Sixth International
BONE MARROW FAILURE DISEASE
SCIENTIFIC SYMPOSIUM

Collaborating to Transform Treatment and Improve Outcomes

Summary for Patients
AAMDSIF would like to thank the corporations whose generous contributions help fund this educational program

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Dear Friends,

It is with great pleasure that we present this Summary for Patients of the Sixth AAMDSIF International Bone Marrow Failure Scientific Symposium held March 22 and 23, 2018 in Rockville, Maryland. Our symposium brought together many of the world’s leading experts on the biology and treatment of aplastic anemia, myelodysplastic syndromes, paroxysmal nocturnal hemoglobinuria, acute myeloid leukemia, and related disorders. The symposium theme was “Collaborating to Transform Treatment and Improve Outcomes,” and the two-day program was a very special opportunity for us to focus on bone marrow failure diseases, consider what is known, and explore new and emerging ideas and research directions.

The Aplastic Anemia and MDS International Foundation (AAMDSIF) is committed to providing patients and their families with an evolving array of programs and services, while continuing to fund clinical investigators who search for the cures and help improve treatments. We are proud to have awarded more than $4.4 million in research grants to 77 researchers to advance the study of bone marrow failure. Several AAMDSIF grantees attended the Scientific Symposium as both presenters and participants.

We are most grateful to the co-chairs of this event, Richard Stone, M.D. and Neal Young, M.D., for their leadership and to the outstanding committee with whom they worked to plan and organize this symposium. The presentations by the internationally respected faculty stimulated discussion and provided new insights to enhance bone marrow failure research. It was especially gratifying to learn about the research being conducted by innovative young investigators as they embark on their careers.

This symposium would not have been possible without the generous support from the Edward P. Evans Foundation and industry partners. The ongoing collaborative effort of academia, government, private industry and AAMDSIF demonstrates the mutual commitment to the discovery of new treatments for patients, and ultimately, cures for bone marrow failure diseases.

We encourage you to read these summaries to learn more about bone marrow failure diseases and the most promising directions for future research.

Sincerely,

Kevin Lyons-Tarr
Chairman, Board of Directors

Kathleen Weis
CEO
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PART I: DNA CHANGES THAT LEAD TO INHERITED PREDISPOSITION

Inherited Bone Marrow Failure and Leukemia Predisposition Syndromes: Open Questions

Lucy Godley, MD, PhD
University of Chicago

Dr. Godley discussed several open questions about inherited syndromes that increase the risk of bone marrow failure (meaning that the bones stop making enough healthy blood cells) or myeloid malignancies (cancers that begin in the stem cells that turn into white blood cells).

When Should a Clinician Consider that a Patient Might Have an Inherited Predisposition Syndrome?

Dr. Godley recommended that doctors and other health-care providers consider inherited predisposition syndromes whenever they see a patient with signs and symptoms of bone marrow failure or myeloid malignancies. In Dr. Godley’s clinic, almost 20% of young patients with these diseases have an inherited predisposition, and this proportion is likely to grow as research identifies more of these syndromes.

Detecting an inherited predisposition is important for choosing the right treatment for an individual patient. Also, early identification of these syndromes makes it possible to provide appropriate care for people who carry the mutation but don’t yet have signs and symptoms of the disease.

To accurately detect an inherited predisposition syndrome, doctors need to be familiar with the known syndromes and their signs and symptoms. Once the doctor suspects that a patient has an inherited predisposition, testing for genes that are often mutated in the inherited syndromes can help confirm the diagnosis.

How Many Inherited Syndromes Are There?

Many inherited syndromes have been identified, and the list continues to grow. Dr. Godley suggested that in the future, doctors might order genetic tests for all patients who undergo a bone marrow biopsy for cancer.

What Types of Mutations Lead to These Syndromes?

Many different types of mutations cause the inherited predisposition syndromes. For example, some patients have a frameshift mutation (insertion or deletion in a DNA sequence that changes the way the sequence is read) or deletion (removal of a piece of DNA). Others have a missense mutation, in which the gene encodes a different amino acid at a specific position in the protein it encodes. This type of mutation can prevent the protein from carrying out its function.

How Does Cancer Develop in Particular People?

Dr. Godley believes that all cancers involve a combination of a genetic predisposition and environmental injury. Research is now focused on understanding the genetic changes that lead to cancers in individuals with inherited syndromes.

Genetic Mutations and Telomeres (Ends of Chromosomes)

Sharon Savage, MD
National Cancer Institute

Telomeres are located at the ends of chromosomes and help keep chromosomes stable. As people age, their telomeres become shorter, and this shortening is fastest in the first 20 years of life.

People with dyskeratosis congenita (DC), a rare inherited bone marrow failure disorder, have very short telomeres. They also have a high risk of bone marrow failure, pulmonary fibrosis (scar tissue in the lungs), and certain kinds of cancer. Some patients have all the signs of DC. Others have just one sign. Some have relatives who have signs of DC, but others have no family history.
DC was the first disorder connected to telomere biology. The DKC1 gene provides instructions for making dyskerin, a protein. Dyskerin helps maintain telomere length. More than 40 different types of inherited mutations have been found in DKC1 in people with DC.

Telomere biology plays a role in other inherited diseases, including aplastic anemia, pulmonary fibrosis, and liver fibrosis. These diseases are associated with mutations in several genes, including DKC1, TERT, or TERC. These genes make components of telomerase, an enzyme that helps maintain telomeres.

One of the diseases associated with short telomeres, Hoyeraal Hreidarsson syndrome, causes low blood cell counts, immune system problems, a small head, and delayed development. Two young girls diagnosed with Hoyeraal Hreidarsson had very short telomeres for their age, mutations in RTEL1, and orthodox Ashkenazi Jewish ancestry. Furthermore, 1% of patients tested at the Center for Jewish Genetics carried this mutation, the carrier rate among those with Ashkenazi Jewish ancestry tested by Mount Sinai was half as high, and the rates in both these groups were much higher than in the general population. This finding led to the recommendation to screen Orthodox Ashkenazi Jews for this mutation if they are undergoing genetic testing.

When telomeres become critically short, the cell dies or the chromosome becomes confused and allows the cells to keep dividing, resulting in more gene mutations and DNA damage. This DNA damage can lead to bone marrow failure or cancer.

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**Debate:**

**What Defines Disease Progression in the Bone Marrow?**

**Cell Form and Structure Matter**

*Inga Hofmann Zhang, MD*

*University of Wisconsin*

If you look at cells carefully enough, you can find some incredible clues that offer answers for patients and maybe information about genetics.

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Cell morphology, or form and structure, is cheaper and faster to analyze than genetics when a patient needs a diagnosis. The patient's bone marrow biopsy specimen is available for pathologist to examine in an hour, and it can at least give a first impression.

According to the World Health Organization's classification system, an MDS diagnosis is based on cell morphology. The factors used to establish an MDS diagnosis include counts of blasts (abnormal young white blood cells), dysplasia (abnormally shaped cells), and low counts of certain types of blood cells.

Many patients with inherited bone marrow failure syndromes have some abnormally formed blood cells (dyspoiesis) that can offer clues about the underlying genetics. For example, patients with Fanconi anemia have low counts of megakaryocytes, a type of large bone marrow cell that produces platelets. Those with Shwachman Diamond syndrome have misshapen neutrophils, a type of white blood cell. And the megakaryocytes in patients with GATA2 deficiency are distinctive.

Dr. Hofmann Zhang described a 6-year-old patient who had been diagnosed with Fanconi anemia. Six months later, the patient's bone marrow biopsy showed fewer cells than normal. The patient had many megakaryocytes, but they were small, which is a feature of MDS. The patient also had a new clone, or abnormal copy of a blood cell. The morphology findings showed that the patient’s Fanconi anemia had progressed.

In another case, a teenaged boy had a platelet shortage and an empty bone marrow, along with large and atypical-looking megakaryocytes. These findings showed that the patient might have had GATA2 deficiency, and genetic testing confirmed this diagnosis.

Morphology can help doctors understand genetic data. A 19-year-old developed bruises easily and had an abnormally high white blood cell count. The patient also had some low blood cell counts and too many cells in the bone marrow. When the morphology findings were combined with the genetic testing results, the doctors were able to confirm that the patient had refractory cytopenia with multilineage dysplasia, a type of MDS, and monosomy 7 (only one copy, not two, of chromosome 7).
Combination of Genetics and Morphology

Jean Soulier, MD, PhD
University of Paris Diderot and 
Hôpital Saint-Louis, Paris, France

In patients with inherited bone marrow failure disorders, stem cells that turn into blood cells become exhausted over time, and normal blood cell formation stops. In that context, any clone, or abnormal copy of an immature blood cell, that is fit (for example, because of its genetic makeup) can outcompete the impaired cells that remain.

As people age, they develop more clones. This does not necessarily mean that they have MDS or leukemia.

In patients with Fanconi anemia, clones can evolve, and 20 to 30% of patients with this genetic disease develop MDS or acute myelogenous leukemia. However, in other patients, the genes with inherited mutations can turn back to normal (a process called genetic reversion) and stop forming clones. This explains why about 15% of patients with Fanconi anemia have normal or only slightly low blood cell counts.

