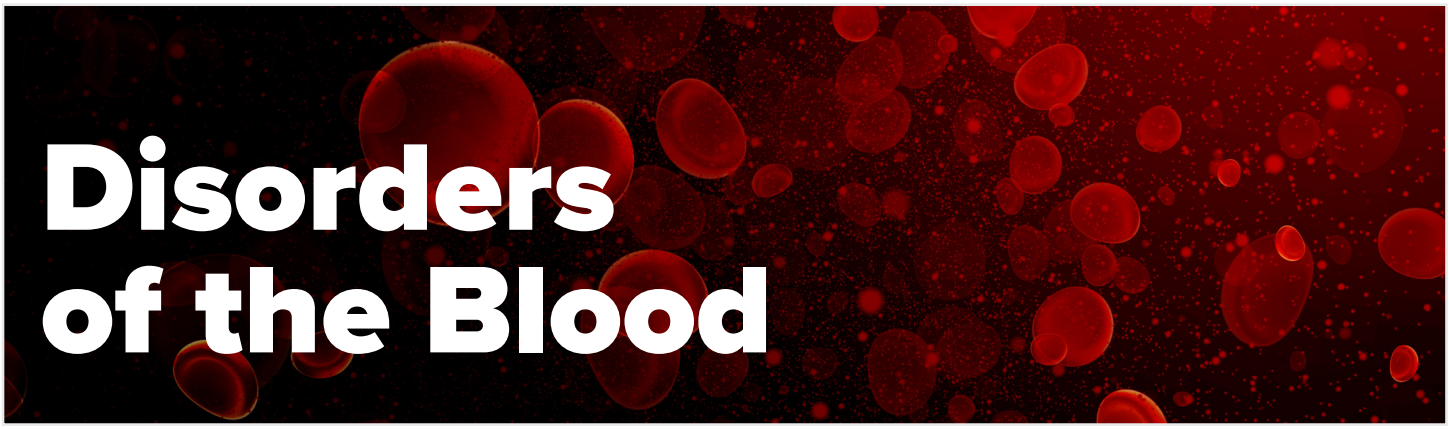


Disorders of the Blood

More Than **500** Medicines in Development for Blood and Bleeding Disorders, Including Blood Cancers

Blood helps the human body perform functions vital to staying alive. Red blood cells deliver oxygen to the tissues while white blood cells fight infection and platelets help blood clot. Any disruption to these activities can pose a serious health threat. Disorders of the blood can include problems with blood cells, platelets, blood vessels, bone marrow, lymph nodes, the spleen and proteins involved in bleeding and clotting. Blood disorders can have genetic causes, while others can develop as a result of other diseases, side effects from other therapies or lack of certain nutrients in the diet.

There are many different types of blood disorders. For example, blood disorders that affect the red blood cells can lead to hemophilia, blood clots and anemia, while disorders that affect the white blood cells may lead to blood cancer, such as leukemia, lymphoma and myeloma.

Patients with blood disorders, including bleeding disorders, can often face tremendous burden in treating and managing their conditions, and often require lifelong treatment, involving routine drug infusions or blood transfusions to manage the condition and help prevent serious complications. Patients with these disorders often experience debilitating pain, disability, reduced life expectancy and quality of life.

JUST THE FACTS

An estimated
184,000
Americans will be diagnosed with a blood cancer in 2022[1]

More than
3.2 million
Americans are living with a bleeding disorder[2]

About
100,000
Americans have sickle cell disease[3]

