



GENETIC CONDITION INFORMATION REPORT

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SUMMARY OF TEST RESULTS FOR SAMPLE ID # 3100000

Name:	XXXX XXXX
Gender:	Female
Year of Birth:	1980
Ethnicity:	Chinese Han
Sample Type:	Saliva
Collection Date:	04/25/2015
Receipt Date:	04/30/2015
Sample ID:	3100000
SOP No.	30005v1.0
Batch No.	BC_16_2PD-107
Report Date:	05/15/2015

INTENDED USE STATEMENT

Per 21 CFR § 812.2

Simple-DNA-Test™ is a genetic wellness testing service which provides personalized genetic information to those who wish to learn more about their own genetic wellness.

Using state-of-the-art next generation sequencing technology, DNA extracted from a saliva sample is sequenced to assess a person's genetic predisposition to certain health conditions or diseases, as reported in the current medical and scientific publications. While the work is performed in a CLIA-certified clinical laboratory, it is not a diagnosis. The test has been developed, and the performance characteristics have been validated by Personal Diagnostix to ensure data accuracy and reproducibility. Results of genetic wellness testing are intended to be used by physicians and other health care providers in conjunction with other clinical factors. It is not a substitute for any diagnostic testing or professional services rendered by a healthcare provider. It is the customer's responsibility to seek consultation from a physician for any medical advice and treatment. The customer is advised not to change or stop taking any medications without consulting with a physician.

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TEST RESULTS FOR SAMPLE ID # 3100000



CONDITION	YOUR ESTIMATED GENETIC RISK	AVERAGE LIFETIME RISK IN YOUR GENDER & ETHNICITY	YOUR GENETIC RISK LEVEL	CHANGE FACTOR
Ovarian cancer	1.1%	0.4%	Increased	2.762
Multiple sclerosis (MS)	0.5%	0.2%	Increased	2.43
Coronary heart disease	25.8%	12.5%	Increased	2.064
Rheumatoid arthritis (RA)	2%	1%	Increased	1.982
Restless leg syndrome	8%	4%	Increased	1.904
Atrial fibrillation (AF)	4.4%	2.5%	Increased	1.77
Graves' disease	1.6%	1.0%	Increased	1.62
Breast cancer	8.3%	5.2%	Increased	1.601
Crohn's disease / Ulcerative colitis	0.8%	0.5%	Increased	1.517
Lung cancer	9.7%	6.5%	Increased	1.497
Age-related macular degeneration (AMD)	3.1%	2.1%	Increased	1.484
Asthma	5.5%	3.9%	Increased	1.417
COPD	16.7%	11.8%	Increased	1.417
Colorectal cancer	4.7%	3.3%	Increased	1.413
Prostate cancer	NA	NA	NA	1.333
Gastric cancer	4.0%	3.0%	Increased	1.332
Lymphoma	1.3%	1.0%	Increased	1.313
Diabetes type 2	25%	20%	Increased	1.273
Bladder cancer	5.2%	4.1%	Increased	1.268
Inflammation	32%	26%	Average	1.215
Peripheral arterial disease	17%	14%	Average	1.185
Brain tumor (Glioma)	0.2%	0.2%	Average	1.16
Basal cell carcinoma	3.5%	3.0%	Average	1.16
Aneurysm	1.3%	1.1%	Average	1.156
MTHFR DNA mutation analysis	20.5%	17.8%	Average	1.149
Venous thromboembolism	6.9%	6.0%	Average	1.149
Celiac disease	1.1%	1.0%	Average	1.148
Migraine	23%	20%	Average	1.147
Hypertension	31%	28%	Average	1.105
Osteoarthritis (OA)	10%	9%	Average	1.056
Allergic rhinitis & grass sensitization	8.6%	8.6%	Average	1
Alzheimer's disease (AD)	5.0%	5.0%	Average	1
Diabetes type 1	1.0%	1.0%	Average	1.000
Gallstones	7%	7%	Average	1
Glaucoma	1.0%	1.0%	Average	1
Lactose intolerance	91%	91%	Average	1
Liver cirrhosis	1.0%	1.0%	Average	1
Lupus	0.25%	0.25%	Average	1
Obesity	25%	25%	Average	1
Psoriasis	0.4%	0.4%	Average	1
Renal disease	10.4%	10.4%	Average	1
Melanoma	0.1%	0.1%	Average	1
Stroke	4.1%	4.1%	Average	1
Parkinson's Disease	1.2%	1.6%	Decreased	0.742
Hereditary hemochromatosis	Negative	2.1%	Decreased	-1

GENETIC CONDITION INFORMATION REPORT

PHARMACOGENOMIC RESULTS FOR SAMPLE ID # 3100000



DRUG METABOLIZING ENZYME	YOUR GENOTYPE	EFFECTS ON DRUG	REPRESENTATIVE DRUGS	INDICATIONS
CYP2C19	*1 / *1 (Normal)	High metabolizer, may need to increase dose	Clopidogrel (Plavix)	An oral antiplatelet agent used to inhibit blood clots in coronary artery disease, peripheral vascular disease, and cerebrovascular disease including stroke.
CYP2C9	*1 / *1 (Normal)	Normal	Warfarin (Coumadin)	To decrease the tendency for thrombosis or as secondary prophylaxis (prevention of further episodes) in those individuals that have already formed a blood clot (thrombus).
VKORC1	*2 / *2 (Low)	Reduced metabolism	Warfarin (Coumadin)	See warfarin above
CYP2D6	*1 / *1 (Normal)	Normal	Dextromethorphan - cough suppressant present in brand names such as Nyquil and Robitussin, beta blockers, antiarrhythmics, antidepressants, antipsychotics. Cancer therapy: tamoxifen	Beta blockers are used for the management of cardiac arrhythmias, protecting the heart from a second heart attack (myocardial infarction) after a first heart attack (secondary prevention), and hypertension.

