MDS Genomics: Providing ‘Street View’ Directions of Disease

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Dr. Cogle is an associate professor of medicine at the University of Florida, Gainesville. He has clinical and research expertise in myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), and allogeneic hematopoietic cell transplant. Dr. Cogle leads a research laboratory that studies the biology of MDS and AML, and his group has successfully translated his discoveries into new treatments for patients. Dr. Cogle’s goal is to find cures for MDS and leukemia, educate patients and providers about the distinct heterogeneity of these diseases, educate policy makers that blood cancers are a public health concern, and advocate for patients to get the best care possible.

Please explain what is meant by genomics and genomic navigation, and how genomics differs from genetics.

“Genomics” is the umbrella term for any study of chromosomes, genes, and DNA in a cell. “Genetics” is a more specific term that pertains to the study of just the 23,000 genes in a cell. The term “genomics” is a better fit when talking about MDS because MDS doctors look at whole chromosomes and specific genes when trying to understand each patient’s disease. DNA, housed in the nucleus of each cell, acts as the software program directing how cells grow, divide, sleep or die. Sometimes DNA gets damaged after exposure to toxins or as a normal consequence of aging. If a blood stem cell suffers DNA damage involving a gene important for blood production, then this can result in MDS. By using new machines that read DNA, we have discovered that MDS cells contain multiple genomic problems and that there is great variability from patient to patient on which genes are damaged.

We compare the DNA of MDS cells to the DNA of normal blood cells, and then we notice where the MDS cells have changed or mutated from their normal state. Depending on what DNA in the MDS cells have mutated, this can tell us how aggressive or responsive to treatment the MDS cells will be. Genomic “navigators” such as genetic counselors and doctors with specialized knowledge of cancer gene mutations help patients and other doctors understand the clinical significance of the genomic mutations. They provide information about disease origin, prognosis, treatment options, and risk of passing on blood problems to children.

In the past with MDS, the way we approached it was like taking a trip with a poorly detailed paper map showing only major highways and cities and vast expanses of blank space. Making a decision on which of the few roads to take was simple, but the small number of roads rarely took us where we needed to go. However, with the new genomic information we have, our MDS map is filling in, much like what you see with detailed online maps. We now have “street view” images, where we are seeing MDS gene mutations, chromosome breakages, methylation patterns, and other molecular level details like we have never been able to before. Our new MDS maps are much more detailed, specific to the patient, and prompt us to talk about more than the few approved drugs that are available for treating MDS. Another impact of new molecular information is the power it brings...
in cinching the diagnosis of MDS. In the MDS clinic, we often have a very basic question: does the patient actually have MDS? A simple blood draw could help confirm the diagnosis when using the new DNA reading machines. Finally, this new understanding of MDS genomics is helping predict aggressiveness of the disease and chances of responding to treatment. Certain MDS mutations in genes (like the gene TP53 that is buried in chromosome 17) indicate more aggressive disease and may call for more aggressive treatment such as allogeneic hematopoietic cell transplant.

What specific advantages are there when genomics is applied to MDS?

There are situations where patients and doctors aren’t completely sure if the patient has MDS or not. The patient may have low blood counts, and their physician has ruled out a list of all other possible causes, such as bleeding and deficiencies in vitamins and minerals. The bone marrow biopsy may suggest MDS, but the chromosome testing may not detect an abnormality, which happens in half of MDS patients. In this common situation, patients and doctors are rightfully frustrated about whether MDS is present or not. Using the new DNA reading machines can help patients and doctors decide whether the patient actually has MDS. Sometimes a simple blood test can pick up MDS gene mutations, and this will confirm the diagnosis.

Once we identify the MDS genetic mutations for each patient, at that point, the enemy is marked and we can follow those enemy clones by looking for their markings in subsequent blood and bone marrow specimens. Enemy identification and tracking is one important facet of ‘personalized medicine.’ Genomics is personalized in MDS because each MDS patient’s DNA damage is different than that of other patients.

The current MDS classification system, which is largely based on older light microscope technology, tries to lump together the many presentations of MDS into groups that doctors and patients can talk about in a clear manner. The number of classifications has grown steadily over the past several years out of frustration by MDS doctors in trying to honor the newly appreciated personalized nature of MDS with a continuing need for an organized system to clearly communicate the many subtypes of MDS. In the coming years, we will see more MDS genomic information included in the MDS classification system and this will bring even greater value to the MDS classification systems.

Can a patient see the results of this progress in the office/treatment setting?