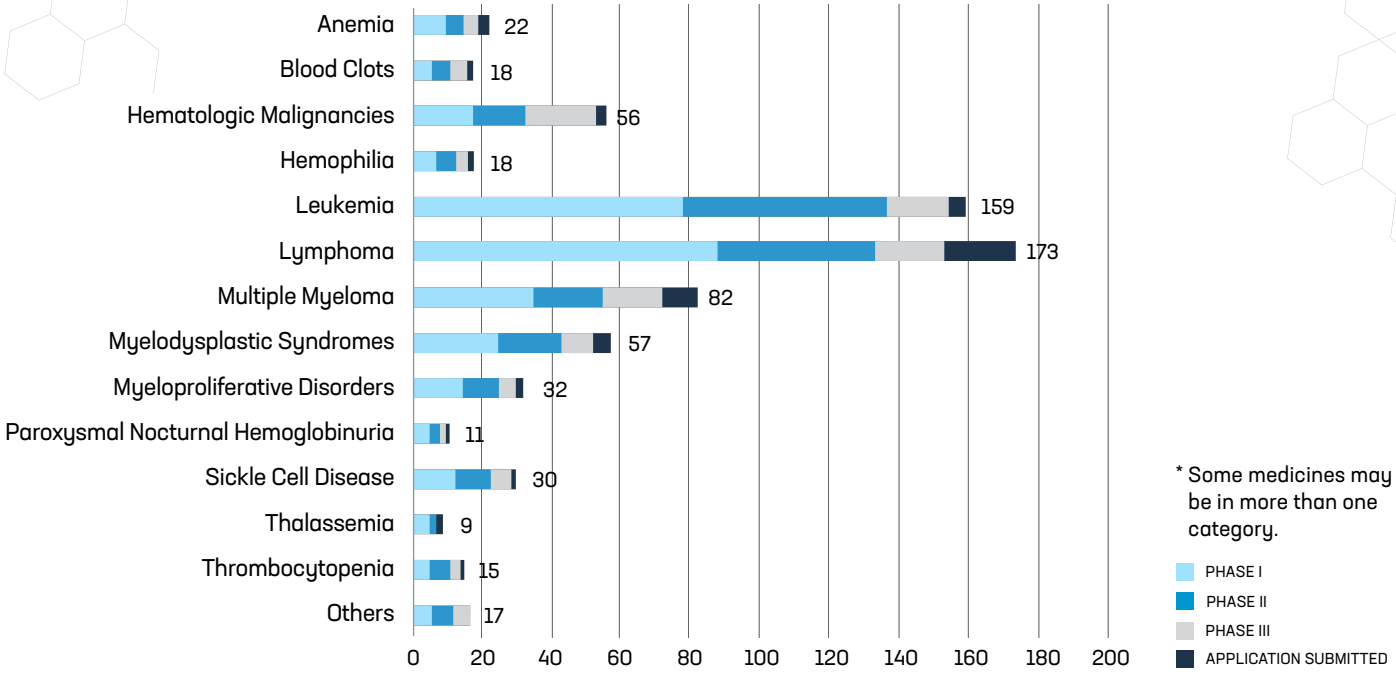
More than
3 million
Americans have a form of anemia[4]

Blood cancers account for nearly 10% of all new cancer diagnoses[1] and include leukemia, lymphoma, hematological malignancies, myelodysplastic syndromes, myeloma and myeloproliferative neoplasms. In recent years, science has advanced quickly and allowed for more precise treatments as our understanding of blood cancers and ability to treat them grows.

This report on medicines in development for blood disorders includes a broad range of diseases with different origins, symptoms and treatments. To address the varying need for new treatments, America's biopharmaceutical research companies are currently developing **549** medicines targeting blood disorders.[5] These medicines are either in clinical trials or under review by the U.S. Food and Drug Administration (FDA) and include:

