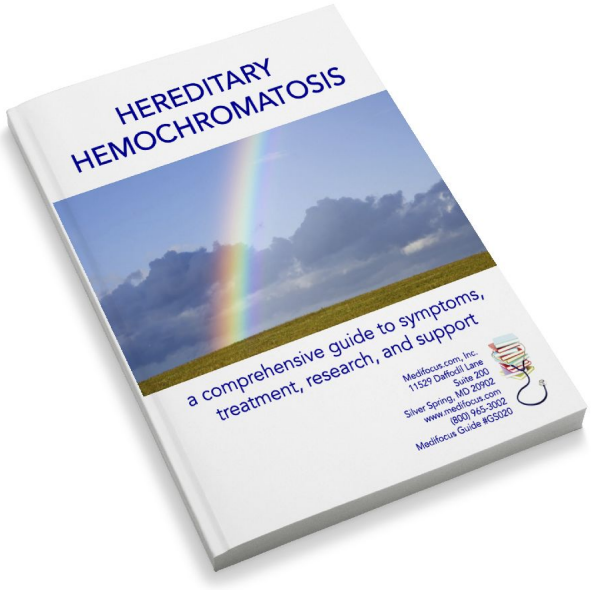
Preview of the Medifocus Guidebook on: Hereditary Hemochromatosis

Updated June 21, 2017



This document is only a SHORT PREVIEW of the **Medifocus Guidebook on Hereditary Hemochromatosis**. 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.

To purchase the **COMPLETE** Medifocus Guidebook on Hereditary Hemochromatosis (113 pages; Updated June 21, 2017), please:

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Table of Contents

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

- New developments
- Important questions to ask your health care provider

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)

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 curently 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

HEREDITARY HEMOCHROMATOSIS

Introduction

What is Hereditary Hemochromatosis?

Hereditary hemochromatosis (HH) is a genetic disorder that is one of a group of conditions known as *iron overload* diseases. It is the most common inherited liver disease in Caucasians, and the most common autosomal recessive genetic disease (see below). In patients with hereditary hemochromatosis, the intestines absorb too much iron from food that is ingested, and they continue to absorb iron, although there are sufficient amounts already stored. The excess iron is distributed throughout the body and slowly accumulates in several organs, including the heart, liver, pancreas, spleen, and skin, as well as in joints and some glands (e.g., the pituitary gland). The degree of iron accumulation affects the presentation and severity of HH symptoms. Signs and symptoms of HH include, joint pain, fatigue, skin darkening, liver cirrhosis, diabetes, sexual dysfunction, and heart failure. Classic biochemical features of hemochromatosis include elevated levels of *serum ferritin* and *serum transferrin saturation percentage* (explained below). Hereditary hemochromatosis affects approximately one million people in the U.S.

While hemochromatosis is not curable at this time, the good news is that early diagnosis and treatment can effectively reduce the body's iron overload, prevent organ damage, and enable people with HH to lead normal and productive lives. Even if organ damage has already occurred, the initiation of treatment usually prevents further progression of complications. If left untreated, progressive accumulation of iron in the liver, pancreas, heart, joints, and the pituitary gland can lead to potentially serious and life-threatening diseases such as:

- Cirrhosis of the liver (formation of scar tissue and fibrosis)
- Liver failure
- Hepatocellular carcinoma (primary liver cancer)
- Arthritis
- Hypogonadism (underactive sex organs)
- Diabetes mellitus
- Arrhythmia (irregular heart beat)
- Congestive heart failure

The severity, frequency, and rate of iron accumulation in patients with HH vary widely and are affected by the presence of several factors, including:

- Middle age
- Male gender

- Dietary habits (alcohol consumption, intake of vitamin C and iron supplements)
- Patterns of genetic mutations
- Presence of other diseases (co-morbid conditions)

Hereditary hemochromatosis is also known as the "Celtic disease" as it is believed to be of Celtic origin. It is most prevalent in locations with significant populations of Celtic descent, such as Ireland, the United Kingdom, Northern Europe, Australia, and the East Coast of the United States. Hereditary hemochromatosis is rarely found in indigenous populations of Africa, Asia, or the Pacific Islands.