If an MDS patient has certain genomic mutations in their blood cells that predict for aggressive disease, then those patients will be treated differently in the clinic. They may be seen more often in the clinic, have labs drawn more frequently, possibly require more blood transfusions, and may be offered chemotherapy or possibly an allogeneic hematopoietic cell transplant. A patient with lower-risk MDS genomics may be seen less often initially and is provided supportive care until evidence of disease progression. The intensity and activity of the care will be more proactive because of what was learned from the MDS genomic landscape.

What is important for health professionals treating MDS to know about test results from genomic cell analysis?

The first thing they should know is that there are now several pathology laboratories that just in the last few months have created new genetic testing panels for patients who are suspected to have or currently have MDS. I recommend that referring physicians consider sending a patient’s bone marrow aspirate or peripheral blood sample to one of these labs, in the event they want to rule in or rule out an MDS diagnosis. In addition, doctors may find helpful the extra information that MDS genetic testing brings to define prognosis or actionable mutations. As examples, genetic mutations in TP53 portend for a more therapy-resistant MDS, and if a patient has mutations in IDH1 or IDH2, then the patient may qualify for ongoing clinical trials of IDH inhibitors.

If hematology-oncology physicians receive a genomic report that is confusing (and many of them can be), I encourage the physician to contact an MDS specialist at one of the specialized MDS centers. The specialist will help clarify the genomic mutations and help determine if they are clinically meaningful. As an MDS specialist, I’m happy to help interpret reports because it gives me the satisfaction of making sure patients have as much information as possible to make their best treatment decision. I see a day soon when community hematologists-oncologists will be able to access MDS and leukemia specialists from afar for quick online consults and assistance in identifying relevant clinical trials. This could help patients by opening access to the latest data on molecular testing and pointing to cutting edge treatments.

What is most important for MDS patients and families to know about the present and potential applications of genomics in MDS?

It’s important for patients to ask their doctor for their MDS genomics report. Also, they should ask their doctors to spend time explaining how that information informs their diagnosis, prognosis, and treatment. Patients should ask questions to understand at least the broad brush strokes of what these reports mean and how that information forms the basis for a treatment strategy. Many patients are reticent to ask for this time because chromosomes, genes, and DNA can be confusing, and it takes time to explain normal function, let alone mutation, and we respect our doctors’ busy schedules. But patients need to know this information and its significance before they leave the doctor’s office.
Understanding MDS Treatment Response

Knowing the terms doctors use to describe how well drug treatments work can help you understand whether or not your therapy is effective.

The terms doctors often use to define degree of MDS treatment success are:

**Complete response (CR) means:**
- No blast cells are in the bloodstream. (Blast cells are young, immature blood cells.) The percent of blast cells in the bone marrow is at or near normal.
- Blood counts (red blood cells, white blood cells, and platelets) are also at or near normal. To be considered a CR, blood counts must remain at or near normal levels for at least four weeks.

**Partial response (PR) means:**
- No blast cells are in the bloodstream.
- The percent of blasts in the bone marrow has been reduced by at least half.
- Blood counts (red blood cells, white blood cells, and platelets) are at least halfway between where they started (baseline) and normal. To be considered a PR, blood count improvements must be maintained for at least four weeks.

**Improvement means:**
- It is not CR or PR, but there is a decrease in bone marrow blasts and/or an improvement in red blood cells, white blood cells, or platelets.

**Stable disease (SD) means:**
- It is not better or worse.

**Complete cytogenetic remission or cytogenetic response means:**
- No signs of a defective chromosome can be found. For example, when a test is done on a patient with chromosome 5q deletion MDS, and there are no signs of that abnormality, then that patient has achieved a complete cytogenetic remission.

**Transfusion independence means:**
- You no longer need blood transfusions of either red blood cells or platelets. Most studies formally define transfusion independence as eight weeks without the need for a transfusion. Reaching transfusion independence is important because it means you will avoid transfusion side effects such as iron overload, transfusion reactions, and infections, as well as the inconvenience of having to spend time getting transfusions.

Speaking Up Around the World

Did you know AA&MDSIF now has MDS patient information available in French, German, Italian, Portuguese, and Spanish?

Your Guide to Understanding MDS

Because patients are looking for answers to the many questions that arise when they are diagnosed with MDS, AA&MDSIF provides expert, reviewed medical information in our comprehensive MDS patient guide.

Video interviews with internationally recognized MDS experts discussing:

1. What is MDS?
2. How is MDS diagnosed?
3. What is the difference between supportive care and active treatment for MDS?
4. How are decisions made about the best approach to treat a patient?
5. What new treatments are on the horizon for MDS patients?