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GENERAL INFORMATION

The Simple-DNA-Test™ service analyzes your DNA for genetic markers associated with a variety of health conditions using next generation DNA sequencing technology. It assesses your genetic predisposition to certain common conditions and helps you make informed decisions and proper adjustments in your diet, life style, living environment and working habits to further improve your health and wellness, and to reduce the chance or delay the development of a disease. The test is based on genetic variants that vary between individuals and their associated risks that have been confirmed in large controlled clinical studies of thousands of individuals. Now you have an opportunity to look at wellness from a genetic perspective.

Personal genetic & pharmacogenomic tests

Our simple salivary DNA test evaluates your genetic influence on 50 common conditions including cardiovascular (heart disease, peripheral vascular disease), general health (renal disease, obesity, lactose intolerance), immune system (multiple sclerosis, lupus, psoriasis, Graves' disease, Celiac disease, Crohn's disease, ulcerative colitis), macular degeneration, glaucoma, rheumatoid arthritis, osteoarthritis, Alzheimer's disease, Parkinson's disease, diabetes (Type 1 and 2), and risk to cancer (breast, lung, bladder, colorectal, gastric, ovarian, prostate and skin cancer). Our pharmacogenomic test identifies sensitivity and possible reactivity to common medicines.

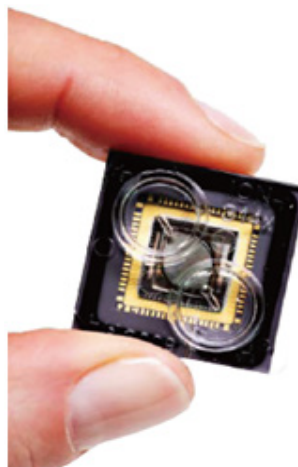
Why would the PDx™ test help you?

We know a medicine may work in some people and not in others having the same disease. The difference in response to treatment is caused by the patient-to-patient genetic variations in their DNA. Pharmacogenomic testing can help explain the differences. Your physician may use the information to prescribe the right medicine for you with the right dose. PDx™ personal genetic test assesses the risk whether certain diseases may develop later in your life. As genetics is not the only cause for diseases, your chance of developing a disease does not depend on genetics alone. Environment and lifestyle also play a critical role. Knowing your genetic risk helps you make informed decision and proper adjustments in your lifestyle to improve your health and wellness, and to avoid or delay development of a disease. Your doctor may be able to establish a proactive sentinel and prevention program for you.

How do you interpret PDx genetic test results?

There are three risk levels for each condition: (1) negative or decreased, (2) positive or increased, (3) average risk of a disease. Test results are given based on your risks versus the prevalence of a disease in your ethnicity, age and gender that are published by various agencies including the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO), American Heart Association (AHA), the National Institutes of Health (NIH), and the National Cancer Institute (NCI). For example, the prevalence for Type 2 diabetes

in European males aged 45-64 is 14%. If you are in this group and your test reveals an increased risk for the disease, it does not mean that you will definitely develop diabetes. Instead, it suggests that you will have a higher than average chance of developing it in your lifetime. As lifestyle plays a major role in the development of Type 2 diabetes, your genetic counselor may be able to advise you on ways to reduce your chance of developing the disease.



In age-related macular degeneration, tissue in the back of your eye that's responsible for your most precise vision begins to deteriorate. This causes a blind spot in the center of your visual field; fine newsprint may become harder to read and street signs more difficult to recognize. In some people, AMD advances so slowly that vision loss does not occur for a long time. In others, the disease progresses faster and may lead to a loss of vision in one or both eyes.

About two million Americans have macular degeneration, and it is the leading cause of severe vision loss in seniors. In the U.S., the lifetime risk of developing AMD is approximately 11.7%. AMD is more common among Caucasians than among African-Americans or Hispanics/Latinos after 70 years of age. At 80 years of age and older, the prevalence in Caucasians is 13.6%, whereas in African-Americans and other races and ethnic groups it is approximately 2.2%.



Knowing from genetic testing whether you have an inherited predisposition for the disease enables you and your doctor to be more alert to symptoms of macular degeneration as they arise, aiding early detection and treatment.

One of the best things you can do for your eye health is to have your vision checked regularly. Another important step in preventing macular degeneration is not to smoke. Smokers are at least two times more likely than non-smokers to have macular degeneration, and are more likely to develop advanced forms of the disease.

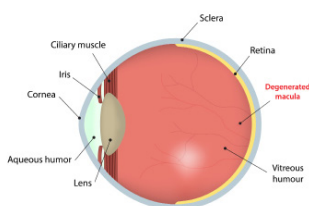
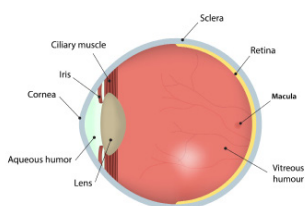
Researchers at the National Eye Institute tested whether taking nutritional supplements could protect against AMD in the Age-Related Eye Disease Studies (AREDS and AREDS2). They found that daily intake of certain high-dose vitamins and minerals can slow progression of the disease in people who have intermediate AMD, and those who have late AMD in one eye.

The first AREDS trial showed that a combination of vitamin C, vitamin E, beta-carotene, zinc, and copper can reduce the risk of late AMD by 25 percent. The AREDS2 trial found that adding lutein and zeaxanthin or omega-three fatty acids to the original AREDS formulation (with beta-carotene) had no overall effect on the risk of late AMD. However, the trial also found that replacing beta-carotene with a 5-to-1 mixture of lutein and zeaxanthin may help further reduce the risk of late AMD.

