Hemoglobinopathies in Pregnancy

The hemoglobinopathies are a heterogeneous group of single-gene disorders that includes the structural hemoglobin variants and the thalassemias. More than 270 million people worldwide are heterozygous carriers of hereditary disorders of hemoglobin, and at least 300,000 affected homozygotes or compound heterozygotes are born each year (1). The purpose of this document is to review the most common hemoglobinopathies and to provide recommendations for screening and clinical management of hemoglobinopathies during pregnancy.

Background

Hemoglobin Structure

Hemoglobin consists of four interlocking polypeptide chains, each of which has an attached heme molecule. The polypeptide chains are called alpha (α), beta (β), gamma (γ), delta (δ), epsilon (ε), and zeta (ζ). Adult hemoglobins consist of two α-chains and either two β-chains (hemoglobin A), two γ-chains (hemoglobin F), or two δ-chains (hemoglobin A₂). Hemoglobin F (fetal hemoglobin, Hb F) is the primary hemoglobin of the fetus from 12 to 24 weeks of gestation. In the third trimester, production of Hb F decreases as production of β-chains and Hb A begins. The genes that code for α-globin chains are located on the short arm of chromosome 16, and the β-globin gene is located on the short arm of chromosome 11.

Sickle Cell Disease

Sickle cell disease refers to a group of autosomal recessive disorders involving abnormal hemoglobin (hemoglobin S). Hemoglobin S differs from the normal Hb A because of a single nucleotide substitution of thymine for adenine in the β-globin gene; this alteration causes a substitution of valine for glutamic acid in the number six position of the β-globin polypeptide. Asymptomatic individuals...
with heterozygous Hb S genotypes (carriers) are said to have sickle cell trait. The most severe form of the disease, Hb SS (homozygous Hb S), is called sickle cell anemia.

Sickle cell disorders are found not only in patients who have the hemoglobin genotype SS, but also in those who have Hb S and one other abnormality of β-globin structure or β-globin production. The most common of these are Hb SC disease and Hb S/β-thalassemia. In Hb C, the same nucleotide involved in the Hb S mutation is altered with the substitution of adenine for guanine, which results in the amino acid substitution of lysine for glutamic acid. This and other abnormal hemoglobins, when inherited with Hb S, may cause clinically significant vasoocclusive phenomena and hemolytic anemia similar to Hb SS.

Sickle cell disease occurs most commonly in people of African origin. Approximately 1 in 12 African Americans has sickle cell trait (2). One in every 300 African-American newborns has some form of sickle cell disease, and approximately 1 in 600 has sickle cell anemia. Hemoglobin S also is found in high frequency in other populations such as Greeks, Italians (particularly Sicilians), Turks, Arabs, Southern Iranians, and Asian Indians (3).

The classical clinical feature of patients with sickle cell disease is seen under conditions of decreased oxygen tension, in which the red blood cells become distorted into various shapes, some of which resemble sickles. The distorted red cells lead to increased viscosity, hemolysis, and anemia and a further decrease in oxygenation. When sickling occurs within small blood vessels, it can cause “logjams” that can interrupt blood supply to vital organs (vasoocclusive crisis). Repeated vasoocclusive crises result in widespread microvascular obstruction with interruption of normal perfusion and function of several organs, including the spleen, lungs, kidneys, heart, and brain. Adults with Hb SS are functionally asplenic, having undergone autosplenectomy by adolescence. Absence of the spleen contributes to the increased incidence and severity of infection in patients with sickle cell disease.

The most significant threat to patients with sickle cell disease is acute chest syndrome. Chest syndrome is characterized by a pulmonary infiltrate with fever that leads to hypoxemia and acidosis. The infiltrates are not infectious in origin but rather are due to vasoocclusion from sickling or embolization of marrow from long bones affected by sickling (4).

