This document is only a SHORT PREVIEW of the Medifocus Guidebook on Myelodysplastic Syndromes. It is intended primarily to give you a general overview of the format and structure of the Guidebook as well as select pages from each major Guidebook section listed in the Table of Contents.

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1 - Background Information

Introduction

Chronic or life-threatening illnesses can have a devastating impact on both the patient and the family. In today's new world of medicine, many consumers have come to realize that they are the ones who are primarily responsible for their own health care as well as for the health care of their loved ones.

When facing a chronic or life-threatening illness, you need to become an educated consumer in order to make an informed health care decision. Essentially that means finding out everything about the illness - the treatment options, the doctors, and the hospitals - so that you can become an educated health care consumer and make the tough decisions. In the past, consumers would go to a library and read everything available about a particular illness or medical condition. In today's world, many turn to the Internet for their medical information needs.

The first sites visited are usually the well known health "portals" or disease organizations and support groups which contain a general overview of the condition for the layperson. That's a good start but soon all of the basic information is exhausted and the need for more advanced information still exists. What are the latest "cutting-edge" treatment options? What are the results of the most up-to-date clinical trials? Who are the most notable experts? Where are the top-ranked medical institutions and hospitals?

The best source for authoritative medical information in the United States is the National Library of Medicine's medical database called PubMed®, that indexes citations and abstracts (brief summaries) of over 7 million articles from more than 3,800 medical journals published worldwide. PubMed® was developed for medical professionals and is the primary source utilized by health care providers for keeping up with the latest advances in clinical medicine.

A typical PubMed® search for a specific disease or condition, however, usually retrieves hundreds or even thousands of "hits" of journal article citations. That's an avalanche of information that needs to be evaluated and transformed into truly useful knowledge. What are the most relevant journal articles? Which ones apply to your specific situation? Which articles are considered to be the most authoritative - the ones your physician would rely on in making clinical decisions? This is where Medifocus.com provides an effective solution.

Medifocus.com has developed an extensive library of MediFocus Guidebooks covering a wide spectrum of chronic and life threatening diseases. Each MediFocus Guidebook is a
high quality, up-to-date digest of "professional-level" medical information consisting of the most relevant citations and abstracts of journal articles published in authoritative, trustworthy medical journals. This information represents the latest advances known to modern medicine for the treatment and management of the condition, including published results from clinical trials. Each Guidebook also includes a valuable index of leading authors and medical institutions as well as a directory of disease organizations and support groups. MediFocus Guidebooks are reviewed, revised and updated every 4-months to ensure that you receive the latest and most up-to-date information about the specific condition.
**About Your MediFocus Guidebook**

**Introduction**

Your *MediFocus Guidebook* is a valuable resource that represents a comprehensive synthesis of the most up-to-date, advanced medical information published about the condition in well-respected, trustworthy medical journals. It is the same type of professional-level information used by physicians and other health-care professionals to keep abreast of the latest developments in biomedical research and clinical medicine. The *Guidebook* is intended for patients who have a need for more advanced, in-depth medical information than is generally available to consumers from a variety of other resources. The primary goal of a *MediFocus Guidebook* is to educate patients and their families about their treatment options so that they can make informed health-care decisions and become active participants in the medical decision making process.

The *Guidebook* production process involves a team of experienced medical research professionals with vast experience in researching the published medical literature. This team approach to the development and production of the *MediFocus Guidebooks* is designed to ensure the accuracy, completeness, and clinical relevance of the information. The *Guidebook* is intended to serve as a basis for a more meaningful discussion between patients and their health-care providers in a joint effort to seek the most appropriate course of treatment for the disease.

**Guidebook Organization and Content**

**Section 1 - Background Information**

This section provides detailed information about the organization and content of the *Guidebook* including tips and suggestions for conducting additional research about the condition.