Dr. Soulier believes that morphology (cell form and structure) as well as abnormalities in genes and chromosomes all need to be assessed carefully to evaluate the evolution of clones in bone marrow failure disorder. He gave the example of a 5-year-old girl who was diagnosed with Fanconi anemia because her older brother had it. A genetic test showed that she had two damaging mutations in FANCA. When the girl turned 10, her blood cell counts and bone marrow morphology were still normal. But she had a chromosome abnormality, which was a sign that her clone had evolved. Because the chromosomal abnormality (a duplication of chromosome 1q) was not considered a sign of a poor prognosis, her doctors decided to wait to treat her disease but to monitor her carefully.

Only when the girl turned 19 did she develop cytopenia (low blood cell counts), and her bone marrow had defective stem cells that could turn into healthy blood cells. She had a new change in a chromosome, and she had developed aplastic anemia. Her abnormal chromosome was associated with a poor prognosis, so her doctors decided to treat her with a stem cell transplant.

She has done well for 7 years, although she did develop a squamous cell carcinoma (a type of cancer) on her cervix that was treated with surgery.

Dr. Soulier and colleagues did a study of specimens from 56 patients with Fanconi anemia that had progressed. Using rigorous criteria for cell morphology along with data on abnormal chromosomes, the investigators were able to determine whether the patients did or did not have MDS. The results showed that 1q mutations are signs of clones but not of cancer progression. Other abnormal chromosomes (including in chromosomes 3, 7, and 21), however, can be associated with a poor prognosis.

Based on what is known in Fanconi anemia and in patients with MDS who don’t have Fanconi anemia, Dr. Soulier and colleagues have suggested a set of criteria to help make treatment decisions for patients with Fanconi anemia. These criteria are based on both morphology and abnormal genes and chromosomes.

Management of Inherited Bone Marrow Failure and Leukemia Predisposition

Akiko Shimamura, MD, PhD
Dana-Farber/Boston Children’s Cancer 
and Blood Disorders Center

Experts are identifying a growing number of inherited bone marrow failure disorders. These disorders include Fanconi anemia, dyskeratosis congenita, Swachman Diamond syndrome, GATA2-spectrum disorders, SAMD9/SAMD9L disorders, and others. Although each one is rare, inherited bone marrow failure syndromes as a whole aren’t rare.

Often, when a patient first comes to a hematology or oncology clinic, he or she already has advanced MDS or acute myelogenous leukemia (AML). At that point, starting therapy is urgent. But it is also important to consider whether the patient might have an inherited disorder because the diagnosis informs the treatment.

It’s also important to figure out whether the patient’s genetic mutations are inherited or acquired after birth to choose the right donor for stem cell transplantation, monitor the patient for complications, and counsel families.
If, for example, a patient’s mutation is inherited, a family member with that mutation who has no symptoms might not be a suitable stem cell donor. A transplant from this individual could fail to cure the disease.

Many patients with inherited bone marrow failure disorders need less intense conditioning treatments to prevent serious side effects. Conditioning treatments are used to prevent the patient’s immune system from attacking the donated cells, eliminate diseased marrow, and make space for the new marrow. Dr. Shimamura recommends stem cell transplantation for patients with severe or symptomatic low blood cell counts, high-risk abnormalities in chromosomes, MDS, or AML. But she recommends again preemptive stem cell transplantation for patients who only have moderately low blood cell counts and no associated symptoms unless additional complications arise. These patients should consult an expert in bone marrow failure.

Treatments for inherited bone marrow failure syndromes are different than for syndromes caused by genetic mutations that patients acquire after conception. For example, immunosuppressive treatment doesn’t usually work well for inherited disorders, although it’s used for noninherited forms of aplastic anemia. Androgens (a male hormone) can be used in some cases, such as to treat Fanconi anemia and dyskeratosis congenita.

The goals of monitoring are to improve the patient’s outcomes and survival. Monitoring can identify problems before the patient’s prognosis becomes poor and the disease is harder to treat. At the same time, monitoring should not make patients and families overly anxious.

Several expert consensus statements are available on how to monitor patients with inherited bone marrow failure disorders. Dr. Shimamura recommends checking complete blood counts every 3 to 6 months if blood counts are stable. For disorders associated with a high risk of progression to leukemia, she recommends annual bone marrow exams. For patients with progressively dropping blood counts or certain types of clones (abnormal blood cells), she recommends more frequent complete blood count testing and closer monitoring of the bone marrow. Depending on the results, the patient might benefit from a stem cell transplant. These patients should consult an expert in bone marrow failure.

PART II: USING GENETICS TO MAKE TREATMENT DECISIONS

Genetic Mutations in Unexplained Cytopenias and Cytopenias of Undetermined Significance

Luca Malcovati, MD
University of Pavia

In the first stage of a bone marrow failure disorder, clones, or abnormal copies of an immature abnormal blood cell, may develop. The last stage in the process is a myeloid malignancy, such as myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). Researchers are now trying to understand the steps in between these stages. Some of the conditions in between these two phases are hard to classify: cytopenia of undetermined significance, unexplained anemia of the elderly, and bone marrow hypoplasia.

A person develops MDS as a result of one or more somatic mutations (changes in genes that happen after conception) in the stem cells that form blood cells. The mutations allow the abnormal stem cells to outcompete healthy cells in the bone marrow. Once the clones take over most or all of the bone marrow, the patient’s blood cell counts drop because of the clone’s abnormal capacity to mature and produce blood cells.

Somatic mutations in more than 40 genes are known to drive the development and expansion of MDS clones. Five of these genes are involved in epigenetic regulation (management of gene alterations not due to DNA sequence changes) or RNA splicing. The RNA splicing genes control the joining together of RNA sequences to form messenger RNA molecules, which contain coding information needed to make proteins. Mutations in these five genes tend to happen early in the clonal process.

Mutations in epigenetic regulator genes drive the expansion of premalignant bone marrow clones. Additional mutations then transform the bone marrow stem cells and expand the MDS clones. These additional mutations determine which type of bone marrow failure the person develops.
If a doctor suspects that a patient has MDS but cannot prove it, the condition is called idiopathic cytopenia of undetermined significance (ICUS). These patients have a low count of at least one type of blood cell that can’t be explained by any other disease but doesn’t meet the MDS criteria. Patients with ICUS and one or more somatic mutations have a much higher risk of MDS than patients without these mutations. The outcomes in these patients are the same as in patients with low-risk MDS or MDS with the same types of mutations. These findings suggest that patients with ICUS who have these mutations actually have MDS, even though they don’t have much dysplasia (abnormally shaped cells, a sign of MDS).

About one in five adults aged 70 or older has anemia, but the causes are uncertain in about a third of these patients, whose condition is known as unexplained anemia. Older adults with unexplained anemia tend to have high levels of abnormal clones in their bone marrow as well as somatic mutations associated with MDS. Unexplained anemia of the elderly could therefore be an early sign of MDS.

**Debate:**
**Should Doctors Base Treatment Decisions on Non-Inherited Mutations in Patients with an Inherited Bone Marrow Failure Syndrome?**

**Side One:** Yes

*Alison Bertuch, MD, PhD*
Baylor College of Medicine

When choosing a treatment for a bone marrow failure disorder, doctors need to balance the risk that the disease could progress to MDS or acute myelogenous leukemia (AML) with the risk of serious complications or even death with certain treatments.

In Fanconi anemia, a rare inherited syndrome, the bone marrow does not make enough red blood cells, white blood cells, or platelets. Today, almost 90% of patients survive for at least 5 years after a stem cell transplant from a related or unrelated donor.

Dr. Bertuch is therefore comfortable recommending transplantation for Fanconi anemia.

Familial platelet disorder with a predisposition to AML is caused by an inherited mutation in RUNX1, and patients tend to have certain acquired (noninherited) mutations as well. About 30 to 50% of these patients develop MDS or AML, and they also have a higher risk of acute lymphocytic leukemia. Interestingly, all patients whose disease progresses to AML acquire additional RUNX1 alterations, but patients with thrombocytopenia (low platelet count) don’t. Doctors can’t yet base treatment decisions on this acquired RUNX1 mutation, but they might be able to soon.

Shwachman-Diamond syndrome (SDS) is a rare inherited disease in which the bone marrow doesn’t make one or more types of blood cells. Up to a quarter of patients with SDS develop MDS or AML, and about half have acquired TP53 mutations. Some patients develop AML at a young age. But the TP53 mutation might not be active at first, which could explain why some patients with SDS develop AML only when they’re older.

In patients with GATA2 deficiency, the immune system doesn’t work properly, so the body can’t fight infections properly. These patients have low blood cell counts, and about 70% develop MDS or AML. They tend to develop serious complications when treated with standard AML therapies. But their outcomes with stem cell transplantation are improving, and Dr. Bertuch recommends transplantation for patients with low blood cell counts and before they develop MDS, AML, or other serious complications. About half of patients who develop MDS acquire a SETBP1 mutation before they develop monosomy 7, a chromosome abnormality that is common in patients with MDS and is associated with a poor prognosis. Outcomes might be better in these patients if they undergo transplantation before their disease progresses to monosomy 7 MDS.
Dr. Corey argued against basing the treatment plan for inherited MDS or AML on whether the patient also has acquired (not inherited) mutations. Although the acquired mutations can be used to predict outcomes in these patients, predictions are often wrong.