The diagnosis of hemoglobinopathies, including sickle cell disorders, is made by hemoglobin electrophoresis. In the homozygous form, nearly all the hemoglobin is Hb S with small amounts of Hb A2 and Hb F. Heterozygous sickle cell trait (Hb AS) is identified by a larger percentage of Hb A and an asymptomatic course. Solubility tests (Sickledex) alone are inadequate for diagnosis of sickle cell disorders because they cannot distinguish between the heterozygous AS and homozygous SS genotypes. In addition, they fail to detect other pathologic variants such as Hb C trait, β-thalassemia trait, Hb E trait, Hb B trait, and Hb D trait.

### The Thalassemias

The thalassemias represent a wide spectrum of hematologic disorders that are characterized by a reduced synthesis of globin chains, resulting in microcytic anemia. Thalassemias are classified according to the globin chain affected, with the most common types being α-thalassemia and β-thalassemia. Many different molecular mechanisms lead to thalassemia in populations from different areas of the world (5).

### Alpha-Thalassemia

Alpha-thalassemia usually results from a gene deletion of two or more copies of the four α-globin genes. Deletion of one α-globin gene (α-/αα) is clinically unrecognizable, and laboratory testing yields normal results. Deletion of two α-globin genes causes α-thalassemia trait, a mild asymptomatic microcytic anemia. The deletions can be on the same chromosome or in cis (αα/--) or on each chromosome or in trans (αα/αα/--) (6). Individuals with these chromosomal abnormalities are referred to as carriers and are at an increased risk for having a child with a more severe form of thalassemia caused by deletions of three or four copies of the α-globin gene (αααα/--) (α-thalassemia major). The possible genetic combinations are summarized in Table 1.

Alpha-thalassemia trait (α-thalassemia minor) is common among individuals of Southeast Asian, African, and West Indian descent. It also is common in individuals with Mediterranean ancestry. Individuals with Southeast Asian ancestry are more likely to carry two gene deletions in cis or on the same chromosome (αα/--) and are at an increased risk for offspring with Hb Bart’s or Hb H disease. Hemoglobin H disease, which is caused by the deletion of three α-globin genes, usually is associated with mild to moderate hemolytic anemia. Alpha-thalassemia major (Hb Bart’s) results in the absence of α-globin (αααα/--) and is associated with hydrops fetalis, intrauterine death, and preeclampsia (3).

In individuals of African descent, α-thalassemia usually is due to a deletion of a single α-globin gene on each chromosome 16 (α-/αα). This is in contrast to the common Asian genotype, which is a deletion of both α-globin genes on one chromosome 16 (cis) (αααα/__). Hemoglobin Bart’s disease does not typically develop in fetuses of α-thalassemia carriers of African origin.

Because Hb S results from an abnormality of the β-chain, both heterozygous (AS) and homozygous (SS)
forms can be inherited with heterozygous or homozygous α⁺-thalassemia. In individuals with sickle cell trait (Hb AS), α-thalassemia lowers the proportion of Hb S, and in those with Hb SS, it lessens the severity of sickle cell disease.

Alpha-thalassemia also may occur as a result of a gene mutation. In this case, the genes are present but not functioning normally. This may result from mutagen in the stop codon leading to synthesis of a longer and unstable α-chain (Hb Constant Spring), from substitutions impairing αβ dimer formation (Hb Qong Sze), and from point substitutions in the poly A region at the 3' end of the gene (αTSaudi).

Betathalassemia is caused by a mutation in the β-globin gene that causes deficient or absent β-chain production, which results in absence of Hb A. Classification of β-thalassemias is based on a description of the molecular mutation or by clinical manifestations. Individuals who are heterozygous for this mutation have β-thalassemia minor. Those who are homozygous have β-thalassemia major (Cooley’s anemia) or a milder form called thalassemia intermedia. Beta-thalassemia major is characterized by severe anemia with resultant extramedullary erythropoesis, delayed sexual development, and poor growth. Elevated levels of Hb F in individuals with β-thalassemia major partially compensate for the absence of Hb A; however, death usually occurs by age 10 years unless treatment is begun early with periodic blood transfusions. With transfusion, the severe anemia is reversed and extramedullary erythropoesis is suppressed. In homozygotes with the less severe β⁺-thalassemia mutations, often referred to as β-thalassemia intermedia, variable but decreased amounts of β-chains are produced and, as a result, variable amounts of Hb A are produced. The genes for Hb S and β-thalassemia usually behave as alleles, with only one gene inherited from each parent. The expression of the resulting Hb S/β-thalassemia is determined by the type of β-thalassemia mutation (6).