**Section 2 - The Intelligent Patient Overview**

This section of your *MediFocus Guidebook* represents a detailed overview of the disease or condition specifically written from the patient's perspective. It is designed to satisfy the basic informational needs of consumers and their families who are confronted with the illness and are facing difficult choices. Important aspects which are addressed in "The Intelligent Patient" section include:

- The etiology or cause of the disease
- Signs and symptoms
- How the condition is diagnosed
- The current standard of care for the disease
- Treatment options
Section 3 - Guide to the Medical Literature
This is a roadmap to important and up-to-date medical literature published about the condition from authoritative, trustworthy medical journals. This is the same information that is used by physicians and researchers to keep up with the latest developments and breakthroughs in clinical medicine and biomedical research. A broad spectrum of articles is included in each MediFocus Guidebook to provide information about standard treatments, treatment options, new clinical developments, and advances in research. To facilitate your review and analysis of this information, the articles are grouped by specific categories. A typical MediFocus Guidebook usually contains one or more of the following article groupings:

- **Review Articles:** Articles included in this category are broad in scope and are intended to provide the reader with a detailed overview of the condition including such important aspects as its cause, diagnosis, treatment, and new advances.

- **General Interest Articles:** These articles are broad in scope and contain supplementary information about the condition that may be of interest to select groups of patients.

- **Drug Therapy:** Articles that provide information about the effectiveness of specific drugs or other biological agents for the treatment of the condition.

- **Surgical Therapy:** Articles that provide information about specific surgical treatments for the condition.

- **Clinical Trials:** Articles in this category summarize studies which compare the safety and efficacy of a new, experimental treatment modality to currently available standard treatments for the condition. In many cases, clinical trials represent the latest advances in the field and may be considered as being on the "cutting edge" of medicine. Some of these experimental treatments may have already been incorporated into clinical practice.

The following information is provided for each of the articles referenced in this section of your MediFocus Guidebook:

- Article title
- Author Name(s)
- Institution where the study was done
- Journal reference (Volume, page numbers, year of publication)
Linking to Abstracts: Most of the medical journal articles referenced in this section of your MediFocus Guidebook include an abstract (brief summary of the actual article) that can be accessed online via the National Library of Medicine's PubMed® database. You can easily access the individual abstracts online via PubMed® from the "electronic" format of your MediFocus Guidebook by clicking on the corresponding URL address that is provided for each cited article. If you purchased a printed copy of a MediFocus Guidebook, you can still access the article abstracts online by entering the individual URL address for a particular article into your web browser.

Section 4 - Centers of Research
We've compiled a unique directory of doctors, researchers, medical centers, and research institutions with specialized research interest, and in many cases, clinical expertise in the management of the specific medical condition. The "Centers of Research" directory is a valuable resource for quickly identifying and locating leading medical authorities and medical institutions within the United States and other countries that are considered to be at the forefront in clinical research and treatment of the condition.

Inclusion of the names of specific doctors, researchers, hospitals, medical centers, or research institutions in this Guidebook does not imply endorsement by Medifocus.com, Inc. or any of its affiliates. Consumers are encouraged to conduct additional research to identify health-care professionals, hospitals, and medical institutions with expertise in providing specific medical advice, guidance, and treatment for this condition.

Section 5 - Tips on Finding and Choosing a Doctor
One of the most important decisions confronting patients who have been diagnosed with a serious medical condition is finding and choosing a qualified physician who will deliver high-level, quality medical care in accordance with currently accepted guidelines and standards of care. Finding the "best" doctor to manage your condition, however, can be a frustrating and time-consuming experience unless you know what you are looking for and how to go about finding it. This section of your Guidebook offers important tips for how to find physicians as well as suggestions for how to make informed choices about choosing a doctor who is right for you.

Section 6 - Directory of Organizations
This section of your Guidebook is a directory of select disease organizations and support groups that are in the business of helping patients and their families by providing access to information, resources, and services. Many of these organizations can answer your questions, enable you to network with other patients, and help you find a doctor in your geographical area who specializes in managing your condition.
2 - The Intelligent Patient Overview

MYELODYSPLASTIC SYNDROMES

Introduction to Myelodysplastic Syndromes

Bone marrow is a semi-liquid tissue that is inside many bones such as the backbones, shoulder blades, ribs, pelvis, and stomach. The hematopoietic (blood-forming) stem cells in the bone marrow are responsible for producing and forming new blood cells. Erythrocytes, or mature red blood cells, help transport oxygen. White blood cells, (leukocytes) are one of the most critical elements of the circulatory system because they help protect the body against infections caused by foreign microorganisms such as bacteria and viruses. Platelets are the smallest cells in the blood and are formed in the red bone marrow. They help control bleeding and bruising.

The term myelodysplastic syndromes (MDS) is used to describe a broad range of chronic myeloid (bone marrow) cancers characterized by ineffective hemotopoiesis (production of blood cells) and the dysplastic (abnormal) appearance of bone marrow cells when observed under a microscope. MDS is the most commonly diagnosed bone marrow failure syndrome in adults.