A number of manufacturers offer nutritional supplements that were formulated based on these studies. The label may refer to "AREDS" or "AREDS2." If you have intermediate or late AMD, you might benefit from taking such supplements. But first, be sure to review and compare the labels. Many of the supplements have different ingredients, or different doses, from those tested in the AREDS trials. Also, consult your doctor or eye care professional about which supplement, if any, is right for you.

Healthy Eye

Eye with Degenerated Macula



Diagnosis and Preventive Actions

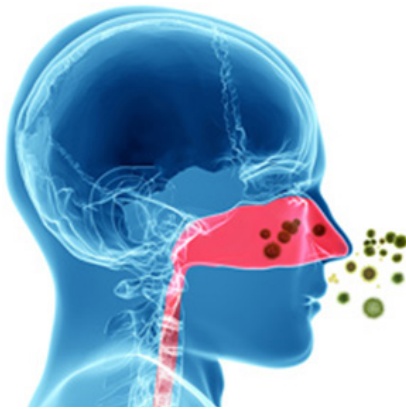
The early and intermediate stages of AMD usually start without symptoms. An eye care professional can help you understand your diagnosis and treatment. Only a comprehensive dilated eye exam by an eye professional can detect AMD. Your eye care professional also may ask you to look at an Amsler grid. Changes in your central vision may cause the lines in the grid to disappear or appear wavy, a sign of AMD. As AMD progresses, a blurred area near the center of vision is a common symptom. Over time, the blurred area may grow larger or you may develop blank spots in your central vision. Objects also may not appear to be as bright as they used to be.

The risk factors for AMD include age, race, gender and family history (genetics). Age is a major risk factor for AMD. The disease is most likely to occur after age 60, but it can occur earlier. People with a family history of AMD are at higher risk. Scientists have identified several common genetic variants that are associated with increased risk of macular degeneration. They include missense mutations in the CFH and HTRA1 genes. These variants can cause your risk of developing AMD to rise steeply, some at earlier ages, depending on whether you have one (carrier or heterozygous) or two copies of the mutations (homozygous). Our test can find out your carrier status for these markers and provides you with your genetic risk assessment.

ALLERGIC RHINITIS & GRASS SENSITIZATION

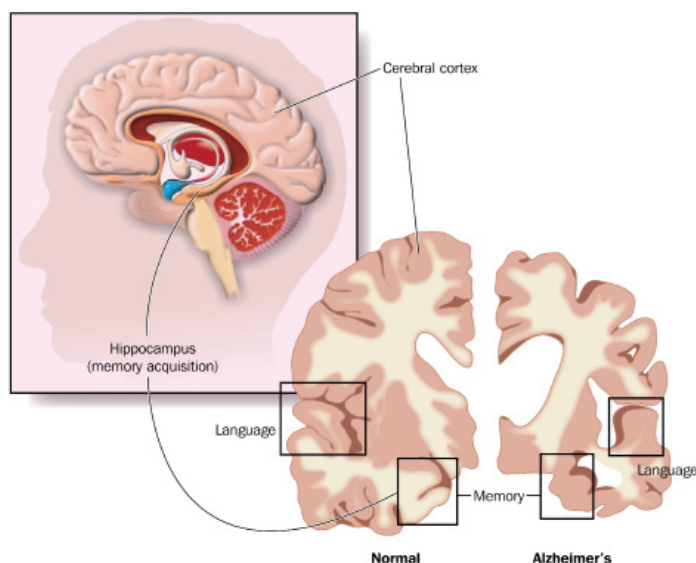
GCIR002

The development of allergic rhinitis entails a complex interaction between genetic predisposition and environmental exposure to different factors, of which the most important is the implicated allergen. There is a clear hereditary component in allergic rhinitis that has been well corroborated by segregation studies and investigations in twins. From the strictly genetic perspective, it is believed that the disease may be the result of the interaction of different genetic alterations, each of which would contribute a small defect.



ALZHEIMER'S DISEASE (AD)

Alzheimer's, the most common form of dementia, is a progressive disease of the brain that causes problems with memory, thinking and behavior. It gradually destroys brain cells, making it increasingly difficult for people to work, participate in hobbies and even care for themselves. It is not a natural part of aging.



More than five million Americans have Alzheimer's. Although the majority cases occur in the elderly, approximately 250,000 people have early-onset AD with onset of symptoms before age 65 years. The incidence of Alzheimer's disease is increasing due, in part, to increased life expectancy and the aging of baby boomer generation. Because the population is living longer, the number of people with this disease is expected to more than triple by 2050. The average lifetime risk of developing AD is 10 – 12%. This risk at least doubles with the presence of a first-degree relative with the disorder.

Although about three-fourths of cases occur in people with no apparent family history, nonetheless genetic changes are likely to play a key role. One of the primary culprits is thought to be the $\epsilon 4$ version of the apolipoprotein E (APOE) gene. This gene carries the code for a protein that helps transport cholesterol in the bloodstream. Those who have one (carrier - heterozygous) or two copies (homozygous) of the $\epsilon 4$ variant of APOE gene are known to have a higher risk for Alzheimer's. Our genetic test looks for the variants in the APOE gene as well as other affected genes and determines your genetic risk.

Diagnosis and Preventive Actions

Most people who develop Alzheimer's are diagnosed after age 80. There is evidence that the number of people who are diagnosed with Alzheimer's doubles between age 79 and age 84, and doubles again between age 85 and age 90. Family history is also a significant factor for Alzheimer's disease.