The various inherited bone marrow failure syndromes have different risks of developing MDS or acute myelogenous leukemia (AML). Because of biases in how data on these diseases have been reported, the risk of MDS or AML might not be as high as experts think. Dr. Corey discussed a patient with severe congenital (inherited) neutropenia (low count of neutrophils, a type of white blood cell). This patient was diagnosed in 1982 and responded to treatment with filgrastim (Neupogen), which increases white blood cell counts. However, within 2 years, the patient developed noninherited mutations in several genes and a clone (abnormal copy of immature white blood cells). The patient developed more mutations over time and was ultimately diagnosed with AML 18 years later. It’s possible that the patient’s bad mutations ultimately led to disease progression and death. When patients with Shwachman-Diamond syndrome acquire a TP53 mutation, they tend to do so early in the disease process. About half the patients who develop these mutations also have clones, as do about half of patients with severe congenital neutropenia who acquire CSF3R mutations. However, clones come and go all the time, so whether the mutations cause the clones and, eventually, MDS or AML isn’t clear.

Using genetics to predict outcomes in inherited bone marrow failure syndromes is challenging. Acquired mutations don’t necessarily correlate with disease features. Also, different types of mutations have different types of effects, and many factors can influence the growth of clones. It’s difficult to predict who will do well with stem cell transplantation and who will have problems. Dr. Corey is trying to use drugs to abolish the clones associated with certain acquired mutations. He believes that doctors should base treatment choices partly on acquired mutations with inherited bone marrow failure syndromes, but when and how to do this depends on the context.

Patients with paroxysmal nocturnal hemoglobinuria (PNH) have a noninherited form of hemolytic anemia. In people with hemolytic anemia, red blood cells are destroyed and removed from the bloodstream prematurely. These patients develop thrombosis, or blood clots, and they might also develop aplastic anemia over time. PNH is rare and hard for primary care doctors to diagnose. Before eculizumab (Soliris) was available, the median overall survival of patients with severe PNH was 22 years.

The abnormal red blood cells in people with PNH lack two important complement proteins, CD59 and CD55. The body’s complement system recruits enzymes and other mediators to fight a foreign invader (such as an injury or virus). Without these proteins that inhibit complement activation on the surfaces of red blood cells, the complement system destroys those cells prematurely, resulting in low counts of healthy red blood cells and, thus, low hemoglobin levels.

PNH: Treatment Options for a Diverse Disease

Until about 10 years ago, the main treatment for PNH was stem cell transplantation. A study showed that 85% of 211 patients who underwent transplantation for hemolysis (red blood cell destruction), aplastic anemia, or thrombosis survived for at least 5 years. However, more than half the survivors developed graft-versus-host disease, which affects quality of life.

The U.S. Food and Drug Administration and European Medicines Agency approved eculizumab (Soliris) in 2007. This treatment doesn’t cure PNH, and it has to be administered by intravenous infusion every 15 days. Eculizumab significantly prolongs survival, but patients can still develop hemolysis just before their next infusion, and some patients still need regular red blood cell transfusions. Furthermore, viral infections can reduce the patient’s absorption of the drug, which can result in breakthrough symptoms.
If a patient with PNH has no hemolysis but develops aplastic anemia, the treatment is the same as for aplastic anemia without PNH. The treatment of choice for patients younger than 40 is stem cell transplantation, and the results with a sibling donor are excellent: the overall survival rate is 95%, and the risk of complications is low. If the patient has no sibling donor, the best option is treatment to suppress the patient's immune system (immunosuppressive therapy, or IST). This treatment can also prolong survival, although it’s most effective in patients with moderate as opposed to severe or very severe aplastic anemia.

The combination of PNH, aplastic anemia, and hemolysis is rare. Treatment can consist of a combination of both eculizumab and IST. Stem cell transplantation can also be an option if a matched donor is available.

All patients with PNH have a risk of thrombosis (blood clot in a vein or artery), a life-threatening complication. Patients with low counts of all types of blood cells, even if they have a small PNH clone (abnormal copy of immature blood cells), can develop thrombosis. Anticoagulants don’t prevent thrombosis, and they can cause abnormal bleeding. But eculizumab can prevent and treat thrombosis, and Dr. Peffault de Latour recommended a combination of anticoagulants and eculizumab for PNH with thrombosis.

Before eculizumab was available, pregnant women with PNH and hemolysis miscarried, and about 20% died. Pregnant women treated with eculizumab tend to need more transfusions, and about half need higher or more frequent eculizumab doses. In a study of 70 pregnancies in 57 women with PNH, only two patients had thrombosis after their baby was born, and none of the women or infants died.

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New Treatments for PNH

Antonio Risitano, MD, PhD
University of Naples

Eculizumab (Soliris) works by attaching to and neutralizing the C5 complement protein, which blocks the activation of the complement system and thus prevents complement proteins from destroying blood cells (hemolysis). However, not all patients with PNH respond to eculizumab. For example, some patients have a rare genetic mutation that prevents eculizumab from binding to C5. Others have “breakthrough” hemolysis in between eculizumab infusions. Eculizumab treatment requires intravenous infusions every 15 days, the drug can be costly, and it’s not available in every country.

Several new anti-C5 agents are in development

- Alexion’s ALXN1210 is similar to eculizumab. It’s just as effective, but it can be administered every other month. Phase I and Phase II clinical trials have been completed, and two Phase III trials of this compound are ongoing in patients with PNH that has never been treated and in patients treated previously with eculizumab.
- Chugai-Roche’s RO7112689 might be effective in patients who have certain genetic mutations that prevent them from responding to eculizumab. A Phase III trial is currently enrolling patients, and data should be available by the end of the year.
- RA Pharma’s RA 101495 can be administered subcutaneously (under the skin). Two Phase II clinical trials of this compound in people with PNH are underway.
- AKARI’s Coversin is a protein that can prevent complement activation.
The perfect complement inhibitor for PNH would:

- Be as safe as eculizumab
- Control hemolysis within blood vessels as effectively as eculizumab
- Control hemolysis outside of blood vessels
- Be effective in patients with rare gene mutations that prevent them from responding to eculizumab
- Be administered less often than eculizumab and be easier to administer
- Be available to all patients with PNH around the world

Some evidence shows that C3, a complement protein, might be a suitable treatment target in PNH. Achillion’s ACH-4471 prevents C3 deposition on red blood cells from patients with PNH and decreases hemolysis. A Phase I trial in people with PNH will start soon. Amyndas Pharmaceuticals is developing AMY-101, which reduces levels of lactate dehydrogenase (high levels of this enzyme are a sign of red blood cell destruction) in untreated patients and, when combined with eculizumab, results in normal hemoglobin. These were small studies, but a Phase III clinical trial is about to start.

Dr. Risitano believes that better drugs are coming and that they will give patients a normal lifespan and preserve their quality of life.
In 2015, the White House launched the Precision Medicine Initiative, led by the National Institutes of Health (NIH). The White House and NIH define precision medicine as "an approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." This field brings together genomic sciences and bioinformatics.

**Prognostic Markers in Aplastic Anemia**

Shinji Nakao, MD, PhD  
Kanazawa University

Prognostic markers are biological signs that can be used to predict patient outcomes. In aplastic anemia, such markers include an increase in the percentage of paroxysmal nocturnal hemoglobinuria (PNH)-type cells and HLA class I allele-lacking leukocytes (HLA-LLs) in the blood. HLA-LLs are a type of white blood cell. These cells are thought to be signs of an immune system attack against hematopoietic stem progenitor cells (HSPCs) in patients with bone marrow failure. HSPCs can turn into all types of blood cells in bone marrow.

Nowadays, most patients with severe aplastic anemia respond to immunosuppressive treatment (IST) with antithymocyte globulin, cyclosporin, and eltrombopag (Promacta). Prognostic indicators might no longer be needed to predict outcomes in this disease. But they're still important for choosing the best treatment for patients with bone marrow failure when the diagnosis isn't clear.

One of the most important uses of prognostic markers is to identify bone marrow failure resulting from an improperly functioning immune system in MDS. Patients with PNH-type cells respond to IST better than those without PNH-type cells, even if less than 0.01% of their granulocytes (a type of white blood cell) are PNH-type cells. Only patients with noninherited aplastic anemia or lower-risk MDS have large numbers of PNH-type cells. This suggests that PNH-type cells are a marker of a benign type of bone marrow failure.

Prognostic indicators are also useful for predicting outcomes in families when several members have aplastic anemia. In these families, some members have PNH-type cells and/or HLA-LLs, and they tend to respond well to IST. Studies of these families might help identify genetic or environmental factors that affect a family member's risk of developing noninherited aplastic anemia.

Finally, prognostic indicators can be useful for choosing the best treatment in patients with late graft failure after a stem cell transplant who have no remaining immune cells of their own. Graft failure means that the transplanted cells don’t support sustained blood cell formation. Graft failure is late when the stem cells start making healthy blood cells and then stop. It’s often hard to find out how this happens and restore the graft’s function without a second stem cell transplant. But some patients with late graft failure have a type of bone marrow failure that is similar to noninherited aplastic anemia. This type of aplastic anemia can be diagnosed by detecting higher counts of PNH-type cells and/or HLA-LLs. In some of these patients, IST can restore the ability of the donor stem cells to function properly.