MDS is a chronic disorder that gradually reduces the body's ability to produce red blood cells, white blood cells, and platelets. This can lead to a variety of problems that can be readily diagnosed by routine blood tests such as:

- Anemia - abnormally low numbers of red blood cells that develops in up to 85% of patients with MDS.
- Thrombocytopenia - abnormally low number of platelets that occurs in about 30% to 45% of MDS patients.
- Neutropenia - abnormally low numbers of white blood cells can be found in up to 40% of MDS cases.

People with myelodysplastic syndromes have a risk of the disease progressing to acute myeloid leukemia (AML), which is a bone marrow malignancy. Some studies suggest that AML is a natural progression of MDS and not a separate disease. In some people, MDS may gradually progress over a period of many years while in others it progresses rapidly to AML.

The risk of myelodysplastic syndromes increases with age as the disease commonly affects older people between the ages of 58 and 75. About 85% of all patients diagnosed with MDS are older than 60 years. The disease is rarely observed in young adults.

The actual incidence and prevalence of MDS have been difficult to estimate accurately. According to data from the U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER), which has captured MDS cases since 2001, about 10,000 to 12,000 new cases of
MDS are diagnosed in the United States each year. This translates to about 3 to 4 cases per 100,000 persons per year. An analysis of Medicare claims in conjunction with the SEER data, however, suggests that the actual incidence of MDS in the U.S. may be in the range of 30,000 to 40,000 new cases per year.

The incidence of myelodysplastic syndromes in children is only 5% to 7% of all pediatric hematologic malignancies. It has been reported that up to 17% of childhood AML may result from a prior myelodysplastic phase. About 2% to 3% of all cases of juvenile leukemia are associated with juvenile myelomonocytic leukemia.

In general, MDS is divided into the following two broad categories:

- **Primary or idiopathic MDS** - represents about 90% of all MDS cases that results from age-related injury to hemopoietic (blood-forming) stem cells.
- **Secondary or therapy-related MDS** - represents up to 15% of cases and is the result of cancer-related chemotherapy or radiation therapy.

### What Causes Myelodysplastic Syndrome?

The exact causes of MDS remain unknown. Myelodysplastic syndromes are referred to as "clonal disorders" and it is believed that a genetic progression or evolution occurs in patients with MDS. The first step, called *initiation*, involves an "attack" on hematopoietic stem cells (actively dividing cells that are the source of blood cells). The second step, called *tumor promotion* or *clonal expansion*, is characterized by ineffective hematopoiesis (the hampering of normal formation and development of blood cells in the bone marrow) and typically a high rate of cell death. The third step, called *malignant transformation*, is characterized by the increase in leukemia blast cells and the progression to AML. These steps may also be characterized as pre-MDS phase, early-MDS phase, and late-MDS phase.

Certain gene mutations, specifically RAS, PTPN11, FLT3, and genes involved in DNA repair, have also been linked to the development of MDS. However, MDS is not caused by a virus nor is it contagious. In childhood MDS, it is believed that some conditions such as Fanconis anemia, Shwachman's syndrome, and Down's syndrome increase the child's risk of developing MDS. About 30% of children with myelodysplastic syndromes are reported to have an inherited genetic disorder.

Researchers have also determined that some people with myelodysplastic syndromes may inherit a genetic predisposition to MDS that may be triggered by cumulative exposure to external or environmental factors such as:

- Radiation or chemotherapy
- Smoking
- Pesticides
- Organic chemicals and solvents
- Benzene
- Heavy metals
Research has also demonstrated that patients with aplastic anemia and paroxysmal nocturnal hemoglobinurea (PNH) are at increased risk for developing MDS.

There is also some speculation that the development of myelodysplastic syndromes may be related to hair dye and alcohol consumption. Because MDS primarily affects older people, this may explain why researchers believe the cumulative exposure to certain environmental factors plays a role in the development of myelodysplastic syndromes.

The incidence of myelodysplastic syndromes has been reported to be higher in cities than rural areas, which also supports the theory that the disease may be caused by certain carcinogens.

