

## Overview

### Useful For

An aid in distinguishing between primary and secondary polycythemia

Differentiating between appropriate secondary polycythemia (eg, high-altitude living, pulmonary disease, tobacco use) and inappropriate secondary polycythemia (eg, tumors)

Identifying candidates for erythropoietin (EPO) replacement therapy (eg, those with chronic renal failure)

Evaluating patients undergoing EPO replacement therapy who demonstrate an inadequate hematopoietic response

### Testing Algorithm

The following algorithms are available in Special Instructions:

[-Erythrocytosis Evaluation Testing Algorithm](#)

[-Myeloproliferative Neoplasm: A Diagnostic Approach to Bone Marrow Evaluation](#)

[-Myeloproliferative Neoplasm: A Diagnostic Approach to Peripheral Blood Evaluation](#)

### Special Instructions

- [Myeloproliferative Neoplasm: A Diagnostic Approach to Peripheral Blood Evaluation](#)
- [Myeloproliferative Neoplasm: A Diagnostic Approach to Bone Marrow Evaluation](#)
- [Erythrocytosis Evaluation Testing Algorithm](#)

### Method Name

Immunoenzymatic Assay

### NY State Available

Yes

## Specimen

### Specimen Type

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Serum

**Specimen Required****Container/Tube:****Preferred:** Serum gel**Acceptable:** Red top**Specimen Volume:** 0.6 mL**Collection Instructions:** Morning collection, 7:30 a.m.-12 p.m. is preferred due to diurnal variation. For more information see Cautions.**Forms**

If not ordering electronically, complete, print, and send 1 of the following forms with the specimen:

[-General Request](#) (T239)[-Benign Hematology Test Request](#) (T755)**Reject Due To**

Gross hemolysis	Reject
Gross lipemia	OK
Gross Icterus	OK

**Specimen Minimum Volume**

0.5 mL

**Specimen Stability Information**

Specimen Type	Temperature	Time	Special Container
Serum	Refrigerated (preferred)	14 days	
	Frozen	14 days	
	Ambient	7 days	

**Clinical & Interpretive****Clinical Information**

Erythropoietin (EPO), a large (193 amino acid residue) glycoprotein hormone secreted by the kidney, regulates red blood cell (RBC) production. Normally, EPO levels vary inversely with hematocrit. Hypoxia stimulates EPO release, which, in turn, stimulates bone marrow erythrocyte production. High blood levels of RBC, hemoglobin, hematocrit, or oxygen suppress the release of EPO.

Primary polycythemia (polycythemia vera) is a neoplastic (clonal) blood disorder characterized by autonomous production of hematopoietic cells. Increased RBCs result in compensatory suppression of EPO levels. Findings consistent with polycythemia vera include hemoglobin greater than 18.5 g/dL, persistent leukocytosis, persistent thrombocytosis, unusual thrombosis, splenomegaly, and erythromelalgia (dysesthesia and erythema involving the distal extremities).

Secondary polycythemias may either be due to an appropriate or an inappropriate increase in red cell mass. Appropriate secondary polycythemias (eg, high-altitude living and pulmonary disease) are characterized by hypoxia and a compensatory increase in red cell mass. EPO production is increased in an attempt to increase the delivery of oxygen by increasing the number of oxygen-carrying RBCs. Some tumors secrete EPO or EPO-like proteins; examples include tumors of the kidney, liver, lung, and brain. Such increases result in inappropriate secondary polycythemias.

Abnormal EPO levels also may be seen in renal failure. The majority of EPO production is in the kidneys. Therefore, chronic kidney failure may result in decreased EPO production and, subsequently, anemia. In addition to the kidneys, the liver also produces a small amount of EPO. Thus, patients who are anephric have a residual amount of EPO produced by the liver.

Patients in chronic kidney failure, as well as patients with anemia due to a variety of other causes including chemotherapy, HIV/AIDS, and some hematologic disorders, may be candidates for treatment with recombinant human EPO. Recombinant EPO compounds used to treat anemia include epoetin alpha and darbepoetin. Epoetin alpha is a 165 amino acid glycoprotein produced in mammalian cells and has an identical amino acid sequence to natural human EPO. It has 3 oligosaccharide chains and a molecular mass of 30.4 kDa. Darbepoetin alpha is a 165 amino acid glycoprotein that is also produced in mammalian cells. It has 2 additional N-linked oligosaccharide chains and a molecular mass of 37 kDa. There are no specific assays for measuring recombinant EPO compounds. Drug levels can only be roughly estimated from the cross reactivity of the compounds in EPO assays. According to in-house studies, epoetin and darbepoetin show approximately 58% and 36% cross-reactivity, respectively, in the EPO assay.

**Reference Values**

2.6-18.5 mIU/mL

**Interpretation**

In the appropriate clinical setting (eg, confirmed elevation of hemoglobin >18.5 g/dL, persistent leukocytosis, persistent thrombocytosis, unusual thrombosis, splenomegaly, and erythromelalgia), polycythemia vera is unlikely when erythropoietin (EPO) levels are elevated but is likely when EPO levels are suppressed.