**Update on Eltrombopag and Immunosuppressive Treatment**

Danielle Townsley, MD  
National Heart, Lung, and Blood Institute

In a recent study, Dr. Townsley and colleagues treated 92 patients with severe aplastic anemia with standard immunosuppressive treatment (IST) and eltrombopag (Promacta). The patients were divided into three groups:

- **Cohort 1**: Started eltrombopag 14 days after starting IST and continued treatment for 6 months
- **Cohort 2**: Started eltrombopag 14 days after starting IST and continued treatment for 3 months
- **Cohort 3**: Started eltrombopag and IST on the same day and continued treatment for 6 months

About 80% of patients responded to the treatment at 3 months and 6 months, and 30–40% of patients had a complete response. Adding eltrombopag increased response rates by 20% compared with IST alone.
The response rates in Cohort 3 were even higher: 94% responded at 6 months, and 58% had a complete response.

Among 36 patients younger than 18 in the study, 25 (69%) responded at 3 months and 26 (72%) at 6 months (including 11, or 31%, who had a complete response). However, the disease progressed in 3 patients (8%), and 10 (28%) had a relapse. These findings suggest that children and teenagers might not benefit from adding eltrombopag to IST.

When the results were published, 97% of patients had survived for at least 2 years. Two patients died during the study: one from a severe infection during relapse at 2 years and one from a cause that was not blood related. Two of 12 patients who underwent stem cell transplantation died after the procedure, and three patients who did not respond to treatment died (of infections in two cases) while waiting for a stem cell transplant.

The study showed that adding eltrombopag to IST is effective and increases response rates. However, this approach might be less beneficial in pediatric patients.

**Eltrombopag for Bone Marrow Failure**

**Tom Winkler, MD**
National Heart, Lung, and Blood Institute

In 2014, the Food and Drug Administration approved eltrombopag (Promacta) in 2014 for severe aplastic anemia that has not responded to other treatments. This decision was based on a clinical trial showing that eltrombopag alone leads to blood cell count increases in about 40% of patients.

Dr. Winkler and colleagues conducted a study that gradually increased eltrombopag doses from 50 mg every 2 weeks until they reached 150 mg daily. The study enrolled 43 patients with severe aplastic anemia. The investigators evaluated patients at 3 or 4 months to find out if their blood counts had increased. Responders continued eltrombopag treatment until they had a robust response or their blood counts stopped changing.

In another study, 40 patients were treated with 150 mg of eltrombopag every day. After 6 months, responders continued eltrombopag treatment until they had a robust response or their blood counts stopped changing. The treatment was stopped in patients who developed chromosome abnormalities. Half the patients responded after 6 months. Of 19 responders who continued the treatment for more than 6 months, 1 stopped responding 3 months later, 2 withdrew from the study, 14 stopped treatment because of a robust response, and 1 stopped because of stable blood counts. Twelve patients still have stable blood counts even though they stopped eltrombopag treatment. Three patients had to restart the drug because of a relapse, but all responded to the drug again. Six patients (18%) developed chromosome abnormalities while undergoing eltrombopag treatment.

An analysis of the 83 patients enrolled in both of these eltrombopag studies found that 15 patients developed chromosome abnormalities, including 6 who lost chromosome 7 or its long (q) arm, which is associated with a poor outcome. Blood counts increased in almost half of those with abnormalities affecting chromosomes other than chromosome 7. Most of the abnormalities were detected at the 3-month assessment, and none of the 15 patients had signs of MDS.

In an analysis of blood samples from 82 patients with aplastic anemia, a third had somatic mutations in genes associated with bone marrow failure syndromes. A somatic mutation develops after birth and is not inherited. About half the patients had developed clones, or abnormal copies, of immature blood cells, and these clones typically had noninherited mutations. The results showed that clones with chromosome abnormalities often develop within 3 to 6 months of starting eltrombopag. These abnormalities don’t necessarily last, and eltrombopag treatment has little effect on the size of these clones.

**Stem Cell Transplantation Progress**

**David Margolis, MD**
Medical College of Wisconsin

In 1976, Bruce Camitta at the Children’s Hospital of Wisconsin and colleagues reported the results of a randomized clinical trial that assigned patients who had
severe aplastic anemia with a matched sibling to stem cell transplantation. Those without a matched sibling were randomly assigned to treatment with androgen (a male hormone) by mouth, androgen treatment by injection, or no androgen treatment. Of 36 patients in the study, 2 died while undergoing immunosuppressive treatment, four died of infection after transplant, and 9 rejected the graft (i.e., the transplanted cells did not reach the bone marrow and start forming healthy blood cells). The problems of graft rejection, infection, and graft-versus-host disease identified in this study are still challenges today.

Before 1988, the survival rate for bone marrow transplantation from an unrelated donor in patients with severe aplastic anemia was only 25%. Between 1988 and 2000, the rate more than doubled, to 50–60% with the use of intensive conditioning treatments to prepare the patient for transplant. However, this treatment included total body irradiation, which had serious consequences in some patients. With changes in conditioning regimens and treatments after the transplant as well as lower radiation doses (or not radiation at all), survival rates are higher than 80%.

Unrelated Donor Stem Cell Transplant in Pediatric Patients

Currently a Reasonable Option

Carlo Dufour, MD
Istituto Giannina Gaslini

About two-thirds of children and adolescents with severe aplastic anemia survive with immunosuppressive treatment (IST) or eltrombopag (Promacta) with poor quality of life and daily limitations. Aplastic anemia progresses to MDS or acute myelogenous leukemia in 8–21% of patients aged 10–15 years, and up to 24% develop cancers not related to bone marrow failure within 30 years.

IST and eltrombopag don’t seem to be the best first treatments for severe aplastic anemia in children and teenagers. Up-front stem cell transplantation from an unrelated donor if no related donor is available might be a better option. In a study in 29 patients aged 18 or younger, the overall survival rates, at more than 90%, were the same as with IST. Rates of acute graft-versus-host disease (GVHD) within 3 months of transplant were low. Although rates of chronic GVHD (after the first 3 months) were higher, this complication was easy to treat. Importantly, quality of life was much better with this approach than with IST.

Other studies have found that although stem cell transplantation with a related donor has better outcomes than from an unrelated donor, the difference wasn’t statistically significant. Also, up-front matched unrelated donor (MUD) transplants result in low rates of acute GVHD and no extensive chronic GVHD.

The outcomes of MUD transplantation up front are better than those of MUD transplant after the patient has not responded to IST, has had to stop IST because of complications, or has stopped responding. Dr. Dufour therefore believes that it doesn’t make sense to try IST in a patient before considering MUD transplantation.

Dr. Dufour also believes that MUD stem cell transplantation in patients aged 0–18 years who have aplastic anemia is better than IST, equivalent to matched sibling donor transplantation, and better than MUD transplantation after IST failure.

However, not all patients can find a MUD. Although Caucasian patients have a 75% chance of finding a donor, the rate is much lower for other ethnic groups or for those of mixed ethnicity. Furthermore, suitability of a MUD transplantation depends on some donor characteristics, such as age and gender, and on some patient issues, such as whether the patient has an infection.

Randomized Trials Are Needed

Michael A. Pulsipher, MD
Children’s Hospital Los Angeles

The outcomes of clinical trials of matched unrelated donor (MUD) stem cell transplantation for severe aplastic anemia have been outstanding. These findings raise the question of whether the current treatment paradigm, which focuses on sibling donor transplantation, should change.
The survival rate for sibling donor transplantation is higher than 95%, and rates of chronic graft-versus-host disease and progression to MDS or acute myelogenous leukemia (AML) are very low. The long-term physical, mental, and psychological health of patients after matched-sibling transplantation are also excellent, as is their quality of life. Children grow at close to normal rates after the procedure. The limited data available imply that very few pregnant women who have undergone matched sibling transplantation have miscarriages or babies with birth defects.

Many men and women who had a matched sibling stem cell transplant as children have had children of their own, showing that it's possible to have children after sibling transplantation. Sibling stem cell transplant is therefore a very reasonable standard of care.

Unrelated donor transplantation outcomes are different from those of sibling transplantation. So the question is whether to offer patients unrelated donor stem cell transplantation as their main therapy.

Both immunosuppressive therapy (IST) and unrelated-donor stem cell transplantation as up-front treatment have risks and benefits. About 12 to 30% of children don't respond to up-front IST and might require stem cell transplant relatively early. Of the 70 to 80% who respond, half stop responding, or they need several IST cycles or long-term IST treatment.

Eventually, 10 to 20% of these children develop secondary MDS or AML. Many develop infections or iron overload (very high iron levels in blood) or their platelets don't increase after a transfusion. Some have fatal complications or other problems that can't be treated with another stem cell transplant.

If a decision is made to use unrelated donor stem cell transplantation as up-front treatment, it might take time to find a donor and start the transplantation process. The patient has a 5 to 10% chance of graft failure (the transplanted cells don't support sustained blood cell formation) and might therefore need a second stem cell transplant. The patient might also develop chronic graft-versus-host disease and therefore need IST for an extended period.

The best therapy is one that cures the most patients and allows the most patients to stop IST and return to normal functioning quickly.

A randomized controlled trial of MUD transplantation in young patients with severe aplastic anemia is possible. Such a trial is likely to be safe now that the disease can be diagnosed quickly and MUDs can be identified within a few days. Only a randomized trial will truly show which therapy is best. A clinical trial is now open through the North American Pediatric Aplastic Anemia Consortium and the Pediatric Blood & Marrow Transplant Consortium at 10 centers in the United States. This pilot trial in 40 patients will test whether a larger trial is possible.