- **162** for lymphoma, which account for nearly 5% of all new cancer diagnoses. Non-Hodgkin lymphoma accounts for 90% of all lymphomas.[1]
- **158** for several types of leukemia, which account for more than 3% of all new cases of cancer. The most common types of leukemia in American adults are chronic lymphocytic leukemia (38%) and acute myeloid leukemia (31%). In children and adolescents, 75% of leukemia cases are acute lymphoblastic leukemia.[1]
- **84** for multiple myeloma, with an estimated 34,470 new cases and 12,640 deaths expected in 2022.[1]
- **73** for hematologic malignancies, cancer that caused by the uncontrolled division of abnormal cells and can lead to leukemia, lymphoma and multiple myeloma.
- **55** for myelodysplastic syndromes, a group of conditions that happen when the blood-forming cells in the bone marrow become abnormal leading to a low number of blood cells.
- **30** for myeloproliferative disorders, such myelofibrosis, essential thrombocytopenia and polycythemia vera.
- **30** for sickle cell disease, a red blood cell disorder that causes normal round, flexible cells to form into a crescent or sickle shape. These malformed blood cells clog blood vessels preventing normal flow of nutrition and oxygen throughout the body, causing pain, organ damage and a low blood cell count.
- **23** for various forms of anemia, which affect more than 3 million Americans and collectively are the most common bleeding disorder in the U.S.[4/6]
- **19** for platelet disorders, including thrombocytopenia, a disease characterized by an excess of platelets.
- **18** for hemophilia, a genetic disorder classified as type A is caused by a factor VIII deficiency, while type B is caused by a factor IX deficiency. Between 30,000-33,000 people in the U.S. have a form of hemophilia.[2]
- **14** for clotting disorders, consisting principally of deep vein thrombosis, where a blood clot is located in the deep veins or the arms or legs, and pulmonary embolism, where a clot has traveled from a deep vein to the lung. About 100,000 Americans die each year from blood clots.[3]
- **13** for paroxysmal nocturnal hemoglobinuria, a rare disease of the blood characterized by the destruction of red blood cells, blood clots and impaired bone marrow function.
- **9** for thalassemia, an inherited blood disorder where the blood doesn't make enough hemoglobin leading to red blood cells that don't function correctly and only last a short time.[3]
- **16** for other blood disorders, such as erythropoietic protoporphyria (an inherited condition that can cause pain when patients are exposed to light), hemorrhage and retinal vein occlusion (blood clots in the eye veins), among others.

Medicines in Development for Disorders of the Blood



Innovative Medicines in the Blood Disorder Pipeline

Among the **549** medicines in development for blood disorders are treatments that employ scientific and technical knowledge in new ways or expand on current knowledge. Many of the medicines represent innovative new ways to target a blood disorder, including:

- A bio-engineered adeno-associated virus (AAV) vector-based gene therapy is being developed to treat **hemophilia A**, or factor VIII deficiency. Hemophilia is a rare, serious inherited bleeding disorder, characterized by mutations in the F8 gene. The mutation leads to deficient blood coagulation and an increased risk of bleeding or hemorrhaging.

- A gene therapy is in development that uses AAV vectors to deliver a high-activity Factor IX gene to the liver for the treatment of **hemophilia B**. Hemophilia B is caused by a mutation in Factor IX, which leads to deficient blood coagulation and an increased risk of bleeding or hemorrhaging. Hemophilia B is four times less common than hemophilia A.[2]

- A potential first-in-class medicine is in development for the treatment of **paroxysmal nocturnal hemoglobinuria (PNH)**, a rare hematopoietic stem cell disorder (affecting .05-1.5 per million people worldwide)[7] where red blood cells become defective and subsequently produce defective red blood cells. These defective red blood cells in PNH are highly susceptible to premature destruction by a part of the body's own immune system called the complement system. The medicine, a complement factor B inhibitor, targets the underlying cause of PNH through its action on the complement system's alternative pathway.

- A therapy in development for **hereditary thrombotic thrombocytopenic purpura (hTTP)** is a bio-engineered version of the naturally occurring protein ADAMTS13 that plays a critical role in blood coagulation. A deficiency of the protein can lead to the formation of blood clots in the small blood vessels throughout the body, leading to TTP. Acquired TTP is often due to antibodies directed against ADAMTS13, while hTTP is caused by mutations of the ADAMTS13 gene, resulting in a severe deficiency of the protein. The therapy is also being studied as a treatment of vaso-crisis related to sickle cell disease. About 4,000 people have hTTP worldwide.