Although the APOE $\epsilon 4$ variant is the single strongest risk factor for late-onset Alzheimer's, individuals with the genetic variant who also have a first-degree relative (such as a parent or sibling) with Alzheimer's and has the same genetic variant can more than double their risk of developing the disease.

Early onset Alzheimer's disease, which begins before age 60, is even more strongly genetic in its cause, but very rare — it represents less than two percent of cases. We also test for this allele's genetic variants.

Fortunately, exercising your body and your mind may improve blood flow to the brain and increase connections between nerve cells, helping compensate for the brain's degeneration. Recent research suggests you can even generate new brain cells. Working on puzzles or picking up a new hobby can be of benefit in preventing Alzheimer's disease. Seniors with an active social life are less likely to suffer cognitive decline. Recent studies have shown that people eating fish and/or taking omega-3 fatty acids regularly have a larger brain mass than the control group.

Eating baked or broiled fish once a week is good for the brain, regardless of how much omega-3 fatty acid it contains, according to researchers from University of Pittsburgh School of Medicine. People who ate a diet that included baked or broiled, but not fried, fish have larger brain volumes in regions associated with memory and cognition. The findings add to growing evidence that lifestyle factors contribute to brain health later in life. The study was published online recently in the American Journal of Preventive Medicine. Scientists estimate that more than 80 million people will have dementia by 2040, which could become a substantial burden to families and drive up health care costs.

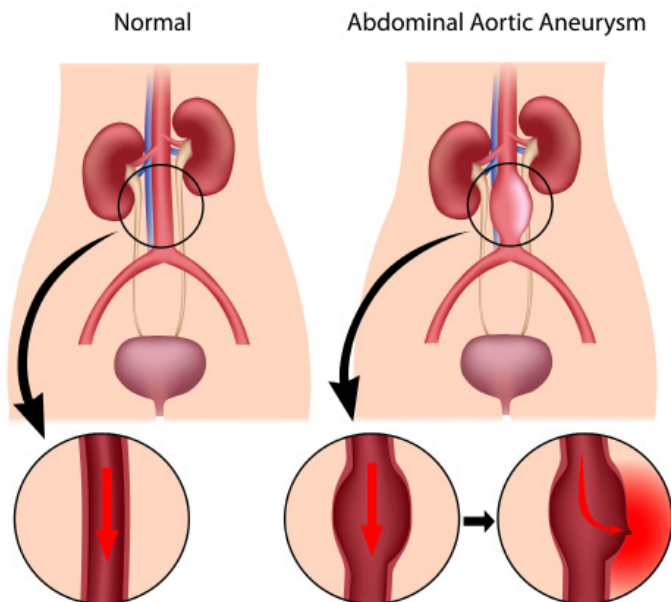
It is important for individuals concerned about their risk of the disease to talk to a medical professional or genetic counselor. If you begin experiencing serious memory loss or confusion, your doctor can give you a simple mental function test to screen for Alzheimer's disease. Brain imaging can also be a helpful test.



AORTIC ANEURYSM

GCIR004

Aortic aneurysm includes abdominal and intracranial aneurysm. An abdominal aneurysm is a weakened, bulging area in the aorta, the major vessel that feeds blood to the body. Most aneurysms are small, grow slowly and cause no symptoms. Those that rupture, however, can result in life-threatening bleeding. Each year, nearly 14,000 Americans die of a ruptured abdominal aneurysm.



This condition is diagnosed in 200,000 people in the United States each year. It is the most common form of aortic aneurysm, which can also occur in the chest. Abdominal aortic aneurysms are rare in people under the age of 60.

Intracranial aneurysm is a cerebral or brain aneurysm which is a cerebrovascular disorder in which weakness in the wall of a cerebral artery or vein causes a localized dilation or ballooning of the blood vessel. A small, unchanging aneurysm will produce few, if any, symptoms. Before a larger aneurysm ruptures, the individual may experience such symptoms as a sudden and unusually severe headache, nausea, vision impairment, vomiting, and loss of consciousness, or the individual may be asymptomatic, experiencing no symptoms at all.

If an aneurysm ruptures, it leaks blood into the space around the brain. This is called a “subarachnoid hemorrhage.” Depending on the amount of blood, it can produce:

- A sudden severe headache that can last from several hours to days
- Nausea and vomiting
- Drowsiness and/or coma

The ruptured aneurysm (hemorrhage) may also damage the brain directly, usually from bleeding into the brain itself. This is called a “hemorrhagic stroke.” This can lead to:

- Weakness or paralysis of an arm or leg
- Trouble speaking or understanding language
- Vision problems
- Seizures

Diagnosis and Preventive Actions

Aneurysms usually stem from a mix of genetic and behavioral causes, with genes being mostly to blame. Our genetic test looks for multiple clinically validated genetic markers on a person’s genome where differences in the genetic code can considerably raise the risk of developing an aneurysm.

Having a good understanding of your overall genetic risk of aneurysm can help you and your doctor determine whether you should undergo screening for aneurysm, and can encourage you to take the steps necessary to improve your odds – and your health.

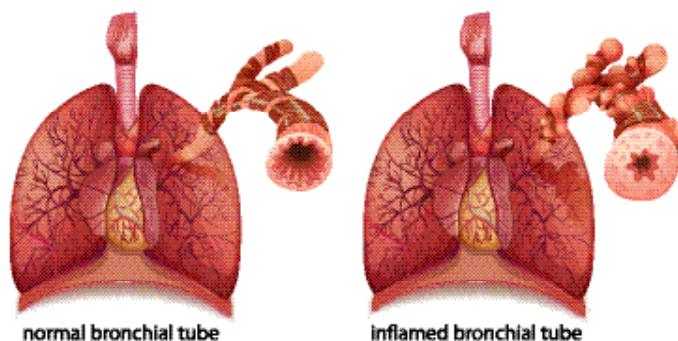
Although your genes contribute the most to your risk, preventing aneurysm – or at least slowing the rate of enlargement – is not impossible. Keeping your blood pressure under control, getting regular exercise, reducing cholesterol and fat in your diet, and abstaining from smoking are all helpful in preventing and controlling abdominal aneurysm. If testing for abdominal aneurysm leads to early detection, then the condition can be treated before it becomes life-threatening.