Iron Metabolism and Hereditary Hemochromatosis

Iron (Fe) is a naturally occurring element in our environment that is essential to the human body in order to carry out many important functions. A well-balanced diet contains about 10-20 milligrams (mg) of iron, of which the body absorbs and uses approximately 10% (1-2 mg). Approximately 1-2 mg per day of iron are eliminated from the body through perspiration, sloughed-off dead skin, hair, urine, and fingernails. Remaining unabsorbed iron is taken up by special cells in the gastrointestinal tract (GI tract) called *enterocytes*. When enterocytes become saturated with iron, they die and are excreted, along with the excess iron, into the feces. This delicate balance of storage and elimination of excess iron is called *homeostasis*.

Iron absorption begins when ingested iron is changed by acids in the stomach into a form that can be absorbed into the duodenum (upper portion of the small intestine) and is then bound to a protein in the blood called *transferrin*. Transferrin transports the iron to tissues, organs, and bone marrow so that the normal process of metabolism (breaking down of iron for different uses) can take place.

Transferrin should be saturated about 25-35% with iron. When it is saturated with too much iron, it cannot effectively keep the iron molecules bound to it. The unbound iron molecules become free to circulate in the body. Free iron molecules (also called *free radicals*) cause cell death and are destructive to body tissue and organs.

If iron is not needed immediately, transferrin transports the excess iron to a protein called *ferritin* where it is temporarily stored. While ferritin is produced by most cells in the body, there are particularly large amounts in the liver and the brain. If there is more iron than ferritin can bind to or store, the unbound iron is changed into *hemosiderin*. While small amounts of hemosiderin may be normal, large amounts collect in organs such as the heart, liver, pancreas, and skin, as well as in joints and some glands, and eventually interfere with normal functioning of any organs where it has collected. Elevated serum ferritin is typically a sign either of inflammation due to disease or iron overload.

The amount of iron absorbed by the body is regulated by a hormone produced mainly in the liver called *hepcidin*. Hepcidin acts by inhibiting intestinal iron absorption and iron release from storage in the liver, and its production is limited in people with hemochromatosis. As a result, they absorb dietary iron at two to three times the normal rate, meaning individuals with hemochromatosis absorb a few extra milligrams of iron per day, leading to the accumulation of 0.5-1.0 grams per year. Over decades, with continued iron overload, total body stores can exceed 50 grams. Storage

of more than 4 grams of iron is considered "iron overload."

Under certain circumstances, such as greater loss of blood (menstruation) or greater demand (pregnancy), more iron is needed and more is then absorbed into the GI tract. Typically, men store approximately 4 grams of iron, while women store 3.5 grams. The iron is distributed throughout the body, with the majority being contained in *hemoglobin*, the component of red blood cells that carries oxygen.

Any process that interferes with the body's normal absorption of iron can lead to potentially serious disease. Lack of sufficient iron in the body (iron deficiency) can lead to a condition called *anemia* that can make a person feel weak and tired. Conversely, if the body absorbs and stores too much iron, it can lead to 'iron-overload disease' which can cause not only generalized weakness and fatigue but can also damage vital organs such as the liver, heart, and pancreas. Understanding the mechanisms involved in iron metabolism is important to understanding HH and the diseases and conditions attributable to iron overload.

HFE Gene, Hepcidin, and Hereditary Hemochromatosis

It is estimated that up to 80% of cases of hereditary hemochromatosis are associated with mutations of the *HFE* gene that regulates the synthesis of *hepcidin*, a hormone that plays a critical role in the regulation of iron absorption and storage in the body. Hepcidin and its role in hemochromatosis were identified in 2003. Other genes that are associated with HH include TfR2 and HJV. There is a carefully coordinated balance between iron "storage" units, namely hepatocytes; iron "utilization" sites, primarily the bone marrow; and the liver, which receives their signals and regulates the production of hepcidin based on demand. In hereditary hemochromatosis, this balance is disrupted, and reduced levels of hepcidin enable iron to accumulate continuously in the blood.

In a healthy person, as iron levels rise with dietary iron, the liver produces more hepcidin which acts to reduce iron absorption by the intestines. However, in people with the mutation of the HFE gene, there is insufficient hepcidin production and, as a result, the liver does not respond to rising levels of iron. Deficiency of hepcidin is associated with iron overload, while overproduction of hepcidin is associated with anemia-related conditions. It is thought that hepcidin levels and the level of its activity is one of the most important determinants of the variability in the severity of HH symptoms.