Beta-thalassemia minor, common in individuals of Mediterranean, Asian, Middle Eastern, Hispanic, and West Indian descent, varies in severity of disease. Depending on the amount of β-chain production, it usually is associated with asymptomatic mild anemia. Beta-thalassemia minor often occurs in association with Hb S. In the most severe form, no normal β-globin chains are produced. This results in a clinically severe syndrome called sickle cell–β0-thalassemia, in which no Hb A is produced.

Clinical Considerations and Recommendations

Who should be screened for hemoglobinopathies and how should this be accomplished?

Genetic screening can identify couples at risk for offspring with hemoglobinopathies and allow them to make informed decisions regarding reproduction and prenatal diagnosis (3). Individuals of African, Southeast Asian, and Mediterranean ancestry are at a higher risk for being carriers of hemoglobinopathies and should be offered carrier screening. Ethnic groups considered to be at low risk for hemoglobinopathies include northern Europeans, Japanese, Native Americans, Inuit (Eskimo), and Koreans. If both parents are determined to be carriers, genetic counseling is recommended. It should be noted...
that ethnicity is not always a good predictor of risk because individuals from at-risk groups may marry outside their ethnic group (3).

A combination of laboratory tests may be required to provide the information necessary to counsel couples who are carriers of one of the thalassemias or sickle cell disease (Fig. 1). To ensure accurate hemoglobin identification, which is essential for genetic counseling, a complete blood count (CBC) is the appropriate initial laboratory test for individuals of non-African descent. In individuals of African descent, a hemoglobin electrophoresis should be performed in addition to a CBC. Several tests, including solubility testing such as a test for the presence of Hb S (Sickledex), isoelectric focusing, and high-performance liquid chromatography (HPLC), have been used for primary screening. However, solubility tests alone are inadequate for screening and fail to identify important transferrable hemoglobin gene abnormalities affecting fetal outcome (eg, Hb C trait, β-thalassemia trait, Hb E trait, Hb B trait, Hb D trait). Many individuals with these genotypes are asymptomatic, but if their partners have the sickle cell trait or other hemoglobinopathies, they may produce offspring with more serious hemoglobinopathies, such as Hb S/β-thalassemia and Hb SC disease. Solubility testing may be valuable, however, for rapid screening for sickling when this information is critical for immediate patient care.

Determination of mean corpuscular volume (MCV) is recommended for patients who are at risk for α- or β-thalassemia. Patients who have a low MCV (less than 80 fL) may have one of the thalassemia traits and are candidates for hemoglobin electrophoresis. These individuals also may have iron deficiency anemia, and measurement of serum ferretin levels is recommended. Beta-thalassemia is associated with elevated Hb F and elevated Hb A₂ levels (more than 3.5%). Neither hemoglobin electrophoresis nor solubility testing can identify individuals with α-thalassemia trait; only molecular genetic testing can identify this condition. If the MCV is below normal, iron deficiency anemia has been excluded, and the hemoglobin electrophoresis is not consistent with β-thalassemia trait (ie, there is no elevation of Hb A₂ or Hb F), then DNA-based testing should be used to detect α-globin gene deletions characteristic of α-thalassemia.

The hematologic features of some of the common hemoglobinopathies are shown in Table 2. If both part-
For couples at risk for having a child with a hemoglobinopathy, genetic counseling may benefit from genetic counseling to review the natural history of these disorders, prospects for treatment and cure, their risk, availability of prenatal genetic testing, and reproductive options. Prenatal diagnostic testing for the single mutation responsible for sickle cell disease is widely available. Testing for α- and β-thalassemia is possible if the mutations and deletions have been previously identified in both parents. These DNA-based tests can be performed using chorionic villi obtained by chorionic villus sampling (CVS) at 10–12 weeks of gestation or using cultured amniotic fluid cells obtained by amniocentesis after 15 weeks of gestation. For some couples, preimplantation genetic diagnosis in combination with in vitro fertilization may be a desirable alternative to avoid termination of an affected pregnancy. Preimplantation genetic diagnosis has been successfully performed for sickle cell disease and most cases of β-thalassemia.