Log on to www.AAMDS.org/Global to see the videos and read or print the MDS patient guide in French, German, Italian, Portuguese, and Spanish!

Terms to Know

Our online glossary, (www.AAMDS.org/Glossary/Terms) helps you understand new words that describe your disease, and its diagnosis or treatment. For this edition of the MDS Connection, we define:

**Supportive Care**

Care given to improve the quality of life, or comfort, of a person with a chronic illness. Supportive care treats the symptoms rather than the underlying cause of a disease. Also called palliative care, or symptom management.

For more information on palliative care, be sure to see our webinar at www.AAMDS.org/Learn.
We’re Helping Doctors Help Patients with Our Updated Treating MDS Toolkit!

Upon hearing a diagnosis of MDS for the first time, many patients may not be able to understand what the disease is, their prognosis, or their treatment options. The Aplastic Anemia & MDS International Foundation has provided the Treating MDS Toolkit to approximately 5000 healthcare professionals across the country. This free patient education resource is designed to help doctors, nurses, and social workers teach patients about their MDS diagnosis, risk classification, and treatment options.

The updated 2014 Treating MDS Toolkit is now available! Among the updates are the addition of the Revised International Prognostic Scoring System (IPSS-R) and a new counseling guide grounded in a recent Cancer study examining perceptions of MDS and treatment effectiveness (Steensma et. al., 2014). Clear presentation of information and active engagement of patients in the management of their disease can help clarify misperceptions and improve patient understanding of MDS.

Tell your healthcare team to email toolkit@aaamds.org or call us at (800) 747-2820 to order a free copy of the newly revised Treating MDS Toolkit and complimentary copies of our 2014 patient guides.

Announcing the MDS Alliance

Originally conceived to address the problem of ageism in the treatment of older MDS patients, leading MDS patient advocacy organizations in North America and Europe have formed the MDS Alliance to better serve the global MDS patient and caregiver community and provide optimal care for all MDS patients worldwide. This new alliance will make it possible for more MDS patients and families to receive the most current and accurate information in multiple languages. Currently, information is on the AA&MDSIF Web site in English, French, German, Italian, Portuguese, and Spanish and may be accessed at www.AAMDS.org/Global.

AA&MDSIF was selected to serve as the convener and the administrative secretariat of this new organization. MDS Alliance members include the Aplastic Anemia & MDS International Foundation, the MDS Foundation, the Aplastic Anemia & Myelodysplasia Association of Canada, the Asociación Linfoma Mieloma y Leukemia, Leukämiehilfe Rhein-Main-MDS, and MDS-UK.

National Institutes of Health Supports Bone Marrow Failure Disease Research

Made up of 27 separate institutes and centers, the National Institutes of Health (NIH) is the nation’s medical research agency. For over a century, NIH scientists have paved the way for important discoveries that improve health and save lives. The NIH’s National Heart, Lung, and Blood Institute (NHLBI) provides global leadership for a research, training, and education program to promote the prevention and treatment of heart, lung, and blood diseases and enhance the health of all individuals. Under the direction of Dr. Neal Young, Chief of the Hematology Branch (and member of the AA&MDSIF Medical Advisory Board), NHLBI is currently supporting research studies related to bone marrow failure diseases.

MDS Webinars

The Affordable Care Act: What does it mean for Aplastic Anemia, MDS and PNH patients

Monday, October 6, 2014 • 2:00 PM ET

Speaker: Brendan Bietry
Director of External Relations/Bilingual Case Manager
Patient Advocate Foundation

During this session, we will discuss the new provisions and benefits mandated by the Affordable Care Act and how individuals can position themselves with the most optimal health insurance coverage to suit their particular needs. We will also detail benefit terminology, premium subsidy, and cost-sharing measures.

Bone Marrow Transplant for MDS and Other Bone Marrow Failure Diseases: Before, During, and After

Tuesday, November 11, 2014 • 3:00 PM ET

Speaker: Christopher Cogle, MD
Associate Professor of Medicine
University of Florida

Dr. Christopher Cogle will share vital information about transplants including how a patient prepares for a transplant, what happens during a transplant and what precautions should be taken immediately following a transplant. Information about locating a donor and when a transplant should be performed will also be discussed, along with an update on complications and other issues.
MDS Clinical Trials

Should you consider a clinical trial? Ask your doctor or contact the study coordinators for further information. Learn more in the Clinical Trials section of www.AAMDS.org. If you are interested in learning more about clinical trials, search for myelodysplastic syndromes studies actively recruiting patients on www.ClinicalTrials.gov. Below is one example of the many open studies for MDS patients in the United States.