Unrelated Donor Transplantation in Adults

Regis Peffault de Latour, MD, PhD, Hôpital Saint-Louis (presentation given by Antonio Risitano, MD, PhD, University of Naples)

In the United States and Europe, the standard treatment for noninherited aplastic anemia in patients younger than 40 who have a suitable sibling donor is matched sibling donor transplantation. The standard treatment for other patients is immunosuppressive treatment (IST) with or without eltrombopag (Promacta). Unrelated donor transplantation is usually considered only after the first treatment fails.

If a patient doesn't have a matched sibling donor (meaning that all of the sibling’s blood markers match those of the patient based on a process known as HLA typing), he or she can have a transplant from a matched unrelated donor (MUD). This treatment offers a potential cure for some pediatric patients, and it is usually safe. To maximize the chance that the procedure will succeed, it's important to find a donor as soon as the condition is diagnosed.

Disadvantages are that a MUD can be hard to find for patients from certain minority groups. Also, the only evidence on the procedure for aplastic anemia come from small, retrospective studies, not randomized controlled trials. Dr. Peffault de Latour recommends starting the search for a MUD as soon as the patient is diagnosed and considering MUD transplantation 3 to 6 months after the patient undergoes IST. Although umbilical cord blood can be used for transplantation, survival rates are low. However, ongoing clinical trials of this source of stem
cells might help improve the results. Other options include transplantation with donors who have 9 of 10 or 7 of 8 markers that match those of the patient.

Also, best supportive care to treat the patient’s symptoms is improving, and doctors can now keep patients alive and comfortable for at least a few years if they don’t respond to IST. This might keep patients going long enough to benefit from new treatments that will become available in the near future.

Experimental options for patients who don’t respond to IST and patients younger than 20 include umbilical cord blood transplantation or transplantation from a partially matching donor with total body irradiation to reduce the risk that the patient will reject the donated cells. These treatments are most successful when they’re done in a center with a lot of experience.

Haploidentical Bone Marrow Transplant for Refractory or Relapsed Severe Aplastic Anemia with Post-Transplant Cyclophosphamide

Amy DeZern, MD, MHS
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

The ideal treatment for severe aplastic anemia is one that is available to all patients, regardless of their age or whether a donor is found whose HLA blood markers match those of the patient. The ideal treatment is also safe, with a low risk of complications, and it leads to rapid acceptance of the donated cells in the patient’s bone marrow (called engraftment) so that they quickly start growing healthy blood cells. Finally, the ideal treatment reduces or eliminates the risk of disease progression to paroxysmal nocturnal hemoglobinuria, MDS, or acute myelogenous leukemia.

In a haploidentical stem cell transplantation, the donor’s HLA markers match half of the patient’s HLA markers. This treatment is reserved for patients whose disease has relapsed or hasn’t responded to initial treatment with immunosuppressive therapy (IST). It should be done as part of a protocol designed to prevent rejection of donated cells and graft-versus-host disease (GVHD).

The advantages of haploidentical stem cell transplantation include that virtually every patient has a donor, and results are similar to those with a matched sibling donor. Many patients can’t wait 3 or 4 months to find a matched unrelated donor, but a haploidentical donor can be found very quickly, given that these donors are usually close family members. The use of cyclophosphamide after transplantation minimizes the risk of GVHD. The procedure is well suited to severe aplastic anemia, which is a nonmalignant disease.

Dr. DeZern’s center at Johns Hopkins uses a conditioning regimen that includes rabbit antithymocyte globulin, fludarabine, cyclophosphamide, and total body irradiation to prepare the patient’s body to receive the transplanted cells. The patient is then treated with two doses of cyclophosphamide intravenously as well as oral tacrolimus after the transplant to prevent GVHD.

Among 24 patients treated with this regimen who had severe aplastic anemia that hadn’t responded to IST, all patients are alive and no longer need regular transfusions. The donor’s cells (the transplant) started making new healthy blood cells within about 3 after infusion in most patients. The donated cells didn’t start making healthy blood cells in one patient (no engraftment), but this patient responded to transplantation with cells from a different donor. None of the patients have had a relapse of their aplastic anemia. Two patients developed acute but limited GVHD, and one had extensive chronic GVHD, but these complications were treated successfully.
Discussion:
How to Integrate Clinical Information and Biological Data From Research in the Precision Medicine Era

Moderator: Phillip Scheinberg, MD
Hospital A Beneficência Portuguesa, São Paulo, Brazil

Many experts at the meeting said that they would not base their treatment decisions for severe aplastic anemia solely on the results of tests for gene mutations. They reasoned that the impact of these mutations on patient outcomes is still not clear. However, participants recognized that some hematologists are referring patients to stem cell transplantation (SCT) up front based solely on the patient’s genetic mutations. Participants considered this practice ill advised.

The experts recommended using currently accepted treatment algorithms, which call for up-front SCT or immunosuppressive therapy (IST). In patients treated with IST, a test of genetic mutations in the bone marrow might be useful, especially when combined with information on whether the patient responded to IST.

The experts at the meeting discussed a hypothetical case of a 22-year-old patient with severe aplastic anemia and a TERT mutation but no other physical signs. The patient has no siblings and a poor chance of finding an unrelated donor because her parents are of mixed ethnicity. So the treatment decision is tricky.

Some clinicians would try to find a matched unrelated stem cell donor for this patient, as long as the transplantation could be completed within 2 months. However, if this is not possible and the patient’s white blood cell counts are dropping, doctors might treat the patient with IST or androgen, a male hormone. Participants were uncertain about the role androgens should play in the initial management of this patient. They noted that data show that patients with TERC or TERT mutation can respond to IST but have a higher likelihood of responding to androgen therapy. The experts also suggested trying to diagnose the disease quickly, including testing for Fanconi anemia, so that treatment can start promptly.

The recommended options might be different for a 49-year-old man with diabetes, overweight, and heart disease along with some chromosome abnormalities, such as del(13q). The initial treatment could consist of a combination of IST with horse antithymocyte globulin, cyclosporine, and eltrombopag (Promacta). First-line treatment with this combination has been effective for severe aplastic anemia. However, eltrombopag does not have regulatory approval for severe aplastic anemia in Europe. Many thought that the presence of the isolated del(13q) mutation should not preclude use of eltrombopag because many reports show that patients with aplastic anemia with or without del(13q) have similar response rates to IST and similar prognoses.

So far, the only factor used in treatment algorithms for severe aplastic anemia is age. Although age plays an important role in patient responses to IST and transplantation, participants identified other factors to consider. These factors include genetic mutations (in genes associated with telomeres at the ends of chromosomes or immature blood cells), telomere length, reticulocyte (immature blood cell) count, and whether the patient has a paroxysmal nocturnal hemoglobinuria clone. These factors are associated with response to IST and/or long-term complications of relapse or disease progression.
BIOLOGY OF MDS AND SECONDARY ACUTE MYELOID LEUKEMIA

Genes and Disease Progression in Bone Marrow Failure Syndromes

Coleman Lindsley, MD, PhD
Dana-Farber Cancer Institute

Clones are abnormal copies of the hematopoietic stem cells (HSCs) that form blood cells. Some genetic mutations cause clones to form in the bone marrow and ultimately lead to MDS. But not all patients with these mutations develop MDS, and Dr. Lindsley believes that this shows that the context of the mutations matters.

Splicing factors are genes that control the splicing together of RNA sequences to form messenger RNA molecules. Messenger RNA contains the genetic coding information needed to make proteins. About half of all patients with MDS have splicing factor mutations, but very few have mutations in more than one splicing factor.

About a third of patients with MDS have a mutation in the RAS pathway. The genes in this pathway make proteins involved in cell signaling to control cell growth and death. But patients rarely have mutations in RAS pathway genes early on—they often develop these mutations when their MDS progresses to acute myelogenous leukemia.

Dr. Lindsley also discussed the role of inherited mutations in MDS. Patients with MDS who are older than 40 are more likely to have gene mutations (such as in DNMT3A, TET2, SF3B1, or SRSF2) linked to the age-related development of clones or MDS. Those younger than 40 tend to have mutations in genes (such as GATA2, PIGA, and SBDS) associated with inherited bone marrow failure syndromes.

Mutations in SBDS cause Shwachman-Diamond syndrome, and 4% of adults with MDS who are younger than 40 have mutations in one copy of this gene. Most adults with MDS who have mutations in both copies of SBDS don’t have a diagnosis of Shwachman-Diamond syndrome, but these patients might still have the disease.

Patients with two copies of the mutated genes have very poor outcomes. These patients often have mutations in the TP53 gene, and TP53 mutations are much more common in these patients than in other patients. These findings suggest that noninherited mutations in TP53 facilitate the progression of Shwachman-Diamond syndrome to MDS.

Insights into MDS from Induced Pluripotent Stem Cells

Eirini Papapetrou, MD, PhD
Mt. Sinai School of Medicine

Induced pluripotent stem cells (iPSCs) are cells that can turn into any type of human cell. Dr. Papapetrou develops iPSCs using cells from patients with MDS or acute myelogenous leukemia (AML). Her laboratory can turn these iPSCs into immature blood cells that can give rise to red blood cells, white blood cells, and platelets for studies of MDS.

Dr. Papapetrou’s laboratory can use the iPSCs to compare genes in MDS and healthy people. They can also use CRISPR-Cas9 gene-editing technology to correct mutations in MDS and AML iPSCs. They can study cells at an early stage of disease progression, before they become leukemia cells.