Recent Advances in Treatment for Blood Disorders

While there is still significant unmet need for patients with certain blood disorders, progress has been made in treating and reducing the burden of disease for many patients. In the first three months of 2022 alone, three new treatments have been approved by the FDA for varying disorders. Some recent medicine approvals provide treatment options for patients where there were few or none previously available include:

- The first disease-modifying therapy for hemolytic anemia in adults with pyruvate kinase deficiency, a rare, inherited life-long debilitating anemia. An inherited mutation in the PKLR gene can cause a deficit in energy within the red blood cell.
- Three new CAR-T cell therapies, two for the treatment of relapsed or refractory multiple myeloma and one for large B-cell lymphoma.
- The first approved treatment for cytopenic myelofibrosis, a rare form of bone marrow cancer. Cytopenic myelofibrosis is a severe form of the disease with thrombocytopenia (very low blood platelet counts). About two-thirds of patients with myelofibrosis suffer from cytopenias.
- An approved medicine for the treatment of von Willebrand disease was recently approved for the prevention of bleeding episodes in a severe form of the disease in adults. The treatment is a recombinant von Willebrand factor replacement therapy.
- The first targeted biologic to reduce pain crises (vaso-occlusion) in sickle cell disease. The medicine binds a protein that plays a key role in the interactions at the cellular level that can lead to pain crises in people with the sickle cell disease. Pain crises are the most common cause of hospitalizations in people with sickle cell disease, leading to approximately 200,000 ER visits each year in the US.
- The first approved medicine that directly targets the root cause of the sickling and destruction of the red blood cells in sickle cell disease. The medicine works by increasing hemoglobin's affinity for oxygen, which in turn inhibits sickle hemoglobin polymerization – a central abnormality in sickle cell disease.

Disparities in Blood Disorders

Blood disorders vary in prevalence and death rates between ages, sex, racial and ethnic groups. For instance, while men have a higher risk for blood clots (thrombosis), women have risks men do not, such as higher estrogen levels, a key ingredient in birth control regimens and postmenopausal hormone therapy.[8]

Many bleeding disorders are genetic or inherited, affecting children at higher rates. For example, sickle cell disease disproportionately affects Black and Hispanic children with an incidence rate of 73.1 cases per 1,000 Black newborns carrying the sickle cell trait and 6.9 cases per 1,000 Hispanic newborns, compared to 3 cases per 1,000 births for white newborns.[3] People with Fanconi anemia, the most common inherited form of aplastic anemia, are born with the disorder, but symptoms may not be apparent at birth. Most people are diagnosed with the disorder between ages 3-14.[9]

Myeloma is most often diagnosed in people age 65 and older. African-Americans are twice as likely to be diagnosed with myeloma than white Americans and at a younger age.[10]

During pregnancy, the amount of blood in a women's body increases by 20-30%, which increases the amount of iron and vitamins the body needs to make hemoglobin. Many women experience anemia due to a lack of iron during pregnancy, especially during the 2nd and 3rd trimesters.[6]

Blood Disorders and Rare Diseases

In the U.S., as many as 30 million people have a rare disease – a disease or condition that affects fewer than 200,000 people – and about 80% of rare diseases are genetic in origin with the vast majority – about 50% – impacting children.[11] Not all rare diseases are blood disorders, but many are. Rare blood disorders can impact significantly smaller groups of patients, sometimes as small as a few hundred or even less.

Examples of some rare diseases that affect the blood are aplastic anemia with fewer than 1,000 people diagnosed each year in the U.S.,[12] myelofibrosis with less than 20,000 people living with the disease in the U.S.[12] and hairy cell leukemia affecting about 6,000 Americans.[7] Several rare bleeding disorders can occur with just a few cases in 1-2 million people, such as Waldenstrom macroglobulinemia,[1] inherited platelet diseases and disorders due to blood factor deficiencies.[2]

For people with a rare blood disorder, as with many rare diseases, simply getting a diagnosis can be a complicated, lengthy and frustrating journey, particularly for patients in underserved communities and others lacking ready access to health care. Inadequate diagnostic tools and limited awareness of rare blood disorders along with limited available treatment options for many rare diseases make it difficult to identify and diagnose rare blood disorders. On average, it can take more than seven years, and an often-burdensome process, for a rare disease patient to receive an accurate diagnosis.[11]

America's biopharmaceutical companies are leveraging new technologies and expanding scientific understanding of the genetic basis of many rare blood disorders to develop groundbreaking therapies for them. Advances in personalized medicine and cell and gene therapies are among some of the innovative approaches that are creating new opportunities to advance research into rare blood disorders and the development of new treatments. But the development of new and effective treatments also face many challenges, such as delayed diagnosis or misdiagnosis, limited scientific and medical knowledge about the disorder and small patient populations.

