The hemoglobin A1C (A1C) test can be unreliable for diagnosing or monitoring diabetes and prediabetes in people with inherited hemoglobin variants, also called hemoglobinopathies. Hemoglobins S and E are prevalent variants in people of African, Mediterranean, or Southeast Asian descent. These variants interfere with some A1C tests—both laboratory and point-of-care tests. If A1C tests are at odds with blood glucose testing results, interference should be considered. Reliable A1C tests that do not cause interference with hemoglobin variants are available. More information about appropriate assay methods to use for hemoglobin variants is available from the NGSP at [www.ngsp.org](http://www.ngsp.org). Also, alternative tests may be needed for people with any disorder that affects red blood cells or hemoglobin.

**When to Suspect that a Patient with Diabetes Has a Hemoglobinopathy**

Most people who are heterozygous—having one variant gene and one standard hemoglobin gene—for a hemoglobin variant have no symptoms and may not know that they carry this type of hemoglobin. Healthcare providers should suspect the presence of a hemoglobinopathy when

- an A1C result is different than expected
- an A1C result is above 15 percent
- results of self-monitoring of blood glucose have a low correlation with A1C results
- a patient’s A1C result is radically different from a previous A1C result following a change in laboratory A1C methods

**Statistically Speaking**

**Hemoglobins S and C**

African Americans have an increased risk of inheriting sickle cell trait, the condition in which people have both hemoglobin A (HbA), the usual form of hemoglobin, and hemoglobin S (HbS), a variant. African
Americans are also at risk for having hemoglobin C (HbC), another variant. About one in 12 African Americans has sickle cell trait. About 13 percent of African Americans ages 20 years or older have diabetes. Therefore, many African Americans have both diabetes and sickle cell trait.

**Hemoglobin E**

People of Southeast Asian descent are at risk for having hemoglobin E (HbE), another hemoglobin variant. Prevalence of diabetes in Asian Americans varies among subpopulations. About 9 percent of Asian Americans ages 20 years or older have diabetes.


**Hemoglobinopathies**

Hemoglobin is composed of heme—the portion of the molecule containing iron—and globin—a protein made up of amino acid chains. Hemoglobin variants occur when mutations in the globin genes result in changes in the amino acids of the globin protein. Hundreds of variants have been identified; a small number of variants are common and have clinical significance. Variants significant to A1C testing are listed in Table 1.

These variants are inherited in an autosomal recessive manner, affecting people in the following ways. People who are

- homozygous, with a condition such as hemoglobin SS (HbSS), have a copy of the variant gene from each parent and generally have sickle cell disease.
- heterozygous, with a condition such as hemoglobin S (HbS), have a copy of the variant gene from one parent and are said to have a trait or to be carriers and are usually asymptomatic.
- compound heterozygous, with a condition such as hemoglobin SC (HbSC), have inherited genes for two variants—HbS from one parent and HbC from the other. These patients may have less severe sickle cell symptoms.

**Detecting Hemoglobinopathies**

If a health care provider suspects that a patient may have a hemoglobinopathy, carrier status can be detected using hemoglobin electrophoresis, high-performance liquid chromatography (HPLC), or isoelectric focusing.
Alternatively, a health care provider can use an assay that does not have interference with any variant. More information is provided in the NIDDK health topic, Information about Assay Methods for Patients with Hemoglobinopathies.

**Technically speaking...**

The A1C test measures the amount of glycated hemoglobin in the blood, which reflects average blood glucose levels over the preceding 3 months. Also called the hemoglobin A1C, HbA1c, or glycohemoglobin test, the A1C test is based on the addition of glucose to hemoglobin over the typical 120-day life span of a red blood cell.

Formation of glycated proteins is proportional to the concentration of glucose in the blood. However, the A1C test is a weighted average, with the glucose level of the preceding 30 days contributing more to the test result than glucose levels 90 to 120 days earlier. Thus, clinically significant changes in glucose can be seen in the A1C without waiting 120 days for red blood cell turnover.

When the A1C test is used for diagnosis, the blood sample must be sent to a laboratory that uses an NGSP-certified method for analysis to ensure the results are standardized.

More information for health care providers about the A1C test is provided in the NIDDK health topics:

- The A1C Test and Diabetes

**Effect of Hemoglobinopathies on A1C Test Results**

Laboratories use many different assay methods for measuring A1C, but some of these methods can give inaccurate results when the patient has a hemoglobin variant such as sickle cell trait or if there is an elevated level of HbF. Health care providers or patients interested in getting information about the accuracy of a particular A1C method for patients with hemoglobin variants should first find out which method their laboratory is using.