In one study, Dr. Papapetrou’s laboratory derived iPSCs from the healthy and abnormal cells of a patient with del(7q) MDS. The patient also had a mutation in SRSF2, which is involved in splicing RNA. Splicing factor genes like SRSF2 control the splicing together of certain sequences in RNA to form messenger RNA molecules. Messenger RNA contains the genetic coding information needed to make proteins.

Dr. Papapetrou’s lab used CRISPR-Cas9 to introduce the SRSF2 mutation into normal iPSCs and to correct the mutation in the MDS iPSCs. She and her colleagues were thus able to create iPSCs that had no mutations, the del(7q) or the SRSF2 mutation, or both mutations.
The laboratory then developed cells showing signs of bone marrow failure. For example, del(7q) mutations were associated with fewer immature blood cells and reduced growth and viability of bone marrow cells. The cells with SRSF2 mutations had abnormal shapes, another characteristic of MDS. These iPSCs could be used to find out, for example, whether drugs that target splicing factor genes (such as SRSF2) are effective for MDS and whether these drugs have effects on healthy cells.

Dr. Papapetrou’s laboratory has used this model to screen 2,000 drugs, most of which have U.S. Food and Drug Administration approval for another purpose, to find out their effects on MDS and healthy cells. Some of the drugs affect cells with del(7q) mutations, and the model could be used to study these drugs in more depth. The studies showed, for example, that niflumic acid, a nonsteroidal antiinflammatory drug, kills cells from patients with del(7q) MDS but not cells without this mutation.

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**Eltrombopag (Promacta) in MDS**

**Britta Will, PhD**  
**Albert Einstein College of Medicine**

Thrombocytopenia (low platelet count) is a common and major problem in MDS. Thrombopoietin (TPO) is a hormone that controls the production of platelets and megakaryocytes (large bone marrow cells that form platelets). Two drugs, romiplostim (Nplate) and eltrombopag (Promacta), that mimic the activity of TPO, have U.S. Food and Drug Administration approval for the treatment of thrombocytopenia in aplastic anemia.

Dr. Will led a study showing that eltrombopag stimulates TPO signaling and formation of megakaryocytes in cells from patients with MDS. The drug also increased numbers of immature blood cells without promoting leukemia cell growth. Follow-up studies showed that eltrombopag kills leukemia cells or inhibits their growth, and it can stimulate the growth of red blood cells, white blood cells, and platelets in patients with severe aplastic anemia.

Dr. Will used patient cells to show that eltrombopag stimulated the formation of megakaryocytes and the differentiation of hematopoietic stem cells (HSCs; which form blood cells in the bone marrow) into healthy blood cells. This drug also increased the number of healthy HSCs.

Previous studies have shown that eltrombopag can lower iron levels in the blood independently of its ability to interact with the TPO receptor. Dr. Will showed that eltrombopag increased numbers of healthy HSCs in mice, but preloading the HSCs with iron prevented eltrombopag from having an effect. Also, eltrombopag leads to higher numbers of HSCs than romiplostim, which doesn’t affect blood iron levels. These findings show that eltrombopag stimulates HSC formation of healthy blood cells by reducing iron levels in blood independently of the drug’s effect on TPO receptors.

A randomized Phase III clinical trial of eltrombopag plus azacitidine (Vidaza) in MDS was stopped early because the patients treated with placebo did better than those treated with eltrombopag and azacitidine. The reason could be that eltrombopag counteracts azacitidine’s ability to stop leukemia cells from growing, although no evidence supports this possibility.

The research to date shows that eltrombopag might be safe to use in patients with MDS undergoing azacitidine treatment. However, treatment with both drugs at the same time is likely to stop eltrombopag from stimulating the formation of megakaryocytes. The data also show that eltrombopag stimulates the formation of red blood cells, white blood cells, and platelets because of its ability to remove excess iron from the blood.

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**Cohesin Mutations in MDS**

**Zuzana Tothova, MD, PhD**  
**Brigham & Women's Hospital/Dana-Farber Cancer Institute**

Cohesin is a protein that keeps duplicated DNA molecules together and regulates their separation during cell division. Cohesin plays important roles in many different processes, including DNA replication and repair of DNA damage.
Some patients develop mutations in the genes that control the cohesin complex of proteins (including STAG2) early in the MDS progression process. Mutations in cohesin complex genes are mutually exclusive, meaning that patients don’t develop more than one of them at a time. Some evidence shows that patients who have MDS and a cohesin complex mutation have poor outcomes.

Dr. Tothova studied STAG2 mutations to understand their function in MDS. She found that cohesin complexes with STAG2 mutations interfere with DNA replication and repair. They also affect the activity of chromatin, the protein, RNA, and DNA substance that forms chromosomes in cells.

The next step was to find out whether cohesin complex mutations could be treatment targets. Cells with a STAG2 mutation were more sensitive to treatment with poly-ADP ribose polymerase (PARP) inhibitors (a type of targeted cancer drugs) than cells without this mutation. The drugs seem to slow down or stall the replication of mutant cells.

### Biology and Treatment of MDS in Laboratory Mice

**Stephanie Halene**, MD, PhD
Yale University

Some of the challenges of studying MDS include the following:

- Although MDS affects hematopoietic stem cells (HSCs), which can turn into all types of blood cells in the bone marrow, HSCs are hard to grow in the laboratory.
- Genetically modified mouse breeds can yield great insights into MDS biology. But they don’t fully mimic human disease.
- Transplantation of human cells into laboratory mice is difficult. The human cells don’t replicate what happens in people, or they’re defective when they are transplanted into mice lacking an immune system.

Dr. Halene’s laboratory, in collaboration with Dr. Richard Flavell’s laboratory at Yale University, has developed a breed of MDS mice lacking a functioning immune system that express human cytokines (proteins released from cells that affect communications and interactions between cells). These cytokines are critical for the formation of healthy blood cells and are tightly regulated to be present in the right place at the right time. In an MDS mouse model, HSCs that come from the bone marrows of patients with different types of MDS travel to the mouse bone marrow. These cells then form immature and mature blood cells that have the same abnormal features as MDS cells in patients.

These humanized mice can be used to compare MDS stem cell function and activity with that of normal stem cells. This human MDS model is ideal for studying and developing new treatments for MDS.

About 5% of patients with MDS and 20% of those with acute myelogenous leukemia (AML) have mutations in IDH1 or IDH2. Dr. Ranjit Bindra’s lab at Yale recently showed that these mutations cause defects in the ability to repair DNA damage in brain tumor.

Dr. Halene and Dr. Bindra and colleagues showed that the same defect occurs in MDS and AML. This defect can be used to kill the mutant cells by inhibiting DNA repair with a new class of drugs known as poly ADP ribose polymerase (PARP) inhibitors. When given to humanized mice engrafted with IDH2 mutant MDS or AML, olaparib (Lynparza), a PARP inhibitor, can inhibit MDS or AML growth.

Thus, studies in patient-derived MDS immature blood cells in humanized mice can lead the way to novel treatments for patients.

### Splicing Factor Mutations in MDS

**Robert Bradley**, PhD
Fred Hutchinson Cancer Research Center

Dr. Bradley focused on treatments for MDS with rare mutations when evidence is lacking on the effects of these mutations. Splicing factors are genes that control the splicing together of certain RNA sequences to form messenger RNA molecules. Messenger RNA
contains the genetic coding information needed to make proteins. About 50% of patients with MDS have a splicing factor mutation, as do about 10–20% of patients with acute myelogenous leukemia.

Most of these mutations are in SF3B1, U2AF1, ZRSR2, and SRF1. The effects of some of these mutations, such as whether they can impair the ability to form healthy blood cells or drive disease progression, aren’t known. Most studies have focused on the most common mutations in these genes.

Which mutations in splicing factors drive MDS progression, which ones play the same roles as other mutations, and which one could be treatment targets needs to be determined. But it’s hard to classify the mutations based on their associations with signs and symptoms in patients. Animal studies aren’t helpful for figuring out the effects of a wide range of mutations because doing all of these studies would be too labor intensive.

Dr. Bradley decided, instead, to use genomics techniques in cell lines that express the same variants in the mutations to compare their effects on biological mechanisms. He then determined whether the effects of the rare variants were similar to those of variants known to drive disease progression in MDS.

His studies showed, for example, that mutations in SRSF2 impair the ability of immature blood cells in bone marrow to form healthy blood cells by changing the gene’s normal ability to bind RNA sequences. As a result, RNA sequences that help control blood cell formation aren’t spliced correctly, leading to abnormal blood cell formation. U2AF1 mutations, in contrast, affect pathways that involve DNA methylation (a chemical process that allows DNA to control cell growth), DNA damage repair, and cell death.

These studies showed that many of the rare variants in SRSF2 have similar effects on biological mechanisms to those of more common mutations. But the rare U2AF1 mutations are more complex than the more common ones, and different types of variants in this gene have different effects.

Dr. Bradley plans to test whether the similarities between rarer and more common variants in splicing factors in MDS mean that these variants have the same effects on the ability of stem cells to form healthy blood cells. He also plans to find out whether drugs that inhibit splicing factors affect cells with the rare variants.

NON-TRANSPLANT TREATMENTS FOR MDS AND SECONDARY AML

In patients with MDS, a chemical process known as ‘methylation’ blocks DNA’s ability to control cell growth. The hypomethylating agents (HMAs) azacitidine (Vidaza) and decitabine (Dacogen) inhibit methylation so that DNA sequences can act normally.