<table>
<thead>
<tr>
<th>Title</th>
<th>Study Purpose</th>
<th>Study Coordinator</th>
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<tbody>
<tr>
<td>Selinexor With Fludarabine and Cytarabine for Treatment of Refractory or Relapsed Leukemia or Myelodysplastic Syndrome</td>
<td>The purpose of this study is to test the safety of selinexor (KPT-330) and to find the highest dose of selinexor (KPT-330) that can be given safely when it is combined with two chemotherapy drugs (fludarabine and cytarabine). This study will be done in two parts: Phase I and Phase II. The goal of Phase I is to find the highest tolerable dose of selinexor (KPT-330) that we can give to patients with leukemia or MDS, when it is combined with fludarabine and cytarabine. The goal of the Phase II portion of the study is to give the highest dose of selinexor (KPT-330) in combination with fludarabine/cytarabine that was found in Phase I to be safe for children with leukemia or MDS. The investigators will examine the effect of this combination treatment.</td>
<td>This study is being conducted at St. Jude Children’s Research Hospital. Contact: Jeffrey E. Rubnitz, MD, PhD, (866) 278-5833, <a href="mailto:info@stjude.org">info@stjude.org</a>. Please refer to this study by its ClinicalTrials.gov identifier: NCT02212561</td>
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Diagnosis, Treatment, and Managing the New Normal

Agenda

(SEE WEBSITE FOR MORE DETAILED AGENDA)

7:30 - 8:30 AM | Check-in and Breakfast
8:30 - 8:50 AM | Conference Welcome
9:00 - 10:30 AM | Session A: Your Life Changing Phase of Diagnosis
10:30 - 10:45 AM | Break
10:45 - 12:15 PM | Session B: Your Life Changing Phase of Treatment
12:15 - 1:45 PM | Lunch and AA&MDSIF Program
2:00 - 3:00 PM | Session C: The Life Long Phase of Living with a Chronic Disease
3:00 - 3:15 PM | Break
3:15 - 5:00 PM | Session D: Finding Strength in Numbers - Peer Support Forums

Special thanks to Celgene Corporation, Amgen Inc., and Novartis Oncology for providing unrestricted educational grants to support this program.

NO INTERNET ACCESS AT HOME?
Internet-connected computers are found in many locations, including:
- Retirement homes
- Apartment community rooms
- Public libraries
- Senior centers

And it’s almost certain you know someone (relatives, neighbors, friends) who is connected!

Contact Us
help@aamds.org (301) 279-7202 or (800) 747-2820
Facts for Life
Tips and Online Resources for Managing the New Normal of MDS

MDS is typically diagnosed in older populations, but even prior to your diagnosis, you may have noticed some limitations to your lifestyle. MDS may cause a further decrease in your physical abilities or interest in favorite activities. Here are a few tips and resources to help you manage your new normal with MDS:

• It is important to discuss your feelings openly with your friends, relatives, and doctors, and it is okay to let someone know you are tired or no longer have interest in a particular activity.

• Eating a healthy diet may help you avoid other medical conditions linked to poor nutrition. Some MDS treatments may dull your appetite, so you should make the most of the calories you take in. Many of the hospitals where you are treated have registered dietitians to help you learn more about the best kinds of foods to eat.

• Exercise has many benefits that may help you withstand the physical and emotional stresses of MDS and its treatment, such as improving overall fitness and increasing your energy level.

• MDS treatments can add to the fatigue you already feel from cancer. In fact, fatigue is the most frequently experienced symptom of cancer and cancer treatments. It is important to allow your body time to rest. This will help your body have the strength to heal itself. Prioritize the things you need to do, and focus on the most important ones. Scheduling times throughout the day when you can rest may help prevent becoming overly tired.

Living Well Webinars

We offer many online resources on living well with MDS at www.AAMDS.org/Learn.

| Managing Side Effects to Improve Quality of Life with Myelodysplastic Syndromes |
| Managing Beyond Medicine in Bone Marrow Failure Disease: Building Resilience |
| Relax, Relate, Release: Restoring Your Life Balance When Bone Marrow Failure Disrupts Your Life |
| Sexuality and Bone Marrow Failure Disease: A Conversation About Sex, Sexuality and Bone Marrow Failure Disease |
| Living Well with MDS: Optimizing Emotional Health |
| Nutrition in Bone Marrow Failure Disease |
| Managing Bone Marrow Failure Disease with Complementary and Alternative Medicine and Integrative Medicine |

HOPE IS IN THE FUTURE
It’s not too early to consider making your year-end gift and investing the future.

