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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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)
• Link to Abstract (brief summary of the actual article)

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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.
Introduction to Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) represent a group of myeloid (bone marrow) stem cell disorders that gradually affect the ability of a person's bone marrow to produce normal red blood cells, white blood cells, and platelets.

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.

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.

It is estimated that MDS affects 15 to 50 people per 100,000 Americans who are over the age of 70. According to the American Cancer Society's most recent estimates, between 10,000 and 15,000 new cases of MDS are diagnosed in the United States each year. However, since there are no actual registries listing the incidence of myelodysplastic syndromes, some researchers estimate that the numbers may actually be much higher. For example, anemia in older individuals may be ascribed to "old age" without consideration of the possibility of myelodysplastic syndrome.

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.

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 Fanconi's 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 hemoglobinuria (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. Researchers are studying the effect a person's enzymes have on environmental carcinogens and the development of MDS to see if the disease may be prevented.

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.

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.

Although the introduction of lenalidomide represents a major advance in the management of patients with del 5q MDS, there are several major issues regarding its clinical use that still must be resolved through further research:

• The optimal time for discontinuation of lenalidomide therapy once patients go into remission is currently not know.
• Although many MDS patients who are treated with lenalidomide go into remission, they also often relapse with disease recurrence and progression. Essentially, these patients become "resistant" to lenalidomide therapy. More research is needed to determine why this occurs and how to overcome this resistance.
• Since lenalidomide is a relatively new drug, currently there are no long-term studies that have evaluated its effectiveness beyond 5-years and longer in terms of prolonging overall
survival and preventing progression to AML.

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
- New Developments in Myelodysplastic Syndromes
- Questions to Ask Your Health Care Provider about Myelodysplastic Syndromes

To Order the Complete Guidebook on Myelodysplastic Syndromes Click Here
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3 - Guide to the Medical Literature

Introduction

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 - 44 Articles
- General Interest Articles - 33 Articles
- Drug Therapy Articles - 23 Articles
- Clinical Trials Articles - 68 Articles
- Stem Cell Transplantation Articles - 13 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.
1. Iron overload in myelodysplastic syndromes (MDS).

   **Author:** Gattermann N  
   **Institution:** Department of Hematology, Oncology and Clinical Immunology, Heinrich Heine University Dusseldorf, Dusseldorf, Germany.  

2. Immune dysregulation in myelodysplastic syndrome: Clinical features, pathogenesis and therapeutic strategies.

   **Authors:** Wang C; Yang Y; Gao S; Chen J; Yu J; Zhang H; Li M; Zhan X; Li W  

3. Recent advances in the treatment of lower-risk non-del(5q) myelodysplastic syndromes (MDS).

   **Authors:** Almeida A; Fenaux P; List AF; Raza A; Platzecker U; Santini V  
   **Institution:** Instituto Portugues de Oncologia de Lisboa Francisco Gentil, Departamento de Hematologia, CIPM, Rua Prof. Lima Basto, 1099-023, Lisbon, Portugal. Electronic address: amalmeida@ipolisboa.min-saude.pt. France. Dresden, Germany.  
4.

Success in bone marrow failure? Novel therapeutic directions based on the immune environment of myelodysplastic syndromes.

Authors: Cull AH; Rauh MJ
Institution: Department of Pathology and Molecular Medicine, Queen's University, Kingston, Ontario, Canada. Ontario, Canada rauhm@queensu.ca.

5.

Myelodysplastic Syndromes: Updates and Nuances.

Author: Dao KT
Institution: Hematology and Medical Oncology, Knight Cancer Institute, Oregon Health & Science University, Mail Code: UHN73C, 3181 South West Sam Jackson Park Road, Portland, OR 97239, USA. Electronic address: daok@ohsu.edu.

6.

Decision points in the treatment of transfusional iron overload in patients with myelodysplastic syndromes: why, when, and how to chelate.

Authors: Imran F; Phatak P
Institution: a Lipson Cancer and Blood Center, Rochester Regional Health System, Rochester, NY, USA. NY, USA.
Abstract Link: http://www.medifocus.com/abstracts.php?gid=HM017&ID=27923273
The **Guide to the Medical Literature** in the complete Medifocus Guidebook on **Myelodysplastic Syndromes** includes the following sections:

- Review Articles - 44 Articles
- General Interest Articles - 33 Articles
- Drug Therapy Articles - 23 Articles
- Clinical Trials Articles - 68 Articles
- Stem Cell Transplantation Articles - 13 Articles

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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

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<th>Name of Author</th>
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<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>
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#### CA - California

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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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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
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aicrweb@aicr.org
www.aicr.org

Aplastic Anemia & MDS International Foundation
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www.aamds.org

Aplastic Anemia & Myelodysplasia Association of Canada
11181 Yonge Street Suite 321; Richmond Hill, Ontario; L4S 1L2 CANADA
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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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