MAYO CLINIC LABORATORIES

Test Definition: REVEI

Erythrocytosis Interpretation

Overview

Useful For

Interpretation of the Erythrocytosis Evaluation profile test

Definitive, comprehensive, and economical evaluation of an individual with *JAK2*-negative erythrocytosis associated with lifelong sustained increased hemoglobin or hematocrit

Method Name

Only orderable as part of a profile. For more information see REVE2 / Erythrocytosis Evaluation, Blood.

Medical Interpretation

NY State Available

Yes

Specimen

Specimen Type

Whole Blood EDTA

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Whole Blood EDTA	Refrigerated	7 days	

Clinical & Interpretive

Clinical Information

Erythrocytosis (polycythemia) is identified by a sustained increase in hemoglobin or hematocrit. An isolated increase in red blood cell count (in the absence of chronic phlebotomy or coincident with iron deficiency) may occur in thalassemia or other causes and does not indicate erythrocytosis. Erythrocytosis may occur as a primary disorder, due to an intrinsic defect of bone marrow stem cells, or secondary, in response to increased serum erythropoietin (EPO) levels. Secondary erythrocytosis is associated with a number of disorders, including chronic lung disease, chronic increase in carbon monoxide, cyanotic heart disease, high-altitude living, kidney cysts and tumors, hepatoma, and other EPO-secreting tumors. Rare plasma cell dyscrasia-associated syndromes such as POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) and TEMPI (telangiectasias, elevated EPO and erythrocytosis, monoclonal gammopathy, perinephric fluid collections, and intrapulmonary shunting) can be associated with increased hemoglobin levels. When these causes of secondary erythrocytosis are excluded, a heritable cause involving hemoglobin or erythrocyte regulatory mechanisms may be present. It is important to differentiate polycythemia vera (PV) from

heritable causes of erythrocytosis, the latter of which can be passed to progeny but does not carry the risks of clonal evolution or marrow fibrosis associated with PV.

The most common cause of hereditary erythrocytosis is the presence of a high-oxygen-affinity (HOA) hemoglobin variant. A subset of hemoglobins with increased oxygen (O2) affinity result in clinically evident erythrocytosis caused by decreased O2 unloading at the tissue level. Many are asymptomatic; however, some patients have recurrent headaches, dizziness, fatigue, and restless legs. A subset of patients experience thrombotic episodes. Affected individuals can be plethoric, and many are misclassified as polycythemia vera, particularly prior to more recent genetic testing availability. The O2-dissociation curve is left-shifted (p50 values are decreased) in HOA variants. Changes to the amino acid sequence of the hemoglobin molecule may distort the protein structure, affecting O2 transport or unloading and the binding of 2,3-bisphosphoglyceric acid (2,3-BPG). 2,3-BPG stabilizes the deoxygenated state of hemoglobin. Therefore, a decrease in the 2,3-BPG concentration results in greater O2 affinity of the normal hemoglobin molecule. Rare cases of erythrocytosis have been associated with a reduction in 2,3-BPG formation. This is due to variants in the converting enzyme, bisphosphoglycerate mutase (BPGM). Truncating variants in the erythropoietin receptor gene, *EPOR,* have been shown to be a cause of the autosomal dominant primary familial and congenital polycythemia (OMIM 133100).

In addition, O2-sensing pathway variants, *EPAS1*(*HIF2A*) (OMIM 611783)*; EGLN1*(*PHD2*) (OMIM 609820), and *VHL* (OMIM 263400) cause hereditary erythrocytosis, and a subset are associated with pheochromocytoma and paragangliomas. All have shown an autosomal dominant pattern of inheritance, except *VHL*-associated erythrocytosis, which is an autosomal recessive disorder. Homozygous *VHL* R200W alterations have been shown to be causative of Chuvash polycythemia, an endemic heritable erythrocytic disorder first described in Russia but subsequently found in other ethnic groups. The prevalence of causative variants in *EPOR* and the O2-sensing pathway genes is unknown; however, in our experience, they are less prevalent than genetic variants that cause HOA hemoglobin variants and are much less prevalent than polycythemia vera. Because there are many causes of erythrocytosis, an algorithmic and reflexive testing strategy is useful for evaluating these disorders. Initial *JAK2* V617F alteration testing and serum EPO levels are useful. Importantly, a significant subset of HOA hemoglobin variants can be electrophoretically silent on multiple routine screening platforms; however, most, and possibly all, HOA hemoglobin variants can be identified with addition of the intact mass spectrometry method. Our extensive experience with these disorders allows an economical, comprehensive evaluation with high sensitivity.