Although the advances in prenatal diagnosis of hemoglobinopathies have been impressive, use of the technology has been somewhat limited because of ethical, social, and cultural concerns. Prenatal diagnosis is most commonly requested by families who have had a child with sickle cell disease and who wish to be certain that their next child is not affected. In many respects, these families are “self-counseled.” The difficulty in counseling families who have not had an affected child lies in the variable severity of the disease and the inability to predict its course (6). One investigator found that nearly 70% of families in whom prenatal diagnosis confirmed that the fetus was affected with Hb SS elected to continue the pregnancy (7).

For couples with an increased risk for having an affected offspring, what methods are available for genetic diagnosis of the fetus or embryo?

How is sickle cell disease in pregnancy managed?

Pregnancy in women with sickle cell disease is associated with an increased risk of morbidity and mortality because of the combination of underlying hemolytic anemia and multiorgan dysfunction associated with this disorder. Morbidity and mortality have decreased markedly over the past 3 decades because of improvements in general medical care for patients with sickle cell disease, improvements in transfusion medicine, and advancements in neonatal care (8, 9). In spite of the decline in maternal and perinatal mortality rates, however, pregnancy is still a significant clinical risk for many patients with sickle cell disease. The magnitude of the

Table 2. Hematologic Features of Main Hemoglobinopathies

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Heterozygous State</th>
<th>Homozygous State</th>
<th>DNA Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>α⁺ Thalassemia (-α)</td>
<td>0–2% Hb Bart’s at birth</td>
<td>S–10% Hb Bart’s in the neonatal period, low MCV</td>
<td>S. blot: α-gene probe, abnormal band with Bam H1</td>
</tr>
<tr>
<td>α⁻ Thalassemia (−)</td>
<td>5–10% Hb Bart’s in the neonatal period, low MCV, normal Hb A₂</td>
<td>Hb Bart’s hydrops fetalis</td>
<td>S. blot or PCR: absence of: α-gene band in homozygote</td>
</tr>
<tr>
<td>β⁺ Thalassemia (severe)</td>
<td>Low MCH &amp; MCV, Hb A₂ 3.5–7.0%</td>
<td>Thalassemia major: Hb F 98% Hb A₂ 2%</td>
<td>PCR, ASO – dot blot, S. blot β-gene probe</td>
</tr>
<tr>
<td>β⁺ Thalassemia (mild)</td>
<td>Low MCH &amp; MCV, Hb A₂ 3.5–7.0%</td>
<td>Thalassemia intermedia: Hb F 20–40%</td>
<td>PCR, ASO – dot blot, S. blot β-gene probe</td>
</tr>
<tr>
<td>Hb S</td>
<td>Hb A, Hb S, Hb A₂</td>
<td>Hb S, Hb F (1–15%), Hb A₂</td>
<td>PCR: Dde 1 digestion, PCR, ASO – dot blot</td>
</tr>
<tr>
<td>Hb S/β-Thalassemia</td>
<td>—</td>
<td>If β⁺ thalassemia, severe sickle cell anemia; if β⁺ thalassemia, less severe</td>
<td>PCR: Dde 1 digestion, PCR, ASO – dot blot</td>
</tr>
<tr>
<td>Hb E/β-Thalassemia</td>
<td>—</td>
<td>Thalassemia major or intermedia: Hb E 60–70%, Hb F 30–40%</td>
<td>PCR: Hb E by Mnl 1 digestion</td>
</tr>
</tbody>
</table>

Abbreviations: ASO, allele specific oligonucleotide; Hb, hemoglobin; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; PCR, polymerase chain reaction; S. blot, Southern blot.

risk varies with genotype and severity of anemia. When compared with Hb AA patients, women with Hb SS have increased risk for maternal complications, such as preterm labor, premature rupture of membranes, antepartum hospitalization, and postpartum infection. In addition, patients with Hb SS are at higher risk for fetal complications, such as intrauterine growth restriction (IUGR), low birth weight, and preterm delivery (9, 10). Patients with Hb SC disease also are at risk for the aforementioned complications but to a lesser extent than patients with Hb SS disease (10).