**Risk Factors for Myelodysplastic Syndromes**

A *risk factor* is anything that increases a person's chances for developing a disease or condition such as myelodysplastic syndromes (MDS). Risk factors that have been associated with MDS include:

- Male gender
- Being older than 60 years of age
- Being caucasian
- Past treatment with chemotherapy or radiation therapy
- Smoking
- Exposure to certain chemicals such as pesticides, organic solvents, and heavy metals such as mercury or lead.
- Genetic disorders such as trisomy 21, trisomy 8 mosaicism, and familial monosomy 7
- DNA repair deficiencies such as Fanconi anemia
- Alcohol consumption

**Myelodysplastic Syndromes with 5q Deletion**

Although the exact cause of MDS remains unknown, chromosomal abnormalities are thought to play a key role in the disease process. Researchers have shown that abnormalities in two specific regions located on chromosome 5q are linked to MDS:

- A 5q31 chromosomal abnormality is associated with aggressive MDS with a high risk for progression to AML that usually carries a guarded prognosis;
- A 5q33 chromosomal abnormality associated with a specific mutation known as a deletion 5q (del 5q) is the most common type of genetic mutation in MDS and is found in about 10% to 15% of patients. Fortunately, MDS patients with an isolated del 5q chromosomal abnormality usually have a more favorable prognosis with long disease duration prior to progression to AML.

The chromosomal abnormalities found in patients with MDS lead to the activation of a protein called P53 in the blood-forming marrow stem cells that renders them incapable of producing healthy blood cells. Blocking the activation of P53 with specific targeted drugs has been shown to
restore the capacity of the bone marrow stem cells to produce healthy blood cells.

Lenalidomide (Revlimid) is an immunomodulatory agent that specifically targets the del 5q clone in MDS and overcomes the activation of P53. The National Comprehensive Cancer Network guidelines recommend lenalidomide as first-line treatment for patients with del 5q MDS. Clinical trials of lenalidomide in low-risk and intermediate-risk MDS showed that it can reduce the requirement for blood transfusions and increase overall survival in MDS patients with del 5q. However, lenalidomide alone is not effective in patients with high-risk MDS and, therefore, combination therapy with lenalidomide and azacitidine is recommended for this group of MDS patients.

**Summary of Key Points**

- MDS is a broad group of hematopoietic (blood-forming) stem cell disorders that affect a person's ability to produce normal red blood cells, white blood cells, and platelets.
- Anemia is the most common blood abnormality in people with MDS, although some patients also develop abnormally low levels of platelets (thrombocytopenia) and abnormally low levels of white blood cells (neutropenia).
- MDS increases a person's risk for developing acute myelogenous leukemia (AML).
- The cause of MDS is currently not known. Although a variety of risk factors for MDS have been identified, the most important risk factor is advancing age.
- A subgroup of MDS patients have a specific chromosomal abnormality called MDS with 5q deletion (del 5q). The treatment of choice for MDS del 5q is lenalidomide (Revlimid), an immunomodulatory drug that has been shown in clinical trials to reduce the requirements of blood transfusions and to also increase overall survival of patients.

The Intelligent Patient Overview in the complete Medifocus Guidebook on Myelodysplastic Syndromes also includes the following additional sections:

- Diagnosis of Myelodysplastic Syndromes
- Treatment Options for Myelodysplastic Syndromes
- The Role of Complementary and Alternative Therapies in Cancer
- Quality of Life Issues in Cancer
- Questions to Ask Your Health Care Provider about Myelodysplastic Syndromes

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This section of your MediFocus Guidebook is a comprehensive bibliography of important recent medical literature published about the condition from authoritative, trustworthy medical journals. This is the same information that is used by physicians and researchers to keep up with the latest advances in clinical medicine and biomedical research. A broad spectrum of articles is included in each MediFocus Guidebook to provide information about standard treatments, treatment options, new developments, and advances in research.