With some assay methods, A1C tests in patients with hemoglobinopathies result in falsely high outcomes, overestimating actual average blood glucose levels for the previous 3 months. Health care providers may then falsely diagnose patients or prescribe more aggressive treatments, resulting in increased episodes of hypoglycemia. Some methods used with certain hemoglobinopathies may result in falsely low outcomes, leading to undertreatment of diabetes.

Health care providers should not use the A1C test for patients with a disease condition such as HbSS, HbCC, or HbSC. Even if an assay does not interfere with their variant, these patients may suffer anemia,
increased red blood cell turnover, and transfusion requirements, which can adversely affect A1C as a marker of long-term glycemic control.

See “Other Conditions That Can Affect A1C Test Results” for information about other conditions that may give false test results. Health care providers should consider alternative forms of testing for these patients, such as glycated serum protein or glycated albumin.

**Common Types of Hemoglobinopathies**

The following table summarizes the affected populations, prevalence, and outcomes of common hemoglobinopathies. These hemoglobinopathies may either falsely raise or lower A1C results, depending on the variant and the assay method.

**Table 1. Common hemoglobinopathies: populations affected, prevalence, and outcomes**

<table>
<thead>
<tr>
<th>Hemoglobin Variant</th>
<th>Populations Affected</th>
<th>Prevalence (in the United States unless otherwise noted)</th>
<th>Outcome with One Abnormal Gene and One Normal Gene (Heterozygous State)</th>
<th>Outcome with Two Abnormal Genes (Homozygous State)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbS</td>
<td>African Americans, Hispanic Americans/Latinos</td>
<td>About one in 12 African Americans has sickle cell trait. About one in 100 Hispanic Americans/Latinos has sickle cell trait.</td>
<td>Sickle cell trait (also called HbAS): usually asymptomatic</td>
<td>Sickle cell anemia (also called HbSS disease): sickled red blood cells that interfere with circulation and decrease life span of red blood cells; can result in hemolytic, splenic sequestration, and aplastic crises and multiple complications</td>
</tr>
<tr>
<td></td>
<td>Also found in Africa, South or Central America (especially Panama), Caribbean islands, Mediterranean countries (such as Turkey, Greece, and Italy), India, and Saudi Arabia</td>
<td>Sickle cell anemia occurs in one of every 500 African American births. Sickle cell anemia occurs in one of every 36,000 Hispanic/Latino births.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbC</td>
<td>African Americans, People of West African descent</td>
<td>About 2.3 percent of African Americans have HbC trait.</td>
<td>HbC trait (also called HbAC): asymptomatic</td>
<td>HbC disease (also called HbCC disease): mild hemolytic anemia, mild to moderate enlargement of the spleen</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbE</td>
<td>Asian Americans, especially those of Southeast Asian descent</td>
<td>Prevalence of HbE may be 30 percent in Southeast Asia.</td>
<td>HbE trait (also called HbAE): asymptomatic</td>
<td>HbE disease (also called HbEE disease): mild hemolytic anemia, microcytosis, and</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin Variant</td>
<td>Populations Affected</td>
<td>Prevalence (in the United States unless otherwise noted)</td>
<td>Outcome with One Abnormal Gene and One Normal Gene (Heterozygous State)</td>
<td>Outcome with Two Abnormal Genes (Homozygous State)</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------------</td>
<td>--------------------------------------------------------</td>
<td>---------------------------------------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>HbSC</td>
<td>Common in Cambodia, Indonesia, Laos, Malaysia, Thailand, and Vietnam</td>
<td>N/A</td>
<td>N/A</td>
<td>HbSC disease (also called sickle-hemoglobin C disease): mild hemolytic anemia and moderate enlargement of the spleen; may have blocking of blood vessels as in sickle cell anemia but milder symptoms</td>
</tr>
<tr>
<td></td>
<td>Also seen in southern China, India, the Philippines, and Turkey</td>
<td>N/A</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>HbF elevated</td>
<td>Occurs in patients with hereditary persistence of fetal hemoglobin, sickle cell anemia, severe anemias, leukemia, and other conditions</td>
<td>About 1.5 percent have more than 2 percent HbF, but some groups may have concentrations as high as 12 percent.</td>
<td>N/A</td>
<td>Those with elevated HbF and sickle cell anemia may have a milder form of sickle cell anemia.</td>
</tr>
</tbody>
</table>