ASTHMA

A tendency to develop asthma is inherited. If one of your biologic parents has or had asthma, then you are more likely to develop asthma than if he or she did not have asthma. If both of your parents have asthma, you are even more likely to develop asthma than if only one parent has this condition.

Asthma - Inflamed Bronchial Tube



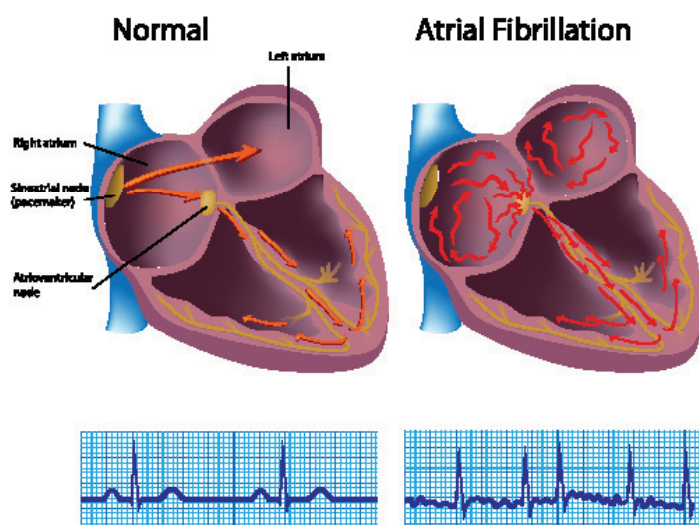
Another confirmation that asthma is inherited comes from studies of twins. If one identical twin has asthma, the other twin (who shares all the same genetic information as identical twin) is more likely to have asthma than when one of two non-identical twin siblings (who share some but not all of their genes in common) has asthma.



ATRIAL FIBRILLATION (AF)

GCIR006

AF is the most common cardiac arrhythmia (abnormal heart rhythm), a heart disease that increases the chance of stroke. Its name comes from the fibrillating (i.e., quivering) of the heart muscles of the atria, instead of a coordinated contraction. AF is usually accompanied by symptoms related to a rapid heart rate. Rapid and irregular heart rates may be perceived as palpitations, exercise intolerance, and occasionally produce angina (if the rate is faster and puts the heart under strain) and congestive symptoms of shortness of breath or edema, or congestive heart failure. Sometimes the arrhythmia will be identified only with the onset of a stroke or a transient ischemic heart attack. It is not uncommon for a patient to first become aware of AF from a routine physical examination or ECG, as it may be asymptomatic in many cases.



Do you know that warfarin, a commonly used generic anticoagulant drug, has long been the standard treatment for AF? Depending on the risk of stroke and systemic embolism, people with AF may use anticoagulants such as warfarin, which substantially reduces the risk of AF but may increase the risk of major bleeding. Our pharmacogenomic test can help you reduce the risk of bleeding caused from taking warfarin by providing the correct genotype information on your drug metabolizing enzymes so that your doctor can prescribe the correct dose of the drug for you (refer to pages 3 – 4 of this report) . Recent new drugs include Pradaxa (Boehringer Ingelheim), Xarelto (Johnson & Johnson and Bayer), and Eliquis (Pfizer and Bristol-Myers Squibb). AF may be treated with medications to either slow the heart rate to a normal range or revert the heart rhythm back to normal. Ask your doctor for further information if you have any concerns on the disease.

Diagnosis and Preventive Actions

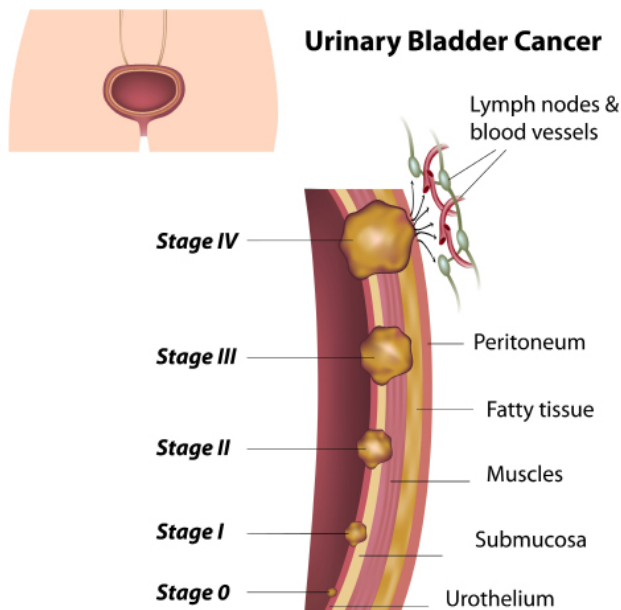
Knowing your genetic risk for AF can help you and your doctor to be better prepared when you ever experience any of the early symptoms related to AF. It can improve your chance of timely treatment of the disease or even taking proactive measurements including screening and diagnosis.