Reference Values

Only orderable as part of a profile. For more information see REVE2 / Erythrocytosis Evaluation, Blood.

Definitive results and an interpretative report will be provided.

Interpretation

The evaluation includes testing for hemoglobinopathy. Reflex testing for *EPOR*, *EGLN1* (*PHD2*), *EPAS1* (*HIF2α*), *VHL*, and *BPGM* will be performed as needed.

Cautions

An isolated increase in red blood cell count in the setting of normal hemoglobin levels (in the absence of chronic phlebotomy or coincident with iron deficiency) may occur in thalassemia or other causes and is not an indication for a thorough erythrocytosis evaluation.

Clinical Reference

1. Patnaik MM, Tefferi A. The complete evaluation of erythrocytosis: congenital and acquired. Leukemia.

2009;23(5):834-844
2. McMullin MF. The classification and diagnosis of erythrocytosis. Int J Lab Hematol. 2008;30(6):447-459
3. Percy MJ, Lee FS. Familial erythrocytosis: molecular links to red blood cell control. Haematologica. 2008;93(7):963-967
4. Huang LJ, Shen YM, Bulut GB. Advances in understanding the pathogenesis of primary familial and congenital polycythaemia. Br J Haematol. 2010;148(6):844-852
5. Maran J, Prchal J. Polycythemia and oxygen sensing. Pathol Biol (Paris). 2004;52(5):280-284
6. Lee F. Genetic causes of erythrocytosis and the oxygen-sensing pathway. Blood Rev. 2008;22(6):321-332
7. Merchant SH, Oliveira JL, Hoyer JD, Viswanatha DS. Erythrocytosis. In: His ED, ed. Hematopathology. 2nd ed. Elsevier Saunders; 2012:722-723
8. Zhuang Z, Yang C, Lorenzo F, et al. Somatic HIF2A gain-of-function mutations in paraganglioma with polycythemia. N Engl J Med. 2012;367(10):922-930
9. Oliveira JL, Coon LM, Frederick LA, et al. Genotype-phenotype correlation of hereditary erythrocytosis mutations, a single center experience. Am J Hematol. 2018. doi:10.1002/ajh.25150
10. Gangat N, Oliveira JL, Hoyer JD, Patnaik MM, Pardanani A, Tefferi A. High-oxygen-affinity hemoglobinopathy-associated erythrocytosis: Clinical outcomes and impact of therapy in 41 cases. Am J Hematol. 2021;96(12):1647-1654. doi:10.1002/ajh.26375
11. Gangat N, Oliveira JL, Porter TR, et al. Erythrocytosis associated with EPAS1(HIF2A), EGLN1(PHD2), VHL, EPOR or BPGM mutations: the Mayo Clinic experience. Haematologica. 2022;107(5):1201-1204. doi:10.3324/haematol.2021.280516

Performance

Method Description
A hematopathologist expert in these disorders evaluates the case, appropriate tests are performed, and an interpretive report is issued.

PDF Report
No

Day(s) Performed
Monday through Friday

Report Available
3 to 25 days if structural or molecular studies are required.

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Main Campus

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.

- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification

Not Applicable

CPT Code Information

83020-26

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
REVEI	Erythrocytosis Interpretation	59466-3

Result ID	Test Result Name	Result LOINC® Value
608426	Erythrocytosis Interpretation	59466-3
608440	Reviewed By	18771-6