As mentioned above, in addition to hepcidin, there are two proteins, namely *ferritin* and *transferrin* that also play a major role in the body's ability to store and distribute iron and are dysfunctional in people with hereditary hemochromatosis.

- *Ferritin* binds to iron and stores iron not needed for immediate use. Each ferritin molecule can bind thousands of iron atoms. Most of the iron stored in the body is bound to ferritin. Ferritin is found in many places, such as the liver, skeletal muscles, spleen, bone marrow, and in the blood. The body increases the production of ferritin when excess iron is absorbed in order to accommodate the excess iron. The amount of ferritin in the blood, known as the *serum ferritin level*, is directly proportional to the amount of iron stored in the liver.

- *Transferrin* is a *carrier protein* synthesized in the liver that transports iron in the bloodstream to red blood cells in all tissue. Transferrin saturation, which is the ratio of serum iron to the total iron binding capacity of transferrin, is thought to be the earliest biochemical change that increases in HH.

Types of Hereditary Hemochromatosis

Four types of hereditary hemochromatosis have been identified:

- Type I - This is the "classic" type of hereditary hemochromatosis and results from a mutation of the HFE gene. Type I is the topic of this Medifocus Guidebook.

- Type II - Also called "juvenile hemochromatosis", Type II hemochromatosis is caused by mutations in either the HFE2 or HAMP gene. It is a rare but severe iron overload disorder that usually develops between the ages of 15 and 30, and affects males and females equally. Clinically, juvenile hemochromatosis is identified by a combination of symptoms including cardiomyopathy (heart muscle disease), hypogonadism, impotence, amenorrhea, cirrhosis of the liver, diabetes, changes of skin pigmentation, and a specific form of arthritis. Cardiac symptoms are typically more dominant than others. Although some of these symptoms overlap with those of Type I hereditary hemochromatosis, the symptoms of juvenile hemochromatosis occur at a much earlier age. Juvenile hemochromatosis is only sporadically reported in various populations around the world.

- Type III - This is an autosomal recessive disorder (meaning each parent must carry the genetic mutation), caused by mutation on the TfR2 gene found on chromosome 7. It typically appears between the ages of 30-40 and can be seen in any ethnic group. Associated complications include cardiomyopathy, endrocrinopathy (hormone imbalance), and liver disease.

- Type IV - Also called "ferroportin disease", this is an autosomal dominant disorder (meaning only one parent needs to be a carrier of the genetic mutation), caused by a mutation of a protein called *ferroportin* (SLC40A1) that moves iron out of the cell and into the blood. It can affect Caucasian or non-Caucasian males or females and may develop at any age, though usually not below the age of ten.

Types II, III, and IV hemochromatosis are classified as *non-HFE-related HH,* meaning that the iron overload is not due to a mutation of the HFE gene.

A final type of HH is called *neonatal hemochromatosis,* a rare disorder that affects the fetus in utero (before birth), resulting in excessive accumulation of iron in the liver and other organs. It is typically associated with extensive injury to the liver, rather than a genetic mutation. Most fetuses with neonatal hemochromatosis die before birth, and those that are born survive only a few hours or days.

Genetic Transmission of Hereditary Hemochromatosis

Hereditary hemochromatosis (HH) is an inherited, autosomal recessive disorder of iron absorption and metabolism. The term *autosomal recessive* refers to a genetic condition in which there are two copies of a gene *mutation* (abnormality) on a particular chromosome.

A major advance in our understanding of the genetics of HH occurred in 1996, when researchers mapped the *HFE gene* (located on chromosome 6) that is associated with iron absorption. Three mutations (genetic alterations or variants) of the HFE gene, known as *C282Y, H63D*, and *S65C*, have been associated with the increased absorption and storage of iron that is characteristic of hereditary hemochromatosis. Because HH is an autosomal recessive disorder, an individual must acquire both copies of either of these mutated genes (one from each parent) in order to develop the disorder or to be considered at high risk for developing it.