Screening for AF is not generally performed, although routine pulse checks or ECGs during a routine office visit can help high risk individuals spot the disease early. However, an electrocardiogram is essential for diagnosis. The evaluation of AF involves diagnosis, determination of the etiology of the arrhythmia, and classification of the arrhythmia. The minimal evaluation of AF is a history and physical examination, ECG, transthoracic echocardiogram, and case specific blood work. Individuals may benefit from an in-depth evaluation which may include correlation of the heart rate response to exercise, exercise stress testing, chest X-ray, trans-esophageal echocardiography, and other studies.

BLADDER CANCER

Bladder cancer is any of several types of malignancy arising from the epithelial lining (i.e., the urothelium) of the urinary bladder. The most common type of bladder cancer recapitulates the normal histology of the urothelium and is known as transitional cell carcinoma or more properly urothelial cell carcinoma. It is estimated that there are 383,000 cases of bladder cancer worldwide.

A 2008 study commissioned by the World Health Organization (WHO) concluded that “specific fruit and vegetables may act to reduce the risk of bladder cancer.” Fruit and yellow-orange vegetables, particularly carrots and those containing selenium, are probably associated with a moderately reduced risk of bladder cancer. Citrus fruits and cruciferous vegetables were also identified as having a possibly protective effect.



Thirty percent of bladder tumors probably result from occupational exposure in the workplace to carcinogens such as benzidine. Occupations at risk are bus drivers, rubber workers, motor mechanics, leather (including shoe) workers, blacksmiths, machine setters, and mechanics. Hairdressers are thought to be at risk as well because of their frequent exposure to permanent hair dyes.

Diagnosis and Preventive Actions

It has been suggested that mutations at HRAS, KRAS2, RB1, and FGFR3 may be associated with bladder cancer in some cases. Many patients with a history, signs, and symptoms suspicious for bladder cancer are referred to a urologist or other physician trained in cystoscopy, a procedure in which a flexible tube bearing a camera and various instruments is introduced into the bladder through the urethra. Suspicious lesions may be biopsied and sent for pathologic analysis.

Tobacco smoking is the main known contributor to urinary bladder cancer; 2-Naphthylamine, which is found in cigarette smoke, has also been shown to increase bladder cancer risk. In most populations, smoking is associated with over half of bladder cancer cases in men and one-third of cases among women. There is a linear relationship between smoking and risk, and quitting smoking reduces the risk. Passive smoking has not been proven to be involved.

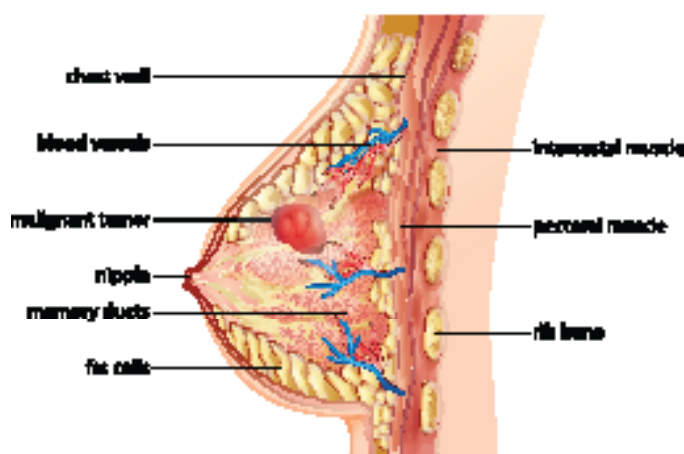
In a 10-year study involving almost 48,000 men, researchers found that men who drank 1.5 liters of water per day had a significantly reduced incidence of bladder cancer when compared with men who drank less than 240mL (around 1 cup) per day.

BREAST CANCER

GCIR008

Breast cancer is a type of cancer originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk. Cancers originating from ducts are known as ductal carcinomas, while those originating from lobules are known as lobular carcinomas. Breast cancer occurs in humans and other mammals. While the overwhelming majority of human cases occur in women, male breast cancer can also occur.

Worldwide, breast cancer accounts for 22.9% of all cancers (excluding non-melanoma skin cancers) in women. In 2008, breast cancer caused 458,503 deaths worldwide (13.7% of cancer deaths in women). Breast cancer is more than 100 times more common in women than in men, although men tend to have poorer outcomes due to delays in diagnosis. Early detection of breast cancer usually produces better prognosis in treatment and can save lives.



Diagnosis and Preventive Actions

Large amounts of clinical data have shown that early detection of breast cancer can save lives and significantly improve the quality of life for those affected. The two most commonly used screening methods are physical examination of the breasts by a healthcare provider and mammography. Pathological testing of biopsy is used to confirm cancerous tissue in the affected area. Genetic susceptibility probably plays a role in most cases. In those with zero, one or two affected relatives the risk of breast cancer before the age of 80 is 7.8%, 13.3%, and 21.1% with a subsequent mortality from the disease of 2.3%, 4.2%, and 7.6% respectively. In those with a first degree relative with the disease the risk of breast cancer between the age of 40 and 50 is double that of the general population. The primary risk factors for breast cancer are female sex and older age. Other potential risk factors include: genetics, lack of childbearing or lack of breastfeeding, higher levels of certain hormones, and obesity.

In about 5% of the cases studied, genetics plays a more significant role. This includes the hereditary breast-ovarian cancer syndrome in women who carry the BRCA1 and BRCA2 gene mutations which confer a lifetime risk of breast cancer of between 60 and 85 percent and a lifetime risk of ovarian cancer of between 15 and 40 percent. These mutations account for up to 90% of the total genetic influence in those affected. Other significant gene mutations include p53 (Li-Fraumeni syndrome), PTEN (Cowden syndrome), STK11 (Peutz-Jeghers syndrome), CHEK2, ATM, BRIP1, and PALB2. Individuals with mutations in BRCA1 and BRCA2 benefit from tailored management aimed at reducing cancer risks and detecting cancers early when they are most treatable.