Gene Therapy and Bleeding Disorders[13]

Because many blood disorders are caused by genetic abnormalities, gene therapies in development hold tremendous promise in offering long-term benefits, or in some cases a cure for patients with these conditions. As a result, they offer to dramatically reduce existing treatment burden and costs.

Hemophilia A

The standard of care for many hemophilia A patients, particularly those with more severe disease, includes lifelong treatment with factor (FVIII) replacement therapy administered up to 2-3 times a week, or 100-150 times a year, to prevent dangerous bleeding events and preserve joint function. More recently, a new type of prophylactic therapy has also become available which may be self-administered less frequently. Gene therapies in the late stages of development for severe hemophilia A have shown evidence of significant and sustained reductions in bleeding rates as well as an almost complete reduction in factor replacement therapy utilization in the years following a one-time administration of therapy.

Hemophilia B

Like hemophilia A, hemophilia B patients often require life-long prophylactic infusions of factor replacement therapy to replace or supplement low levels of IX blood-clotting factor and to prevent life-threatening bleeding events and to reduce joint bleeding events and preserve joint function. Infusions are generally administered 2-3 times a week, or 100-150 times a year. Though some newer factor replacement therapy products offer to extend the frequency of infusion to once every 1-2 weeks.

Gene therapies in the late stages of development for severe and moderately severe hemophilia B have shown evidence of significant and sustained reductions in bleeding rates as well as an almost complete reduction in factor replacement therapy utilization in the years following a one-time administration of therapy.

Sickle Cell Disease

Sickle cell disease is an inherited red blood cell disorder that leads to abnormal hemoglobin, the protein that delivers oxygen throughout the body. It is an extremely painful and dangerous condition. When "sickle" shaped red blood cells become stuck in blood vessels, they can lead to pain crisis, known as vaso-occlusive crisis, and if they prevent the flow of oxygen to the chest, they can cause a serious complication known as acute chest syndrome. Blocked flow of oxygen to the brain can also lead to stroke. Though chronic red blood cell transfusions and medications may help to prevent these serious and life-threatening complications, patients with sickle cell disease experience frequent hospitalizations. For example, sickle cell disease patients on average are hospitalized more than once a year for significant pain, with an average length of stay of 5 days. Additionally, on average patients visit the emergency room two to three times a year, most commonly due to pain crisis.

Success in Treating Blood Cancers

A range of game-changing new approaches to blood cancer treatment have become available to patients with a wide range of cancers over the past decade, contributing greatly to significant reductions in mortality and increases in survival. Many of these significant advancements are due to advancements in CAR-T therapy. CAR-T is a form of gene modified cell therapy which permanently alters the "genetic instructions" of a patient's T-cells to recognize, target and kill cancer cells.

To make the treatment, T-cells are separated from blood taken from a patient and genetically engineered to produce specialized receptors on their cell surface. These receptors, called chimeric antigen receptors (CAR), provide T-cells with the capability to recognize and attack tumor cells with specific proteins called antigens on their surfaces. These potent CAR-T cells are modified and duplicated outside the body and infused into the patient, where they recognize and kill cancer cells.

Currently, there are six FDA approved CAR-T therapies to treat blood cancers, including multiple myeloma, mantle-cell lymphoma, large B-cell lymphoma, acute lymphoblastic leukemia, diffuse large B-cell lymphoma and follicular lymphoma. These therapies have demonstrated unprecedented remission rates as high as 93%[14] and many are having a transformative impact in certain cancers. For example, several CAR-T cell therapies have shown to cure some children and adolescents with advanced leukemia, sparing the short and long-term side effects of previous treatments.