Pregnant patients with sickle cell disease need increased prenatal folic acid supplementation. The standard 1 mg of folate in prenatal vitamins is not adequate for patients with hemoglobinopathies; 4 mg per day of folic acid should be prescribed because of the continual turnover of red blood cells.

Routine cesarean delivery for women with sickle cell disease is not indicated and should be performed only for obstetric indications. Epidural analgesia usually is well tolerated as long as care is taken to avoid hypotension and hypoxemia. Pregnant patients should, if possible, be cared for at institutions that are able to manage both the complications of sickle cell disease and high-risk pregnancies. They also should have regular prenatal care by or in consultation with obstetricians who are experienced in the management of sickle cell disease.

The most common cause of recurrent morbidity in Hb SS disease is painful crisis. If possible, precipitating factors, such as cold environment, heavy physical exertion, dehydration, and stress, should be avoided. Hydroxyurea has been shown to reduce the frequency of painful crises in nonpregnant patients with severe sickle cell disease (11). However, the use of hydroxyurea is not recommended during pregnancy because it is teratogenic.

Painful crises in pregnancy as well as in the nonpregnant patient are managed with rapid assessment of the level of pain and prompt administration of analgesia. Pain, respiratory rate, and level of sedation should be assessed until pain is controlled. Opiates can be given orally or parenterally by the intravenous, intramuscular, or subcutaneous route. Oxygen should be given if the O₂ saturation is less than 95% by pulse oximetry. The initial clinical assessment also should focus on detection of serious medical complications requiring specific therapy, such as acute chest syndrome (fever tachypnea, chest pain, and hypoxia), infection, dehydration, severe anemia, cholecystitis, and hypersplenism. A multidisciplinary approach should be used involving obstetricians, hematologists, and anesthesiologists (12). Painful crises in the third trimester may have a prolonged course and may not resolve until after delivery.

**What is the role of transfusion or prophylactic exchange transfusion for pregnancies complicated by sickle cell anemia?**

Controversy exists regarding the role of prophylactic blood transfusion in the management of sickle cell disease in pregnancy (13–15). By limiting transfusion to situations in which it is clinically indicated, patients are not subjected to the increased risk for alloimmunization (16), viral infections, and iron overload. Major complications (eg, worsening anemia; intrapartum complications such as hemorrhage, sepsisemia, and cesarean delivery; painful crisis; and chest syndrome) may require intervention with an exchange transfusion. There is no consensus regarding the exact hematocrit value below which transfusion should be considered. However, when a transfusion is clinically indicated in the patient with sickle cell disease, the objective is to lower the percentage of Hb S to approximately 40% while simultaneously raising the total hemoglobin concentration to about 10 g/dL. Hemoglobin levels and the percentage of Hb S should be monitored serially during the remainder of the pregnancy to determine the need for subsequent transfusions.

Prophylactic exchange transfusion was first proposed by Ricks in 1965, who recommended exchange transfusion 4–6 weeks before the delivery date (17). Preliminary results appeared to show a benefit in that all women and infants survived (18). Subsequently, several studies have shown improvement in maternal and fetal outcome with prophylactic transfusion (15, 19). However, the evidence is not conclusive that transfusion is responsible for the improvement; similar improvement has been observed in programs that do not use prophylactic transfusion. In the only randomized controlled trial published to date, prophylactic transfusion was associated with a decreased risk for painful crisis and severe anemia, but no difference was observed for pregnancy outcome (14). It appears from the available evidence that the reduction in morbidity and mortality of sickle cell disease in pregnancy is attributable to improvements in general management of pregnancy rather than prophylactic transfusion per se.