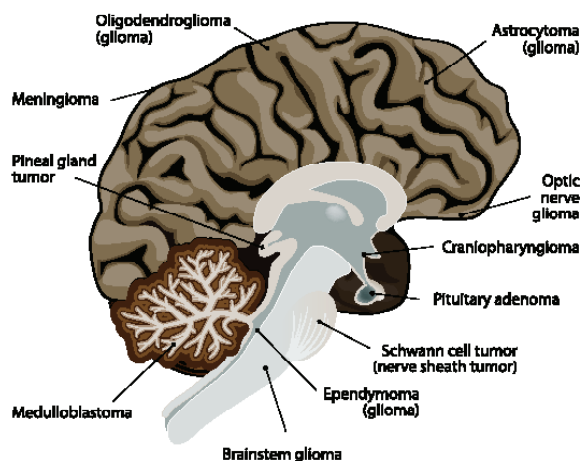
Women may reduce their risk of breast cancer by maintaining a healthy weight, drinking less alcohol, being physically active, and breastfeeding their children. The benefits of moderate exercise, such as brisk walking, are seen at all age groups including postmenopausal women. There is a relationship between diet and breast cancer, including an increased risk with a high fat diet, alcohol intake, higher cholesterol levels, and obesity. Smoking tobacco appears to increase the risk of breast cancer, with the greater the amount smoked and the earlier in life that smoking began, the higher the risk.



BRAIN TUMOR

Scientists have discovered commonly inherited genetic risks for the deadliest types of brain tumors. At least 20 percent of the advanced brain cancers may be attributable to the genetic risks, according to published studies. The most widely studied brain tumors are gliomas, or more specifically glioblastoma and anaplastic astrocytomas. These forms account for about three-quarters of all malignant brain tumors.

The most common primary brain tumors



People with brain tumors often suffer from:

- Headaches
- Seizures
- Sensory (touch) and motor (movement control) loss
- Deep venous thrombosis (DVT, or blood clot)
- Hearing loss
- Vision loss
- Fatigue
- Depression
- Behavioral and cognitive (thinking) changes
- Endocrine dysfunction (hormone/gland changes)

CELIAC DISEASE

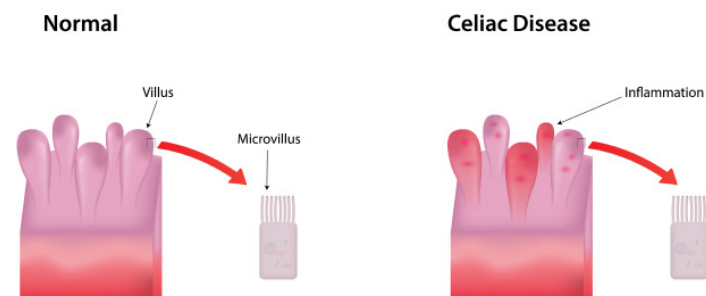
GCI010

Celiac disease is an autoimmune disorder of the small intestine that occurs in genetically predisposed people of all ages from middle infancy onward. Symptoms include pain and discomfort in the digestive tract, chronic constipation and diarrhea, failure to thrive (in children), and fatigue, but these may be absent, and symptoms in other organ systems have been described. Vitamin deficiencies are often noted in people with Celiac disease due to the reduced ability of the small intestine to properly absorb nutrients from food. A person confirmed to have Celiac disease can prevent malnutrition by changing diet and taking multivitamin supplements. This is critical to a person's physical and mental health and well being, especially in children.

While the disease is caused by a reaction to wheat proteins, it is not the same as wheat allergy.



This condition has several other names, including celiac disease, celiac sprue, non-tropical sprue, endemic sprue, gluten enteropathy or gluten-sensitive enteropathy, and gluten intolerance.



Diagnosis and Preventive Actions

The vast majority of people with Celiac have one of two types of the HLA-DQ protein. Almost all people with Celiac disease have either the variant HLA-DQ2 allele or (less commonly) the HLA-DQ8 allele. There are seven HLA-DQ variants (DQ2 and DQ4-DQ9). Over 95% of people with Celiac have the isoform of DQ2 or DQ8, which is inherited in families. The reason these genes produce an increase in risk of celiac disease is that the receptors formed by these genes bind to gliadin peptides more tightly than other forms of the antigen-presenting receptor. Therefore, these forms of the receptor are more likely to activate T lymphocytes and initiate the autoimmune process.

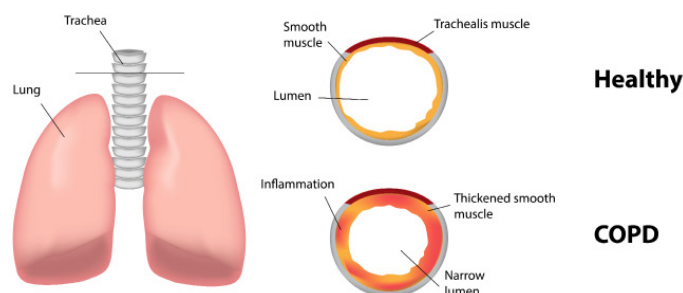
Increasingly, diagnoses are being made in asymptomatic persons as a result of increased screening; the condition is thought to affect approximately 3 million people in the United States. Celiac disease is caused by a reaction to gliadin, a prolamin (gluten protein) found in wheat, and similar proteins found in the crops of the tribe Triticeae (which includes other common grains such as barley and rye).