Immune checkpoint inhibitors are drugs that stop some types of immune system cells from making certain proteins that help control immune responses and can stop the immune cells from killing cancer cells. When these proteins are blocked, the immune system cells can again kill cancer cells.

Next-Generation Hypomethylating Agents

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Survival with MDS, which is less than 2 years on average, is dismal. The current HMAs can increase survival, but they still leave much to be desired. For example, at least half of patients don’t respond to them, and only a minority have a complete response, meaning that their blood cell counts are normal or close to normal. Also, most patients stop responding to these drugs after about a year.

Guadecitabine is a formulation of decitabine that releases the drug gradually, increasing cells’ exposure. A Phase II clinical trial has had promising findings about this drug in patients with high-risk MDS that has not yet been treated. Several studies are assessing guadecitabine as front-line treatment in patients whose acute myelogenous leukemia (AML) or MDS hasn’t responded or stopped responding to other treatments. A Phase III clinical trial is evaluating the drug in patients with high-risk, and Dr. Odenike is conducting a trial of the drug in patients with poor-risk AML.
Formulations of HMAs that patients can take by mouth might allow patients to take the drugs over longer periods. A Phase I clinical trial of oral decitabine plus an oral cytidine deaminase inhibitor (a drug that inhibits the cytidine deaminase enzyme) was designed to find the best dose of the oral drug. The preliminary results are encouraging. Oral formulations of azacitidine are also being studied in patients whose MDS stopped responding to HMAs or who have lower-risk MDS. One Phase III trial is studying oral azacitidine as maintenance treatment for AML in patients who are not eligible for stem cell transplantation.

Some outstanding questions about next-generation HMAs for MDS are:

- What are the best doses and treatment schedules?
- What are the advantages of these new drugs over conventional HMAs?
- How can doctors predict whether patients will respond to the new drugs?
- What drugs should be combined with the new HMAs?

The encouraging results of a Phase I clinical trial of oral decitabine plus an oral cytidine deaminase inhibitor (a drug that inhibits the cytidine deaminase enzyme) led to an ongoing Phase II clinical trial. This trial is testing different doses and schedules of oral decitabine in patients with lower-risk MDS.

Studies have also assessed oral forms of HMAs. For example, a Phase I clinical trial showed that an oral form of azacitidine increased blood cell counts. Furthermore, 73% of patients whose disease hadn’t been treated before responded, as did 35% of those whose disease had relapsed or who hadn’t responded to previous treatment. In a Phase II study, 20% of patients with higher-risk MDS that hadn’t responded to azacitidine or had relapsed after azacitidine treatment did respond to guadecitabine, an oral form of decitabine.

The clinical trial that led to the U.S. Food and Drug Administration’s approval found that about twice as many (51%) patients with MDS treated with 28-day cycles of 75 mg/m2 azacitidine (Vidaza) each day for 7 days survived for at least two years compared with 26% of those treated with best supportive care. Also, those treated with azacitidine survived for about 9 months longer, for a total of 24 months.

More recently, a study assessed decitabine (Dacogen) treatment for AML or MDS in patients with chromosome abnormalities or mutations in TP53 that are associated with poor outcomes. In this study, 67% of these patients responded to treatment with 20 mg/m2 of decitabine daily for 10 days in a row every month. The response rate was lower (34%) in patients who didn’t have risky chromosome mutations. Fewer doses of decitabine per cycle (e.g., 20 mg/m2 intravenously each day for 3 consecutive days, instead of the usual 5 consecutive days, in 28-day cycles) can also be effective in patients with lower-risk or intermediate-risk MDS.

New Immune Checkpoint Inhibitors for MDS and Secondary AML

Dr. Daver started 10 randomized clinical trials of different immune checkpoint inhibitors for MDS and secondary AML about 3 years ago. Three of these treatments are promising enough to test in Phase II or III clinical trials.

HMAs affect immune system function, so the combination of checkpoint inhibitors with HMAs could be effective. A Phase I/II clinical trial combined azacitidine with nivolumab (Opdivo), which inhibits PD-1. The study included 53 patients (median age 68) with AML that had not responded to previous treatment.
Almost half the patients had abnormal chromosomes that are associated with poor outcomes. After three cycles of treatment, 35% of patients responded. Of 11 patients with a complete response, 9 were still alive at 1 year.

In a study of 70 patients with relapsed AML, 35% responded to the combination of azacitidine and nivolumab. Although one fifth of patients developed side effects related to the immune system, these complications responded quickly to steroid treatment. Furthermore, 12 of these 14 patients were able to restart nivolumab treatment. In an ongoing study of this combination as first-line treatment in older patients (median age 73) with untreated AML, 11 of 16 have responded so far.

Patients with more T cells, a type of immune system cell, in the bone marrow before treatment seem to have a better chance of responding to azacitidine and nivolumab. Although mutations in ASXL1 are usually associated with poor outcomes in AML, the response and survival rates of patients with this mutation have been good. The researchers also found that levels of PD-1 before treatment had no effect on response rates.

Combinations of HMAs with Other Treatments

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Researchers are combining HMAs with other drugs to try to improve outcomes, including overall survival. Real-world patients (as opposed to those in clinical trials), even those with lower-risk MDS, typically survive for only a year and a half after HMAs no longer work for them.

One study assessed azacitidine (Vidaza) plus entinostat, which interferes with DNA’s ability to express and repress gene activity by inhibiting the histone deacetylase enzyme. Response rates were similar with azacitidine alone or with the combination, and patients treated with the combination had more serious side effects.

Combinations of HMAs with other histone deacetylase inhibitors (including pracinostat) also don’t seem to be better than HMAs alone.

A Phase II clinical trial compared azacitidine alone to azacitidine plus vorinostat (Zolinza, a histone deacetylase inhibitor) and azacitidine plus lenalidomide (Revlimid, a biologic agent that slows down the growth of blood vessels that feed abnormal cells). In this study in 277 patients with higher-risk MDS or chronic myelomonocytic leukemia (CMML), response rates for azacitidine plus either lenalidomide or vorinostat were similar to those for azacitidine alone. However, they were higher for patients with CMML treated with azacitidine plus lenalidomide. Dr. Sekeres suspects that the sample wasn’t large enough to show whether people treated with one of the combination regimens lived longer than those treated with azacitidine alone.

Although side effect rates were similar for all three treatments, patients treated with one of the combinations were much more likely to stop treatment because of side effects or complications. Also, doctors changed the doses of the combination treatments in ways that weren’t permitted by the protocol more often than for azacitidine alone. This might have affected the efficacy results for the combination treatments.

Immune checkpoint inhibitors might be effective in MDS. The immune checkpoint protein PD-1 and its ligands PD-L1 and PD-L2 help cancer cells escape the immune system. HMAs upregulate PD-1, PD-L1, and PD-L2 in MDS. Pembrolizumab (Keytruda) blocks the interaction between PD-1 and its ligands and restores the ability of T cells in the immune system to block tumor cell growth. In a study in 27 patients with MDS that had stopped responding to HMAs, 4 patients responded to pembrolizumab treatment and 14 had stable disease.

A survey of doctors and patients found that a larger proportion of doctors than patients think that patients’ lives are better because of the treatments that these doctors prescribed and that patients are glad that they received these treatments. At least twice as many doctors think that the treatments they prescribe make their patients too tired or too sick to continue and that side effects interfere with regular activity. In contrast, more patients than doctors believe that their treatment is uneventful and that getting their treatment is easy.
Dr. Sekeres believes that doctors might be stopping treatments too soon because they think that their patients are experiencing side effects that patients themselves don’t think they are having.

New Therapies for Anemia in Low-Risk MDS

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Patients with anemia have low levels of red blood cells or hemoglobin, a protein in red blood cells that transports oxygen. Anemia is common in MDS because the bone marrow doesn’t make enough healthy red blood cells. It can cause fatigue and low levels of energy.

The most common treatment for anemia in low-risk MDS consists of erythropoietin-stimulating agents (ESAs). These drugs can delay the need for red blood cell transfusions. But if a patient doesn’t respond to ESAs or if the ESAs stop working, treating anemia can be challenging.

Some ESAs for anemia in low-risk MDS are being studied. For example, an international Phase III clinical trial compared the efficacy and safety of epoetin alfa (Procrit or Epogen), an ESA, to placebo in 130 patients (median age 75) with low-risk or intermediate-1-risk MDS. Red blood cell counts returned to normal in 32% of the epoetin alfa group and 4% of the placebo group. The proportion of patients needing red blood cell transfusions dropped from 52% before the study to 25% by week 24 in the epoetin alfa group. Epoetin alfa was as safe as placebo.

A patient is most likely to respond to epoetin alfa if his or her blood level of erythropoietin, a hormone that helps the bone marrow form red blood cells, is below 200 units per liter, and the patient has had no red blood cell units transplanted.

Another Phase III clinical trial evaluated darbepoetin alfa (Aranesp), an ESA, for 24 weeks in 147 patients with low-risk or intermediate-1-risk MDS. Darbepoetin alfa reduced the number of transfusions that patients needed significantly compared with placebo. Eleven patients (14.7%) treated with darbepoetin and none treated with placebo had an erythroid response, meaning that their red blood cell counts returned to normal. This response rate might seem surprisingly low. But it is due to the complicated study protocol that required doctors to interrupt treatment at certain points. In the real world, darbepoetin response rates are at least as high as, if not higher than, those of other ESAs.