There are three terms used to denote inherited genetic combinations related to hereditary hemochromatosis:

- *Homozygous* is used to denote people who carry both copies of either the C282Y or H63D mutation
- *Heterozygous* refers to people who carry only one copy of the C282Y or H63D mutation
- *Compound heterozygous* denotes people who carry one copy of each genetic mutation (C282Y/H63D or C282Y/S65C).

H63D and S65C are generally not related to iron overloading, unless either occurs together with C282Y as a compound heterozygote.

It is important to note that not all individuals who carry two mutated copies of the HFE gene will actually develop clinical signs and symptoms of hemochromatosis.

The risk of a person inheriting two mutated copies of the HFE gene is as follows:

- 100% risk - if both parents have been diagnosed with hereditary hemochromatosis
- 50% risk - if one parent AND a sister or brother have been diagnosed with hereditary hemochromatosis
- 25% risk - if a sister or brother (but neither parent) has been diagnosed with hereditary hemochromatosis
- 5% risk - if only one parent (but not a sister or brother) has been diagnosed with hereditary hemochromatosis

- Less than 5% risk - if an uncle, aunt, or a first-cousin has been diagnosed with hereditary hemochromatosis

Following are probabilities of children inheriting hereditary hemochromatosis from parents:

- If both parents are carriers, on the average, one-quarter of the children will not have any genetic mutation, one-half will be carriers, and one-quarter will develop hemochromatosis.
- If the father is a carrier and the mother has been diagnosed with HH, one-half of the children will be carriers and one-half of the children will develop hemochromatosis.
- If both parents have been diagnosed with HH, all of the children will have two gene mutations and will develop hemochromatosis.

Some statistics regarding the genetic prevalence of the HFE mutation include:

- Approximately one in ten (10%) of North American Caucasians are heterozygous for the HFE C282Y mutation (i.e., they are carriers).
- Approximately one in 227 (0.44%) of North American Caucasian people are homozygous for the HFE C282Y mutation (i.e., will typically develop HH).
- In Europe, the estimated prevalence of homozygosity of the C282Y mutation among patients with HH ranges from 52% to 96%, depending upon specific geographic location.
- The highest prevalence in the world of both HFE C282Y homozygosity (i.e., will typically develop HH), and of HFE C282Y heterozygosity (i.e., they are carriers), is in Ireland, where it is one in 83 people (1.2%) and one in every 5 people (20%), respectively.
- According to the American Association for the Study of Liver Diseases (AASLD), 80-85% of people with HH are homozygous for the C282Y mutation, and approximately 10% of individuals are compound heterozygous (C282Y/H63D or C282Y/S65C), which may be associated with elevated iron markers, but not with iron overload or damage.

While individuals who are homozygous for the C282Y genotype (C282Y/C282Y) are at highest risk for developing hereditary hemochromatosis, it is not clear what percentage of those individuals actually develops hereditary hemochromatosis. Emerging research is showing that the actual percentage may be much less than originally thought (about 85%). It appears that in general, homozygosity for the C282Y mutation is necessary for the development of HH, but not sufficient on its own for the development of the disease. It is not known at this time what other factors (e.g., biochemical, environmental, or genetic) may determine which individuals will develop hereditary hemochromatosis, making it impossible to predict the incidence of hereditary hemochromatosis in the presence of homozygous C282Y.

The AASLD noted that data from large population screening studies indicates that only 70% of C282Y homozygotes have elevated ferritin levels that would indicate increased iron stores, and only a small percentage of those people develop clinical consequences of iron overload disease.

A systematic review carried out by the U.S. Preventive Services Task Force and published in 2006 in *Annals of Internal Medicine* (Vol.145:pp.209-233) indicated that:

- Up to 38-50% of C282Y homozygotes may develop iron overload.
- Up to 10-33% of those who develop iron overload eventually develop hemochromatosis-related morbidity (illness) with end-organ manifestations.
- The risk for developing hemochromatosis-related morbidity was higher (32%-35%) for individuals with family members who had hemochromatosis than for subjects identified through population-based studies.

To read more about this report, please click on the following link:
http://www.ncbi.nlm.nih.gov/pubmed/16880463

Individuals with either the homozygous H63D genotype (H63D/H63D) or those with the compound heterozygous genotype (C282Y/H63D) are much less likely to develop hereditary hemochromatosis than individuals who are homozygous for the C282Y genotype (C282Y/C282Y).