A potential gene therapy in the late stages of development has shown evidence in clinical trials of an almost complete reduction in painful vaso-occlusive crisis and acute chest syndrome in the years following a one-time administration of therapy.

Beta Thalassemia

Beta thalassemia impacts red blood cells by reducing the production of oxygen-carrying hemoglobin, resulting in a lack of oxygen carried to many parts of the body. Patients with severe beta thalassemia and debilitating anemia may be eligible to receive a curative stem cell transplant. But few can find suitable donors and even less – approximately 10% – ultimately receive a stem cell transplant. Instead, most severe patients are treated through a regimen of lifelong blood transfusions to maintain levels of functional hemoglobin. On average, patients in the U.S. will require 17 transfusions a year, lasting multiple hours per procedure. These transfusions can also lead to various side effects, the most notable of which is iron overload. To counter iron overload, patients often need iron chelator therapies to manage the disease. Unfortunately, many patients with severe beta thalassemia often die from cardiac complications of iron overload by 30 years of age.

A gene therapy in the late stages of development for transfusion dependent adults and children with beta thalassemia has shown evidence in clinical trials of the potential to eliminate dependence on regular blood transfusions and medicines to manage side effects of treatment in the years following a one-time administration of therapy.

Facts for Selected Blood Disorders

Anemia

More than 3 million Americans affected by anemia1 and 5,633 people died from a form of anemia[2]

Blood Clots

As many as 900,000 American experience a blood clot (venous thrombosis) and about 100,000 people will die each year[2]

Hemophilia

A genetic disorder that is more common in males than females. Hemophilia A is 4X as common as hemophilia B. As many as 33,000 people have hemophilia in the US[2]

Leukemia

It is estimated that 60,650 Americans will be diagnosed with a form of leukemia in 2022 (35,810 males, 24,840 females) and 24,000 will die (14,020 males, 9,980 females)[3]

Lymphoma

It is estimated that 89,010 Americans will be diagnosed with a form of lymphoma in 2022 (48,690 males, 40,320 females) and 21,170 will die (12,250 males, 8,920 females)[3]

Myelodysplastic Syndrome

A group of conditions where cells in the bone marrow are abnormal. In 2020, 6,881 Americans died[2] from the disease and an estimated 10,000 live with the disease[3]

Myeloma

It is estimated that 34,470 Americans will be diagnosed with myeloma in 2022 (19,100 males, 15,370 females) and 12,640 will die (7,090 males, 5,550 females)[3]

Sickle Cell Disease

An inherited disorder affects about 100,000 Americans and is more common in Black Americans. About 1 out of every 365 Black newborns have the disease and 1 in 13 have the sickle cell trait.[2]

Von Willebrand Disease

The most common bleeding disorder affects about 1 in every 100 people.[2]

Sources: 1. National Heart Lung and Blood Institute, 2. Centers for Disease Control and Prevention, 3. American Cancer Society

Sources:

1. American Cancer Society, 22 Cancer Facts & Figures
2. National Hemophilia Foundation
3. U.S. Centers for Disease Control and Prevention (CDC)
4. National Heart, Lung and Blood Institute, National Institutes of Health
5. Number of medicines obtained through public, government and industry sources, and the Adis "R&D Insight" database; current as of **May 5, 2022**.
6. American Society of Hematology
7. National Organization for Rare Disorders
8. American Society of Hematology, Women and the Risk of Blood Clots
9. National Library of Medicine, Medline Plus, www.medlineplus.gov/ency/article/000334.htm
10. National Cancer Institute, Multiple Myeloma Awareness and African American Disparities
11. Global Genes, www.globalgenes.org
12. Health Grades, www.healthgrades.com/right-care/blood-conditions/7-rare-diseases-that-affect-the-blood
13. PhRMA, Potential Gene Therapies Hold Promise for Transforming the Trajectory of Many Blood Disorders and in Reducing Significant Treatment Burden and Costs
14. Labiotech UG, www.labiotech.eu/in-depth/car-t-therapy-cancer-review/