To facilitate your review and analysis of this information, the articles in this MediFocus Guidebook are grouped in the following categories:

- Review Articles - 51 Articles
- General Interest Articles - 29 Articles
- Drug Therapy Articles - 23 Articles
- Clinical Trials Articles - 61 Articles
- Stem Cell Transplantation Articles - 9 Articles

The following information is provided for each of the articles referenced in this section of your MediFocus Guidebook:

- Title of the article
- Name of the authors
- Institution where the study was done
- Journal reference (Volume, page numbers, year of publication)
- Link to Abstract (brief summary of the actual article)

Linking to Abstracts: Most of the medical journal articles referenced in this section of your MediFocus Guidebook include an abstract (brief summary of the actual article) that can be accessed online via the National Library of Medicine's PubMed® database. You can easily access the individual abstracts online via PubMed® from the "electronic" format of your MediFocus Guidebook by clicking on the URI that is provided for each cited article. If you purchased a printed copy of the MediFocus Guidebook, you can still access the abstracts online by entering the individual URI for a particular abstract into your computer's web browser.
Recent Literature: What Your Doctor Reads

Database: PubMed <January 2015 to January 2020>

Review Articles


   Authors: Affentranger L; Bohlius J; Hallal M; Bonadies N
   Institution: Department of Hematology and Central Hematology Laboratory, Inselspital, Bern University Hospital, University of Bern, Switzerland. University Hospital, University of Bern, Switzerland; Department for BioMedical Research, University of Bern, Switzerland. University Hospital, University of Bern, Switzerland; Department for BioMedical Research, University of Bern, Switzerland. Electronic address: Nicolas.Bonadies@insel.ch.


   Authors: Daher-Reyes GS; Merchán BM; Yee KWL
   Institution: Division of Medical Oncology and Hematology, University Health Network - Princess Margaret Cancer Centre, Toronto, Ontario, Canada.
The **Guide to the Medical Literature** in the complete Medifocus Guidebook on Myelodysplastic Syndromes includes the following sections:

- Review Articles - 51 Articles
- General Interest Articles - 29 Articles
- Drug Therapy Articles - 23 Articles
- Clinical Trials Articles - 61 Articles
- Stem Cell Transplantation Articles - 9 Articles

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4 - Centers of Research

This section of your MediFocus Guidebook is a unique directory of doctors, researchers, medical centers, and research institutions with specialized research interest, and in many cases, clinical expertise in the management of this specific medical condition. The Centers of Research directory is a valuable resource for quickly identifying and locating leading medical authorities and medical institutions within the United States and other countries that are considered to be at the forefront in clinical research and treatment of this disorder.

Use the Centers of Research directory to contact, consult, or network with leading experts in the field and to locate a hospital or medical center that can help you.

The following information is provided in the Centers of Research directory:

• Geographic Location

  • United States: the information is divided by individual states listed in alphabetical order. Not all states may be included.

  • Other Countries: information is presented for select countries worldwide listed in alphabetical order. Not all countries may be included.

• Names of Authors

  • Select names of individual authors (doctors, researchers, or other health-care professionals) with specialized research interest, and in many cases, clinical expertise in the management of this specific medical condition, who have recently published articles in leading medical journals about the condition.

  • E-mail addresses for individual authors, if listed on their specific publications, is also provided.

• Institutional Affiliations

  • Next to each individual author's name is their institutional affiliation (hospital, medical center, or research institution) where the study was conducted as listed in their publication(s).

  • In many cases, information about the specific department within the medical institution where the individual author was located at the time the study was conducted is also provided.
# Centers of Research

## United States

### AL - Alabama

<table>
<thead>
<tr>
<th>Name of Author</th>
<th>Institutional Affiliation</th>
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</thead>
<tbody>
<tr>
<td>Erba HP</td>
<td>Mikkael A. Sekeres and Aziz Nazha, Cleveland Clinic, Cleveland; Clara D. Bloomfield, The Ohio State University Comprehensive Cancer Center, Columbus, OH; Megan Othus and Anna Moseley, SWOG Statistical Center; Min Fang and Frederick R. Appelbaum, Fred Hutchinson Cancer Research Center, Seattle, WA; Alan F. List, H. Lee Moffitt Cancer Center, Tampa, FL; Olatoyosi Odenike, University of Chicago, Chicago; Mario R. Velasco, Heartland NCORP/Cancer Care Specialists of Central Illinois, Decatur, IL; Richard M. Stone, Dana Farber Cancer Institute; Eyal C. Attar, Massachusetts General Hospital, Boston, MA; Steven D. Gore, Yale University, New Haven, CT; Mark R. Litzow, Mayo Clinic, Rochester, MN; Rena Buckstein, Sunnybrook Health Sciences Centre, Toronto; Elina K. Cook, Alyssa H. Cull, and Michael J. Rauh, Queen's University, Kingston, Ontario, Canada; Diane Roulston, University of Michigan, Ann Arbor, MI; Yanming Zhang, Memorial Sloan-Kettering Cancer Center, New York, NY; Rakesh Gaur, Kansas City National Cancer Institute Community Oncology Research Program, Prairie Village, KS; Ehab Atallah, Medical College of Wisconsin, Milwaukee, WI; and Harry P. Erba, University of Alabama, Birmingham, AL.</td>
</tr>
</tbody>
</table>