Incidence of Hereditary Hemochromatosis

Hereditary hemochromatosis (HH) is the most common genetic disorder that affects Caucasians, which makes it surprising that most people have never heard of it. Lack of appreciation for the frequency of this genetic disorder often leads to underdiagnosis or misdiagnosis of the condition. The U.S. Centers for Disease Control and Prevention (CDC) reports that most patients visit three doctors before being correctly diagnosed with hereditary hemochromatosis.

Information about the incidence of HH in North America:

- One out of every 200-250 people of northern European origin, particularly Nordic or Celtic ancestry, is susceptible to HH (C282Y homozygosity).
- Men are twice as likely to develop HH as women.
- According to the CDC, the average age at diagnosis for men is 51, and for women, age 66.
- Women are typically diagnosed in the postmenopausal years, since menstruation naturally depletes iron levels so that evidence of iron overload is masked.
- Prevalence of HH in Caucasians is six times higher than in African-Americans.

- Prevalence of HH among the Hispanic population is rising.

An article on "Iron-Overload-Related Disease in HFE Hereditary Hemochromatosis" that was published in 2008 in the *New England Journal of Medicine* (Vol.383(3):pp.221-30) reported that the proportion of C282Y homozygotes that developed hemochromatosis-related disease (e.g., cirrhosis, liver fibrosis, hepatocellular carcinoma, and arthropathy) was 28% for men and 1.2% for women, indicating that men who are C282Y homozygous are much more likely to develop iron-overload-related disease than women. The summary of this article is available by clicking on the following link: http://www.ncbi.nlm.nih.gov/pubmed/18199861

Risk Factors for Hereditary Hemochromatosis

In addition to the genetic mutations of the HFE gene which must be present in order for hereditary hemochromatosis to develop, other factors that may increase the risk of developing HH include:

- Family history of hemochromatosis
- Northern and Western European (Celtic) descent
- Male gender
- Middle age
- Family history of liver disease
- Family history of type II diabetes
- Bronze colored skin

Screening for Hereditary Hemochromatosis

Guidelines for screening people for hereditary hemochromatosis (HH) have been published by various medical organizations, including these:

- American College of Physicians
- American College of Gastroenterology
- American Association for the Study of Liver Diseases
- U.S. Preventive Services Task Force
- U.S. Centers for Disease Control and Prevention (CDC)

Despite the availability of numerous guidelines, there is still a lack of general consensus regarding the issue of screening the general population for HH for a variety of reasons, including:

- Lack of adequate information regarding the normal distribution of the C282Y and H63D genetic mutations in the general population.

- Lack of accuracy in predicting which individuals with either of these genetic mutations will actually develop hereditary hemochromatosis.

- Growing evidence that a lower percentage of individuals who are homozygous for the

C282Y genetic mutation actually develop hereditary hemochromatosis than previously thought. Research suggests that less than 50% of homozygous individuals will develop iron overload and only 30% of those individuals will develop actual hereditary hemochromatosis.

- Recent research that suggests that the number of people who actually develop hereditary hemochromatosis in the presence of elevated levels of serum transferrin saturation percentage and elevated serum ferritin may actually be lower than formerly thought, which reduces the value of wide-scale screening.

- Limited evidence that starting therapy before clinical signs of hereditary hemochromatosis actually develop confers any benefits in terms of disease prevention or life expectancy.

- Concern that individuals who are identified through screening to be homozygous for the HFE gene mutation but who are asymptomatic may be stigmatized in the workplace, may face discrimination regarding health insurance with higher premiums or coverage denial, or may suffer psychological distress in perceiving themselves as ill or at high risk for illness.

General Screening Recommendations

Proponents of screening of the general population for hereditary hemochromatosis cite the importance of early treatment in order to prevent complications associated with the condition, such as damage to major organs. As noted above, the issue of general population screening for HH is still the subject of debate in the medical community. Most experts, however, generally agree that screening for HH is warranted for a select subgroup of people, including:

- First-line relatives of anyone who is diagnosed with hereditary hemochromatosis, including children above the age of 18, siblings, and parents.