**Information about Assay Methods for Patients with Hemoglobinopathies**

The NGSP provides a table on its website at www.ngsp.org External Link Disclaimer describing the effects of frequently encountered Hb variants and derivatives on glycohemoglobin measurement for more than 20 assay methods. The NGSP website also includes a list of references for the information summarized in the table.
The NGSP has worked with manufacturers and developed a network of reference laboratories to ensure the availability of assay methods without clinically significant HbAS or HbAC interference. In 2011, per the NGSP website, only about 4.2 percent of laboratories were using methods resulting in significant HbAS or HbAC interference. See www.ngsp.orgExternal Link Disclaimer for updates.

**Alternative Tests**

Health care providers may wish to consider using other measures of average blood glucose levels, such as the fructosamine test, also called glycated serum protein or glycated albumin, with patients who have hemoglobinopathies where an accurate A1C result cannot be obtained. However the fructosamine test shows average glucose levels over a much shorter period of time than the A1C test, usually about 2 to 3 weeks. Also, the fructosamine test is not standardized and the relationship of results of this test to glucose levels or risk for complications has not been established.

**Other Conditions That Can Affect A1C Test Results**

False A1C results may also occur in people with other problems that affect their blood or hemoglobin, regardless of which assay is used. For example, a falsely low A1C result can occur in people with

- anemia
- heavy bleeding

A falsely elevated A1C result can occur in people who

- are very low in iron, for example, those with iron deficiency anemia

Other causes of false A1C results include

- kidney failure
- liver disease

More information is available for patients with diabetes about hemoglobin variants and the A1C test in the NIDDK health topic, [For People of African, Mediterranean, or Southeast Asian Heritage: Important Information about Diabetes Blood Tests](#).

**Points to Remember**

- The hemoglobin A1C (A1C) test can be unreliable for diagnosing or monitoring diabetes and prediabetes in people with inherited hemoglobin variants, also called hemoglobinopathies.
• Hemoglobins S and E are prevalent variants in people of African, Mediterranean, or Southeast Asian descent. These variants interfere with some A1C tests—both laboratory and point-of-care tests.
• With some assay methods, A1C tests in patients with hemoglobinopathies result in falsely high outcomes, overestimating actual average blood glucose levels for the previous 3 months. Health care providers may then falsely diagnose patients or prescribe more aggressive treatments, resulting in increased episodes of hypoglycemia.
• Some methods used with certain hemoglobinopathies may result in falsely low outcomes, leading to undertreatment of diabetes.
• Most people who are heterozygous—having one variant gene and one standard hemoglobin gene—for a hemoglobin variant have no symptoms and may not know that they carry this type of hemoglobin.
• Health care providers should suspect the presence of a hemoglobinopathy when
  o an A1C result is different than expected
  o an A1C result is above 15 percent
  o results of self-monitoring of blood glucose have a low correlation with A1C results
  o a patient’s A1C result is radically different from a previous A1C result following a change in laboratory A1C methods
• Health care providers or patients interested in getting information about the accuracy of a particular A1C method for patients with hemoglobin variants should first find out which method their laboratory is using.
• Reliable A1C tests that do not cause interference with hemoglobin variants are available.
• When the A1C test is used for diagnosis, the blood sample must be sent to a laboratory that uses an NGSP-certified method for analysis to ensure the results are standardized.
• Health care providers should not use the A1C test for patients with a disease condition such as HbSS, HbCC, or HbSC. Even if an assay does not interfere with their variant, these patients may suffer anemia, increased red blood cell turnover, and transfusion requirements, which can adversely affect A1C as a marker of long-term glycemic control.
• Alternative tests may be needed for people with any disorder that affects red blood cells or hemoglobin.
• More information about appropriate assay methods to use for hemoglobin variants is available from the NGSP at www.ngsp.org.

This content is provided as a service of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), part of the National Institutes of Health. The NIDDK translates and disseminates research findings through its clearinghouses and education programs to increase knowledge and
understanding about health and disease among patients, health professionals, and the public. Content produced by the NIDDK is carefully reviewed by NIDDK scientists and other experts.

The NIDDK would like to thank:
Charles M. Peterson, M.D., M.B.A., Division of Blood Diseases and Resources at the National Heart, Lung, and Blood Institute, National Institutes of Health; Randie R. Little, Ph.D., NGSP, University of Missouri School of Medicine

This information is not copyrighted. The NIDDK encourages people to share this content freely.

June 2014