |
| 81451 | Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants, and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis |
| 81455 | Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis |
| 81456 | Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; RNA analysis |
| 0017U | Oncology (hematolymphoid neoplasia), JAK2 mutation, DNA, PCR amplification of exons 12-14 and sequence analysis, blood or bone marrow, report of JAK2 mutation not detected or detected (JAK2 Mutation, University of Iowa, Department of Pathology) |
| 0027U | JAK2 (Janus kinase 2) (e.g., myeloproliferative disorder) gene analysis, targeted sequence analysis exons 12-15 (JAK2 Exons 12 to 15 Sequencing, Mayo Clinic, Mayo Clinic) |



**HCPCS Codes**

| Code | Description |
|---|---|
| No Codes | |

**ICD10 Codes**

| Code | Description |
|---|---|
| C96.2 | Malignant mast cell tumors |
| C92.10-C92.12 | Chronic myeloid leukemia code range |
| D45 | Polycythemia vera |
| D47.3 | Essential (hemorrhagic) thrombocythemia |
| D47.4 | Osteomyelofibrosis |

## REFERENCES

*American Society of Hematology, from Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391.

Arber DA, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood 2022 Sep 15;140(11):1200-1228.

*Baxter EJ, et al. Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. Lancet Mar 2005; 365(9464): 1054-61.

*Campbell PJ, et al. Definition of subtypes of essential thrombocythaemia and relation to polycythaemia vera based on JAK2 V617F mutation status: a prospective study. Lancet Dec 2005; 366(9501):1945-53.

*Cazzola M and Kralovics R. From Janus kinase 2 to calreticulin: the clinically relevant genomic landscape of myeloproliferative neoplasms. Blood Jun 2014;123(24):3714-9.

*James C, et al. A unique clonal JAK2 mutation leading to constitutive signaling causes polycythaemia vera. Nature Apr 28 2005; 434(7037):1144-8.

*Campbell PJ, et al. V617F mutation in JAK2 is associated with poorer survival in idiopathic myelofibrosis. Blood Mar 01 2006;107(5):2098-100.

Chen K, Shih AH. Murine Modeling of Myeloproliferative Neoplasms. Hematol Oncol Clin North Am 2021 Apr;35(2):253-265.

*Dickstein JI and Vardiman JW. Hematopathologic findings in the myeloproliferative disorders. Semin Oncol 1995 Aug;22(4):355-73.

Easwar A, Siddon AJ. Genetic Landscape of Myeloproliferative Neoplasms with an Emphasis on Molecular Diagnostic Laboratory Testing. Life (Basel) 2021 Oct 30;11(11):1158.

*Harrison C, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl JMed Mar 01 2012;366(9):787-98.

*Hussein K, et al. Chronic myeloproliferative diseases with concurrent BCR-ABL junction and JAK2V617F mutation. Leukemia 2008 May;22(5):1059-62.

Jang MA, Choi CW. Recent insights regarding the molecular basis of myeloproliferative neoplasms. Korean J Intern Med 2020 Jan;35(1):1-11.

Kanagal-Shamanna R, et al. Myelodysplastic/myeloproliferative neoplasms-unclassifiable with isolated isochromosome 17q represents a distinct clinico-biologic subset: a multi-institutional collaborative study from the Bone Marrow Pathology Group. Mod Pathol 2022 Apr;35(4):470-479.

*Khoury JD, et al. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia 2022 Jul;36(7):1703-1719.

*Kralovics R, et al. A gain-of-function mutation of JAK2 in myeloproliferative disorders. N Engl J Med Apr 28 2005; 352(17):1779-90.

Kvasnicka HM. The differential diagnosis of classical myeloproliferative neoplasms (MPN): the updated WHO criteria. Rinsho Ketsueki. 2019;60(9):1166-1175.

Lee J, et al. Genomic heterogeneity in myeloproliferative neoplasms and applications to clinical practice. Blood Rev 2020 Jul;42:100708.

*Levine RL, et al. Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis. Cancer Cell Apr 2005; 7(4): 387-97.

*Li W. The 5th edition of the World Health Organization classification of hematolymphoid tumors. Brisbane (AU): Exon Publications 2022 Oct 16. Chapter 1.

*Mesa RA, et al. The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international Internet-based survey of 1179 MPD patients. Cancer 2007 Jan 1;109(1):68-76.

Makarik TV, et al. Low JAK2 V617F Allele Burden in Ph-Negative Chronic Myeloproliferative Neoplasms Is Associated with Additional CALR or MPL Gene Mutations. Genes (Basel) 2021 Apr 12;12(4):559.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Myeloproliferative neoplasms. Version.1.2024. [https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf] accessed 01/18/24.

*NIH Genetics Home Reference. JAK2 gene: Janus kinase 2. 2014; [https://ghr.nlm.nih.gov/gene/JAK2]. accessed 01/18/24.

*Siemiatkowska A, et al. JAK2 and MPL gene mutations in V617F-negative myeloproliferative neoplasms. Leuk Res Mar 2010;34(3):387-9.

Stivala S, Meyer SC. Recent Advances in Molecular Diagnostics and Targeted Therapy of Myeloproliferative Neoplasms. Cancers (Basel) 2021 Oct 9;13(20):5035.

*Tefferi A, et al. Concomitant neutrophil JAK2 mutation screening and PRV-1 expression analysis in myeloproliferative disorders and secondary polycythaemia. Br J Haematol Oct 2005; 131(2):166-71.

*Tefferi A, et al. The JAK2(V617F) tyrosine kinase mutation in myelofibrosis with myeloid metaplasia: lineage specificity and clinical correlates. Br J Haematol Nov 2005;131(3):320-8.

*Verstovsek S, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med Mar 01 2012;366(9):799-807.

*Verstovsek S, et al. Efficacy, safety, and survival with ruxolitinib in patients with myelofibrosis: results of a median 3-year follow-up of COMFORT-I. Haematologica Apr 2015;100(4):479-88.

*Wolanskyj AP, et al. JAK2 mutation in essential thrombocythaemia: clinical associations and longterm prognostic relevance. Br J Haematol Oct 2005;131(2) 208-13.

*Xia D, Hasserjian RP. Molecular testing for JAK2, MPL, and CALR in myeloproliferative neoplasms. Am J Hematol 2016 Dec;91(12):1277-1280.

*Zhao R, et al. Identification of an acquired JAK2 mutation in polycythemia vera. J Biol Chem Jun 17 2005; 280(24):22788-92.

## KEY WORDS

Janus kinase 2, JAK2, Myeloproliferative Leukemia, MPL, calreticulin, CALR, polycythemia vera, PV, essential thrombocythemia, ET, primary myelofibrosis, PMF, myeloproliferative neoplasms, MPNs.

## CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently a Local Coverage Determination (LCD) for Molecular Pathology Procedures (L35000). Please refer to the following LCD website for Medicare members https://www.cms.gov/medicare-coverage-

database/view/lcd.aspx?lcdid=35000&ver=138&ContrId=298&ContrVer=1&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=1&bc=AIIAAACAAAAA&= accessed 01/19/24.

There is currently a Local Coverage Article (LCA) for Molecular Pathology Procedures (A56199). Please refer to the following LCA website for Medicare Members: https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleid=56199&ver=99&LCDId=35000&ContrId=298&ContrVer=1&CntrctrSelected=298*1&Cntrctr=298&s=41&DocType=1&bc=AIIAAACAIAAA&= accessed 01/19/24.