Instead of an ESA, a third Phase III study assessed the effects of lenalidomide (Revlimid) in 205 patients with lower-risk del(5q) MDS who needed regular red blood cell transfusions to treat their anemia. Significantly more patients stopped needing transfusions for at least 26 weeks with either 10 mg or 5 mg lenalidomide than with placebo. In another study, 27 patients with lower-risk del(5q) who needed regular transfusions halted lenalidomide treatment when they stopped needing the transfusions, which was safe and didn’t lead to disease progression. Lenalidomide seems to work best in patients who have del(5q) MDS and erythropoietin levels of 100 units per liter or less. However, patients who have MDS but not del(5q) don’t respond to lenalidomide for long—less than a year on average.

Luspatercept is an investigational drug that increases red blood cell levels in patients who have anemia due to MDS. A Phase II clinical trial assessed various doses of this drug in 73 patients (median age of 72 years) with lower-risk MDS. Sixteen of 22 patients (73%) who had needed fewer units of transfused red blood cells before the study and were treated for more than 3 months had increased red blood cell counts and hemoglobin levels, as did 16 of 20 (80%) of those who had needed more units of transfused red blood cells. Furthermore, 17 of 28 patients (61%) who had needed red blood cell transfusions before the study stopped needing them for at least 8 weeks after 3 months of luspatercept treatment. Response rates were highest in patients with erythropoietin levels of 500 units per liter or less and those who had an SF3B1 mutation. Most side effects were mild.

MEDALIST is an ongoing Phase III study of luspatercept in patients with very low-risk, low-risk, or intermediate-risk MDS with ring sideroblasts who need red blood cell transfusions. The patients have not responded or stopped responding to previous ESA treatments or their erythropoietin levels are higher than 200 units per liter.
Treatments for Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN)

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MDS/MPN is a disease of the blood and bone marrow with features of both MDS and myeloproliferative diseases. The most common form of MDS/MPN is chronic myelomonocytic leukemia (CMML). In this disease, abnormal blood cells (known as myeloblasts and myelocytes) accumulate in the bone marrow and other organs, and they interfere with the production of healthy blood cells.

Most patients with CMML have mutations in at least one of a small group of genes, including TET2, ASXL1, and SRSF2. On average, patients survive just 32 months after diagnosis. Azacitidine (Vidaza), the standard treatment for MDS, doesn’t benefit patients with CMML, even though this treatment has Food and Drug Administration approval for use in this disease.

Because the disease has no cure, doctors can choose two types of treatment: those based on whether the patient has lower-risk or higher-risk CMML and those designed to reduce symptoms. Dr. Padron believes that both types of treatment are needed.

Very little evidence is available on stem cell transplantation for CMML. But based on what happens in other bone marrow failure syndromes, Dr. Padron recommends considering stem cell transplantation for higher-risk CMML based on 10 retrospective studies showing that this procedure prolongs survival. This is the only treatment that he chooses based on whether the patient’s CMML is lower or higher risk.

All of the other treatments Dr. Padron uses focus on reducing symptoms. Although CMML is always lethal in his patients, many patients have no symptoms. He usually starts treatment when they have symptoms caused by shortages of certain types of blood cells or myeloproliferative disease (such as weakness, fatigue, and loss of appetite).

If the patient’s symptoms are similar to those of MDS, Dr. Padron tends to use the hypomethylating agents azacitidine (Vidaza) or decitabine (Dacogen). There isn’t enough evidence yet to tell whether one of these drugs is better than the other for CMML. If the symptoms are more like those of myeloproliferative diseases, he uses cytoreductive chemotherapy drugs, which reduce the high numbers of blood cells in the patient’s bone marrow.

Studies are ongoing of different treatments in CMML. In the Phase II component of a Phase I/II clinical trial, for example, 46% of 49 patients with CMML responded to treatment with ruxolitinib (a type of drug known as a JAK inhibitor), and patients survived for a median of 28 months from the start of treatment.

Emerging Agents for Secondary Acute Myelogenous Leukemia

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Secondary acute myelogenous leukemia (AML) happens when MDS or another blood cancer progresses or because of previous chemotherapy or radiation treatment for an unrelated disease. About 15–20% of all cases of AML might be secondary.

Patients with secondary AML have a higher risk than those with primary AML of chromosome abnormalities associated with poor outcomes. Also, patients with secondary AML tend to be older, are more likely to have other diseases and conditions that affect their health, and are less likely to be treated with intensive chemotherapy. The standard treatments for primary AML are inadequate for secondary AML.

Several new therapies are being studied for secondary AML that don’t include the hypomethylating agents azacitidine (Vidaza) or decitabine (Dacogen). CPX-351 (Vyxeos) is a combination of two chemotherapy drugs, daunorubicin and cytarabine. In a Phase III clinical trials in 309 patients aged 60–75, 34 of 52 patients (65%) with secondary AML who subsequently had a stem cell transplant were still alive after about one and a half years, compared with 13 of 39 patients (33%) treated with traditional cytarabine and daunorubicin.
CPX-351 is now the only treatment for secondary AML with Food and Drug Administration (FDA) approval.

Older patients don’t always do well with stem cell transplantation, even though this procedure is the most effective treatment in many cases. But more people treated with CPX-351 did well after transplantation than those in the comparison group. Also, CPX-351 seems to be safer than the chemotherapy combination. But although the drug is approved for patients of all ages, it’s only been studied in patients older than 60. So whether this drug works in younger patients isn’t clear. Another question is whether patients with MDS would benefit from CPX-351.

Venetoclax (Venclexta) inhibits the Bcl-2 protein, which stops cells from dying. It has FDA approval for chronic lymphocytic leukemia. A Phase I/II open-label study combined venetoclax with low-dose cytarabine in 71 patients (median age 74 years) with previously untreated AML. Of these patients, 26% achieved a complete response, 36% had a complete response with incomplete blood cell count recovery, and 2% had a partial response. All patients who achieved a complete response were still alive a year later. However, those with secondary AML or who had been treated with HMAs before had lower complete response rates than those whose AML hadn’t been treated before.

Glasdegib is an experimental drug that disrupts the hedgehog signaling pathway. The hedgehog protein family controls cell growth and survival and plays important roles in the development of embryos. In a study of 132 patients in their mid-70s with previously untreated AML or high-risk MDS, median survival with low-dose cytarabine and glasdegib was almost twice as long, at 8 months, than with cytarabine alone, 5 months. The combination also prolonged survival in those with good- or intermediate-risk disease and those with poor-risk disease. The treatment had an acceptable safety profile.
YOUR GIFT IS IMPORTANT

90% of funding received is used for education and research.

Individuals and private foundation funding is critical to our ability to provide quality education, engage the top experts in the field and utilize the best of technology.

Pharmaceutical and biotech companies with drugs and treatments for bone marrow failure disease provide educational grants that help support our publications, webinars and conferences.

MAXIMIZE YOUR GIVING

Monthly giving supports our services efficiently and easily:

- $10 per month sends information packets to 20 patients
- $25 per month helps support a leading expert to present an educational webinar
- $100 per month helps support one disease specific session at a Patient & Family or health professional conference

OPPORTUNITIES FOR MAJOR IMPACT

- $60,000 supports a 2-year research grant
- $7,500 supports 3 medical experts at a full day education conference
- $3,000 supports family visits to a specialist

OTHER WAYS TO SUPPORT PATIENTS AND FAMILIES

- Organize or participate in a local event such as March for Marrow and Golf for Marrow.
  Contact Margaret at (301) 279-7202 x103 or fitzgerald@aamds.org

- Designate AAMDSIF as a beneficiary in your estate planning or IRA account in your yearly distribution.
  Contact Serap at (301) 944-1072 or akisoglu@aamds.org

- Give stocks as a gift to AAMDSIF.
  Contact your broker or investment advisor

- Increase your impact if your company has a Matching Gift program.
  Ask your Human Resources department for necessary forms

- Designate AAMDSIF in your workplace giving or state giving campaign.
Many FREE services and programs are available to anyone impacted by, or just interested in, bone marrow failure diseases:

- **Personalized Support** from Information Specialists at (800) 747-2820 or help@aamds.org

- **Educational Materials** on diseases and treatments at www.aamds.org/materials

- **Global Educational Materials** in Spanish, French, German and Portuguese at www.aamds.org/global-education

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- **Patient and Family Conferences** connecting patients with professionals and building community with each other at www.aamds.org/conferences

- **Print and Electronic Newsletters** with the latest news in treatment and research

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- **Peer Support Network** staffed by specially-trained volunteers who listen and offer guidance at www.aamds.org/support-networks

- **Community Connections** support groups run by volunteers for fellowship and support

Looking for a way to help? Volunteer and help raise awareness for bone marrow failure diseases! Your work can directly help newly diagnosed patients and their families. Call 301-279-7202 or email fitzgerald@aamds.org to learn how you can get involved.

- **Online Supporters** who hold digital fundraisers in their community or workplace

- **Event Organizers** who plan “March for Marrow” fundraising walks or other events

- **Awareness Campaigners** who teach their community about bone marrow failure

- **Community Connections leaders** who coordinate local patient support groups

Learn more about volunteering at ambassadors@aamds.org or (301) 279-7202 x122.