EPO levels are also increased in patients with anemia of bone marrow failure, iron deficiency, or thalassemia.

Patients, who have either a poor or no erythropoietic response to EPO therapy, but high-normal or high EPO levels, may have additional, unrecognized causes for their anemia. If no contributing factors can be identified after adequate further study, the possibility that the patient may have developed EPO-antibodies should be considered. This can be a serious clinical situation that can result in red cell aplasia and should prompt expeditious referral to hematologists or immunologists skilled in diagnosing and treating this disorder.

**Cautions**

Erythropoietin (EPO) levels alone cannot reliably distinguish between primary and secondary polycythemia; EPO levels are within normal limits in some patients with primary polycythemia.

People living at high altitudes may have higher EPO levels than people living at lower altitudes.

This assay cannot distinguish between endogenous and exogenous EPO.

There are no specific assays for measuring recombinant EPO compounds. Drug levels can only be roughly estimated from the cross reactivity of the compounds in EPO assays. According to Mayo Clinic in-house studies, epoetin and darbepoetin show approximately 58% and 36% cross reactivity, respectively, in the EPO assay.

Because results obtained with one commercial EPO assay may differ significantly from those obtained with any other, it is recommended that any serial testing performed on the same patient over time should be performed with the same commercial EPO test.

Heterophile antibodies may interfere in this assay. Results markedly at variance with presentation should be questioned. Additional specimen workup to eliminate heterophile antibody interference can be performed; call 800-533-1710 for additional information.

Lower EPO levels than expected have been seen with anemias associated with the following conditions: rheumatoid arthritis, AIDS, cancer, ulcerative colitis, sickle cell disease, and in premature neonates.

After allogeneic bone marrow transplant, impaired EPO response may delay EPO recovery.

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Patients with hypergammaglobulinemia associated with multiple myeloma or Waldenstrom disease have impaired production of EPO in relation to hemoglobin concentration. This has been linked to increased plasma viscosity.

There is some diurnal variation in EPO levels. For optimal results in serial patient monitoring, all specimens should be collected at the same time of day. The diurnal variation is minimal in normal individuals (<20%), but in hospitalized patients with a variety of illnesses, as well as ambulatory patients with chronic lung disease, serum EPO concentrations can be 20% to 60% higher at night than early in the morning. This phenomenon is most pronounced in patients with EPO levels within approximately 2-times the upper limit of the normal population reference interval.

### Clinical Reference

1. Tefferi A: Diagnosing polycythemia vera: a paradigm shift. *Mayo Clin Proc.* 1999;74:159-162
2. Hoagland HC: Myelodysplastic (preleukemia) syndromes: the bone marrow factory failure problem. *Mayo Clin Proc.* 1995;70:673-677
3. Casadeval N: Pure red cell aplasia and anti-erythropoietin antibodies in patients treated with epoetin. *Nephrol Dial Transplant.* 2003;18 (Suppl. 8):viii37-viii41
4. Fisher JW: Erythropoietin: physiology and pharmacology update. *Exp Biol Med.* 2003;228:1-14
5. Strippoli GFM, Manno C, Schena FP, Craig JC: Haemoglobin and haematocrit targets for the anaemia of chronic kidney disease. *Cochrane Database Syst Rev.* 2006 Oct 18;(4):CD003967
6. Tefferi A: Polycythemia vera and essential thrombocythemia: 2012 update on diagnosis, risk stratification, and management. *Am J Hematol.* 2012 Mar;87:285-293. doi: 10.1002/ajh.23135
7. Moore E, Bellomo R: Erythropoietin (EPO) in acute kidney injury. *Ann Intensive Care.* 2011 March;1(3). doi: 10.1186/2110-5820-1-3
8. Macdougall I: Anaemia and chronic renal failure. *Medicine.* 2011;39(7):425-428. doi: 10.1016/j.mpmed.2011.04.009

### Performance

#### Method Description

The Access erythropoietin (EPO) assay is a 2-site immunoenzymatic (sandwich) assay. A sample is added to a reaction vessel along with the paramagnetic particles coated with mouse monoclonal anti-EPO, blocking reagent and the alkaline phosphatase conjugate. After incubation in a reaction vessel, materials bound to the solid phase are held in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos 530 is added to the vessel and light generated by the reaction is measured with a luminometer. The light production is directly proportional

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to the concentration of EPO in the sample. The amount of analyte in the sample is determined from a stored, multi-point calibration curve. (Instruction manual: Beckman Coulter Access EPO. Beckman Coulter, Inc; 2019)

**PDF Report**

No

**Specimen Retention Time**

14 days

**Performing Laboratory Location**

Rochester

**Fees & Codes****Test Classification**

This test has been cleared, approved, or is exempt by the US Food and Drug Administration and is used per manufacturer's instructions. Performance characteristics were verified by Mayo Clinic in a manner consistent with CLIA requirements.

**CPT Code Information**

82668

**LOINC® Information**

Test ID	Test Order Name	Order LOINC Value
EPO	Erythropoietin (EPO), S	15061-5

Result ID	Reporting Name	LOINC®
EPO	Erythropoietin (EPO), S	15061-5