- People with symptoms associated with hereditary hemochromatosis, such as hepatomegaly (enlarged liver), elevated liver enzymes, cardiomyopathy (structural or functional changes in the heart), and arthritis.

- People with non-specific symptoms such as fatigue, abdominal pain, weight loss, or skin "bronzing" that cannot be attributed to another underlying medical condition.

- Individuals with abnormal serum markers (such as iron or ferritin) discovered during routine checkups or diagnostic testing for other medical conditions.

Serum transferrin saturation percentage is considered to be the most clinically useful test for the diagnosis of iron overload. Some health agencies recommend that if the serum transferrin saturation and serum ferritin are abnormal, genetic counseling should be considered. For individuals with ferritin levels above 1000 ng/mL (nanograms per milliliters), a liver biopsy may be necessary for final confirmation of the diagnosis of HH, and in order to determine the extent of liver damage.

People who have the HFE gene mutation, but who have normal serum ferritin and serum

transferrin saturation levels should be followed for disease progression. There are no strict guidelines regarding how frequently such individuals should be tested for iron overload. Some doctors suggest delaying screening children of individuals who are homozygous for C282Y until their teenage years because manifestation of iron overload in children is very rare, unless there is a suspicion of juvenile hemochromatosis.

The American Hemochromatosis Society (AHS) has published its own guidelines regarding screening for hereditary hemochromatosis and recommends that every person above the age of 18 be screened for iron storage status by performing an *iron profile* every one to two years. Children between the ages of 2-18 should be monitored every two to three years if they have a blood relative who has been diagnosed with hereditary hemochromatosis. An *iron profile* includes the following blood tests:

- Serum iron levels
- Total iron-binding capacity
- Fasting serum transferrin saturation
- Serum ferritin

The AHS also recommends that physicians should not prescribe any iron supplements or vitamin pills containing iron before testing the iron storage status of any patient.

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 - 25 Articles
- General Interest Articles - 75 Articles
- Clinical Trials Articles - 11 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 2011 to June 2017>

Review Articles

1.

Haemochromatosis.

Authors: Powell LW; Seckington RC; Deugnier Y
Institution: Centre for the Advancement of Clinical Research, Royal Brisbane and Women's Hospital, Brisbane, The University of Queensland, Brisbane, Australia. Electronic address: lawrie.powell@qimrberghofer.edu.au. Brisbane, Australia.
Journal: Lancet. 2016 Aug 13;388(10045):706-16. doi: 10.1016/S0140-6736(15)01315-X. Epub 2016 Mar 12.
Abstract Link: http://www.medifocus.com/abstracts.php?gid=GS020&ID=26975792

2.

Epidemiology and diagnostic testing for hemochromatosis and iron overload.

Author: Adams PC
Institution: Western University, London, ON, Canada.
Journal: Int J Lab Hematol. 2015 May;37 Suppl 1:25-30. doi: 10.1111/ijlh.12347.
Abstract Link: http://www.medifocus.com/abstracts.php?gid=GS020&ID=25976957

3.

HFE gene: Structure, function, mutations, and associated iron abnormalities.

Authors: Barton JC; Edwards CQ; Acton RT
Institution: Southern Iron Disorders Center, Birmingham, AL, USA and Department of Medicine; University of Alabama at Birmingham, Birmingham, AL, USA. Electronic address: ironmd@isp.com. Lake City, UT, USA. Electronic address: corwin.edwards@imail.org. Department of Microbiology, University of Alabama at Birmingham, Birmingham, AL, USA. Electronic address: rtakma@bellsouth.net.
Journal: Gene. 2015 Dec 15;574(2):179-92. doi: 10.1016/j.gene.2015.10.009. Epub 2015 Oct 9.
Abstract Link: http://www.medifocus.com/abstracts.php?gid=GS020&ID=26456104

The **Guide to the Medical Literature** in the complete **Medifocus Guidebook on Hereditary Hemochromatosis** includes the following sections:

- Review Articles - 25 Articles
- General Interest Articles - 75 Articles
- Clinical Trials Articles - 11 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