AA&MDSIF is:
• Advancing research to find better treatments and a cure
  ♦ Awarding nearly $4 million in research grants to 67 researchers
  ♦ Hosting educational programs for physicians, nurses and researchers
• Supporting patients and families living with MDS
  ♦ Connecting you to others through regional conferences, live webcasts, and online learning programs
  ♦ In a strong partnership with you today, tomorrow, and always

You can make a difference today with a one-time or monthly gift at www.AAMDS.org/DonateNow or by mail:

Aplastic Anemia & MDS International Foundation
100 Park Avenue, Suite 108
Rockville, MD 20850

Your gift will go to immediate work to help fight MDS.

Thank you.
Story of Hope

Barbara Weinstein - “Being able to help and empower people really appealed to me.”

At AA&MDSIF, we deeply appreciate the vital role nurses play in patient care – they are wonderful listeners, educators, motivators, and knowledgeable professionals who make a difference every day in the lives of so many patients and families. This past May, in celebration of National Nurses Week, we asked patients to tell us about their favorite nurse. Four different individuals wrote to tell us about one particular nurse - Barbara Weinstein, RN, BSN, CCRP, a research nurse specialist at the National Heart, Lung, and Blood Institute (NHLBI) – and what she has meant to them.

Wanda was the first to write to us: “Since day one, I have felt great comfort in knowing that Barbara is my nurse. She has always been there whether it was over the phone or in person, with all the answers to any questions I may have. When anybody is going through a life changing experience ... it’s nice to have someone in your life other than family who really cares.”

A longtime member of the AA&MDSIF Patient Education Council, Barbara talked to us about why she went into nursing and how she ended up as a research nurse at the National Institutes of Health (NIH). “I had not considered nursing at first, but my younger sister was going into nursing, so I decided to do that, too. I found as I got further into the program, I was really enjoying what I was doing. I saw the possibilities of what a nurse could do. Being able to help and empower people really appealed to me.”

Barbara’s career as a nurse started on a medical-surgical nursing unit at a small community hospital in New Jersey, 27 years ago. She subsequently worked as a charge nurse at Brigham & Women’s Hospital in Boston, on a cardiothoracic surgical step-down unit at the Washington Hospital Center, followed by the Occupational Medical Service at the NIH. When a position opened up in the NHLBI Hematology Branch 10 years ago, Barbara stepped into the role that she has so successfully pursued ever since. Aplastic anemia patient Mary is glad that she did! “She was welcoming and comforting from day one. She makes me feel she is my advocate, and Barbara is always available to respond to my needs or to alleviate fears. She is extremely kind and thoughtful.”

Barbara enjoys the multitasking, behind-the-scenes work required by her job as a research nurse as well. She spends a lot of time on the phone talking to patients who call with questions and concerns. They call Barbara to be sure everything is okay and to find out what to do. Nadia writes, “She entered my life during a very frightening period for me. However busy she is, she has always made time for me. She is a personal, warm, and encouraging contact when I see her. Barbara gets answers to my questions and concerns from afar. I feel like I have a real ally in her, and that is so important when dealing with a serious disease.” Sally adds, “I believe that NIH and Barbara Weinstein saved my husband’s life. Barbara is efficient, pleasant, and kind - everything one would want in a nurse and friend.”

Barbara truly enjoys her interactions with patients and their families. She recalls how, recently, one of her patients said, “You listen to me and you heard me.” She notes, “This reminder of why I am here and the impact I have on patients’ lives always puts a smile on my face.”

We are smiling, too! AA&MDSIF thanks Barbara for all that she and her many colleagues in the nursing field do to help patients and families with bone marrow failure diseases.

AA&MDSIF Annual Report Now Available

Our 2013 Annual Report tells the stories about our programs and services through the eyes and words of the people we’ve served, helped, or supported, as well as those who have helped us. These stories are examples of what we do, how we serve, and what you have helped make possible through your confidence in us and your partnership in our work. Learn about the growth of our programs and services in 2013. Download the Annual Report at www.AAMDS.org/AnnualReports.

Thank you for all you have helped us to accomplish.

HOPE has many faces

Are you a federal employee or do you know someone who is?

Designate CFC #10302.

Your gift makes a difference.