### CA - California

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<th>Name of Author</th>
<th>Institutional Affiliation</th>
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<tbody>
<tr>
<td>Bejar R</td>
<td>Leukemia Program, Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, OH, USA. Cancer Center, 3855 Health Sciences Drive MC 0820, La Jolla, CA, 92093-0820, USA. <a href="mailto:rabejar@ucsd.edu">rabejar@ucsd.edu</a>.</td>
</tr>
</tbody>
</table>
The **Centers of Research** in the complete *Medifocus Guidebook on Myelodysplastic Syndromes* includes the following sections:

- Centers of Research for relevant states in the United States
- Centers of Research listed for relevant countries outside the United States

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5 - Tips on Finding and Choosing a Doctor

Introduction

One of the most important decisions confronting patients who have been diagnosed with a serious medical condition is finding and choosing a qualified physician who will deliver a high level and quality of medical care in accordance with currently accepted guidelines and standards of care. Finding the "best" doctor to manage your condition, however, can be a frustrating and time-consuming experience unless you know what you are looking for and how to go about finding it.

The process of finding and choosing a physician to manage your specific illness or condition is, in some respects, analogous to the process of making a decision about whether or not to invest in a particular stock or mutual fund. After all, you wouldn't invest your hard earned money in a stock or mutual fund without first doing exhaustive research about the stock or fund's past performance, current financial status, and projected future earnings. More than likely you would spend a considerable amount of time and energy doing your own research and consulting with your stock broker before making an informed decision about investing. The same general principle applies to the process of finding and choosing a physician. Although the process requires a considerable investment in terms of both time and energy, the potential payoff can be well worth it--after all, what can be more important than your health and well-being?

This section of your Guidebook offers important tips for how to find physicians as well as suggestions for how to make informed choices about choosing a doctor who is right for you.

Tips for Finding Physicians

Finding a highly qualified, competent, and compassionate physician to manage your specific illness or condition takes a lot of hard work and energy but is an investment that is well-worth the effort. It is important to keep in mind that you are not looking for just any general physician but rather for a physician who has expertise in the treatment and management of your specific illness or condition. Here are some suggestions for where you can turn to identify and locate physicians who specialize in managing your disorder:

• **Your Doctor** - Your family physician (family medicine or internal medicine specialist) is a good starting point for finding a physician who specializes in your illness. Chances are that your doctor already knows several specialists in your geographic area who specialize in your illness and can recommend several names to you. Your doctor can also provide you with information about their qualifications, training, and hospital affiliations.
The **Tips on Finding and Choosing a Doctor** in the complete *Medifocus Guidebook on Myelodysplastic Syndromes* includes additional information that will assist you in locating a highly qualified and competent physician to manage your specific illness.

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6 - Directory of Organizations

American Cancer Society
1599 Clifton Road, N.E.; Atlanta, GA 30329
800-227-2345;  866-228-4327 (TTY)

American Institute for Cancer Research: Nutrition Hotline
1759 R Street NW Washington, DC 20009
800.843.8114;   202.328.7744
aicrweb@aicr.org
www.aicr.org

Aplastic Anemia & MDS International Foundation
PO Box 310 Churchton, MD 20733 USA
800.747.2820;   410.867.0242
help@aamds.org
www.aamds.org

Aplastic Anemia & Myelodysplasia Association of Canada
11181 Yonge Street Suite 321; Richmond Hill, Ontario; L4S 1L2 CANADA
888.840.0039;   905.780.0698
info@aamac.ca
www.aamac.ca

Association of Cancer Online Resources
www.acor.org

Cancer Care
275 Seventh Avenue; New York, NY 10001
800.813.4673
www.cancercare.org

Cancer Caring Center
4117 Liberty Avenue; Pittsburgh, PA 15224
412.622.1212
info@cancercaring.org
www.cancercaring.org
The Directory of Organizations in the complete Medifocus Guidebook on Myelodysplastic Syndromes includes a list of selected disease organizations and support groups that are helping people diagnosed with Myelodysplastic Syndromes.

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