Name of Author	Institutional Affiliation
Acton RT	Southern Iron Disorders Center, Birmingham, AL, USA and Department of Medicine; University of Alabama at Birmingham, Birmingham, AL, USA. Electronic address: ironmd@isp.com. Lake City, UT, USA. Electronic address: corwin.edwards@imail.org. Department of Microbiology, University of Alabama at Birmingham, Birmingham, AL, USA. Electronic address: rtakma@bellsouth.net.
Adams PC	Southern Iron Disorders Center, Birmingham, Alabama, USA. ironmd@isp.com
Barton JC	Southern Iron Disorders Center, Birmingham, Alabama, USA. ironmd@isp.com

AZ - Arizona

Name of Author	Institutional Affiliation
Vincelette ND	Department of Medicine, University of Arizona, Tucson, AZ 85721, USA. Electronic address: syun@email.arizona.edu. 55902, USA.
Yun S	Department of Medicine, University of Arizona, Tucson, AZ 85721, USA. Electronic address: syun@email.arizona.edu. 55902, USA.

CA - California

Name of Author	Institutional Affiliation
Balagtas JM	Division of Pediatric Hematology/Oncology, Department of Pediatrics, Stanford School of Medicine, Stanford, California 94304, USA. balagtas@stanford.edu
Dahl GV	Division of Pediatric Hematology/Oncology, Department of Pediatrics, Stanford School of Medicine, Stanford, California 94304, USA. balagtas@stanford.edu

The **Centers of Research** in the complete **Medifocus Guidebook on Hereditary Hemochromatosis** 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 eared 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 Hereditary Hemochromatosis** 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 Hemochromatosis Society
4044 West Lake Mary Blvd.; Unit #104 PMB 416; Lake Mary, FL 32746
407.829.4488; 888.655.4766
mail@americanhs.org
www.americanhs.org

American Liver Foundation
75 Maiden Lane; Suite 603; New York, NY 10038
212.668.1000; 800.465.4837
info@liverfoundation.org
www.liverfoundation.org

Canadian Hemochromatosis Society
272-7000 Minoru Blvd.; Richmond, BC; V6Y 3Z5 CANADA
877.223.4766; 604.279.7135
office@toomuchiron.ca
www.toomuchiron.ca/

GeneticHealth.com
POB 182; Palo Alto, CA 94302
feedback@geneticheath.com
www.geneticheath.com

Haemochromatosis Australia
POBOX 154, Coopers Plains QLD 4108
1300 019 028
information@haemochromatosis.org.au
www.haemochromatosis.org.au

Hemochromatosis Information Society
3017 Princeton Drive; Plano, TX 75075
214.893.6960
info@hemoinfo.org
www.hemoinfo.org

The **Directory of Organizations** in the complete **Medifocus Guidebook on Hereditary Hemochromatosis** includes a list of selected disease organizations and support groups that are helping people diagnosed with Hereditary Hemochromatosis.

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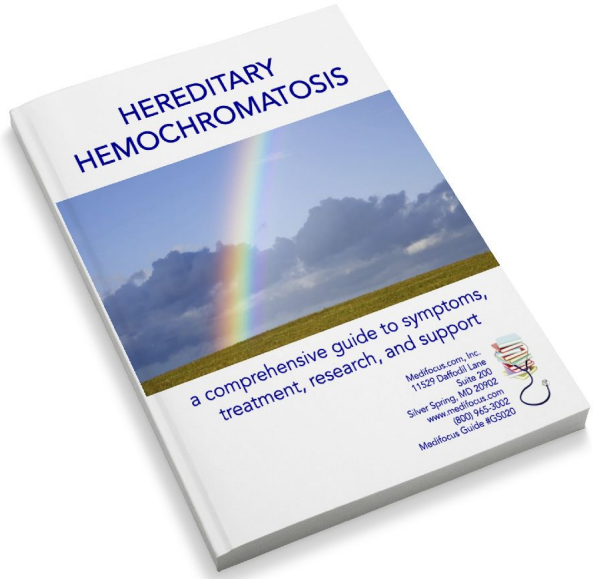

This document is only a SHORT PREVIEW of the **Medifocus Guidebook on Hereditary Hemochromatosis**. It is intended primarily to give you a general overview of the **format and structure** of the Guidebook as well as select pages from each major Guidebook section listed in the Table of Contents.

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