**Is fetal surveillance useful in pregnancies complicated by sickle cell anemia?**

Pregnancies in women with sickle cell disease are at increased risk for spontaneous abortion, preterm labor, IUGR, and stillbirth (20). For this reason, a plan for serial ultrasound examinations and antepartum fetal testing is reasonable. Published data on antenatal fetal surveillance in women with sickle cell disease are limited. In a
retrospective review of 58 pregnancies in women with sickle cell disease undergoing prophylactic transfusion, no patients had a nonreactive nonstress test result or positive contraction stress test result (21). All pregnancy outcomes were normal. The investigators concluded that placental reserve and fetal reactivity were uncompromised and that these tests were as sensitive for assessment of fetal well-being in women with sickle cell disease as for women with other indications for antenatal testing.

Because patients with sickle cell crisis usually require narcotics for pain control, the results of abnormal antepartum testing should be interpreted with caution. One small study has shown that nonstress test results and biophysical profiles may be abnormal during an episode of crisis but revert back to normal with resolution of the episode (22). The clinical significance of this is unclear.

How is thalassemia in pregnancy managed?

The course of pregnancy in women with the α-thalassemia trait is not significantly different from that of women with normal hemoglobin. Pregnancy in women with Hb H disease has been reported, and with the exception of mild to moderate chronic anemia, outcomes have been favorable. However, the number of reports is too few to draw definite conclusions regarding pregnancy outcome in all women with Hb H disease (23).

Until recently, pregnancy in women with β-thalassemia major was extremely rare. Initially, this was because delay of growth and sexual development and early death in untreated patients prevented reproduction. After the introduction of transfusion therapy in the 1960s, pregnancy was still uncommon because of infertility (secondary to hypothalamic dysfunction and anovulation caused by hemosiderin deposition). Since the introduction of hypertransfusion and iron chelation therapy with deferoxamine in the late 1970s, several reports and case series have documented favorable pregnancy outcomes in women with β-thalassemia major (24, 25). Pregnancy in women with β-thalassemia major is recommended only for those with normal cardiac function who have had prolonged hypertransfusion therapy to maintain hemoglobin levels at 10 g/dL and iron chelation therapy with deferoxamine (25). During pregnancy, hemoglobin levels should be maintained at or near 10 g/dL with transfusions. Deferoxamine usually is discontinued because the safety of iron chelation therapy during pregnancy has not been established. Fetal growth should be monitored with serial ultrasonography. In cases in which fetal growth is suboptimal, patients should have fetal surveillance. The mode of delivery should be individualized, with cesarean delivery reserved for obstetric indications.

Beta-thalassemia minor usually causes mild asymptomatic anemia. In the absence of documented iron deficiency, replacement beyond prophylactic doses of iron is not indicated. Studies involving fairly small numbers of patients suggest that pregnancy outcome is favorable in women with β-thalassemia minor. A study of 261 pregnant women with β-thalassemia minor found a significantly higher rate of IUGR and oligohydramnios than is found in nonthalassemic patients (26). No differences were noted in perinatal outcomes such as low Apgar scores, congenital malformations, or perinatal mortality (26).

Summary of Recommendations and Conclusions

The following recommendations are based on good and consistent scientific evidence (Level A):

- Individuals of African, Southeast Asian, and Mediterranean descent are at increased risk for being carriers of hemoglobinopathies and should be offered carrier screening and, if both parents are determined to be carriers, genetic counseling.
- A complete blood count and hemoglobin electrophoresis are appropriate laboratory tests for screening for hemoglobinopathies. Solubility tests alone are inadequate for screening because they fail to identify important transmissible hemoglobin gene abnormalities affecting fetal outcome.
- Couples at risk for having a child with sickle cell disease or thalassemia should be offered genetic counseling to review prenatal testing and reproduction options. Prenatal diagnosis of hemoglobinopathies is best accomplished by DNA analysis of cultured amniocytes or chorionic villi.

References

The MEDLINE database, the Cochrane Library, and ACOG’s own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and March 2005. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.