Upon exposure to gliadin, and specifically to three peptides found in prolamins, the enzyme tissue transglutaminase modifies the protein, and the immune system cross-reacts with the small-bowel tissue, causing an inflammatory reaction. That leads to a truncating of the villi lining the small intestine (called villous atrophy). This interferes with the absorption of nutrients, because the intestinal villi are responsible for absorption. The only known effective treatment is a lifelong gluten-free diet.

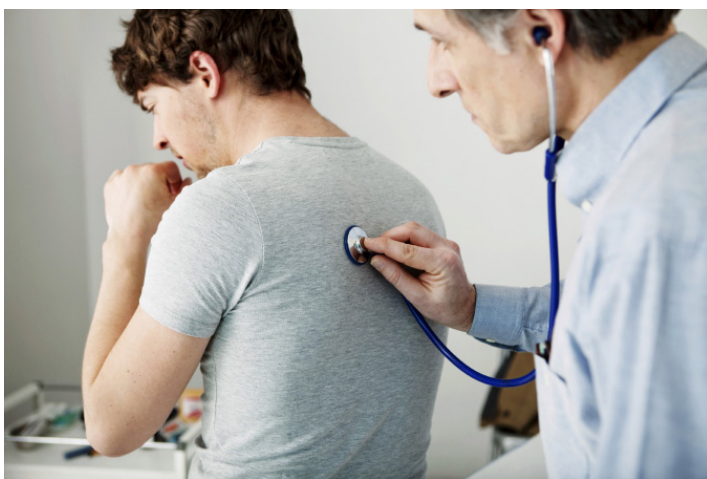
CHRONIC OBSTRUCTIVE PULMONARY DISEASE

GCIR011

COPD (chronic obstructive pulmonary disease) is a type of obstructive lung disease characterized by chronically poor airflow. It gets worse over time and in advanced age. Worldwide, COPD affects 329 million people or nearly 5% of the population. In 2012, it ranked as the third-leading cause of death, killing over 3 million people. The number of deaths is projected to increase due to higher smoking rates, air pollutions in developing countries such as China and India, and an aging population in many countries.



COPD can be prevented by reducing exposure to the known causes. This includes quitting smoking and to improve indoor and outdoor air quality. COPD in some people is resulted from a genetic condition known as alpha-1 antitrypsin (or AAT) deficiency. While very few people know themselves have alpha-1 antitrypsin deficiency, it is estimated that about 100,000 Americans have such condition. The risk is particularly high if someone deficient in alpha 1-antitrypsin also smokes. People with alpha-1 antitrypsin deficiency can get COPD even if they have never smoked or had long-term exposure to harmful pollutants.



COLORECTAL CANCER

GCIR012

Colorectal cancer, commonly known as colon cancer or bowel cancer, is a cancer from uncontrolled cell growth in the colon or rectum (parts of the large intestine), or in the appendix. Colon cancer and rectal tumors present genetically as the same cancer. Symptoms of colorectal cancer typically include rectal bleeding and anemia which are sometimes associated with weight loss and changes in bowel habits.

Most colorectal cancer occurs due to lifestyle and increasing age with a minority associated with underlying genetic disorders. It typically starts in the lining of the bowel and if left untreated, can grow into the muscle layers underneath, and then through the bowel wall.

Cancers that are confined within the wall of the colon are often curable with surgery while cancer that has spread widely around the body is usually not curable and management then focuses on extending the person's life via chemotherapy and improving quality of life. Colorectal cancer is the third most commonly diagnosed cancer in the world, but it is more common in developed countries. Around 60% of cases were diagnosed in the developed world. IN 2008, it was estimated that 1.23 million new cases of colorectal cancer were clinically diagnosed, and that it killed 608,000 people.

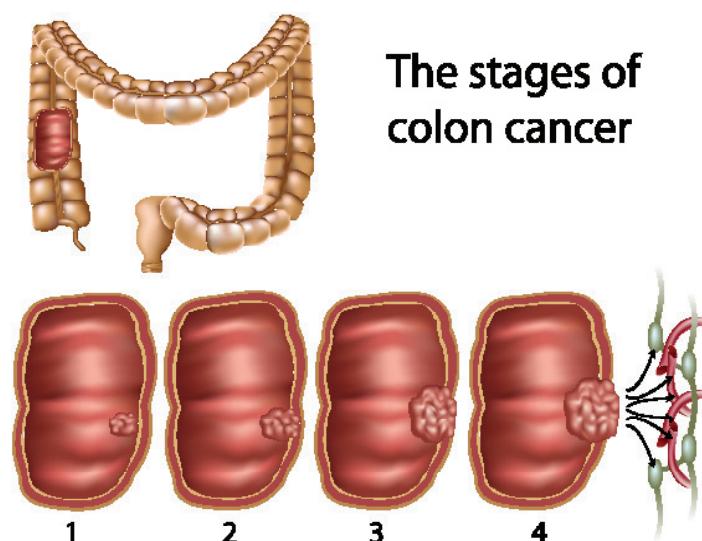
Greater than 75% of colon cancer occurs in people with little or no genetic risk. Other risk factors include older age, male gender, high intake of fat, alcohol or red meat, obesity, smoking and a lack of physical exercise. Approximately 10% of cases are linked to insufficient activity. The risk for alcohol appears to increase at greater than one drink per day.



Diagnosis and Preventive Actions

The risk is greater the longer a person has had the disease and the worse the severity of inflammation. Screening is effective at decreasing the chance of dying from colorectal cancer and is recommended starting at the age of 50 and continuing until a person is 75 years old. Localized bowel cancer is usually diagnosed through colonoscopy. Diagnosis of colorectal cancer is via tumor biopsy typically collected during sigmoidoscopy or colonoscopy. The extent of the disease is then usually determined by a CT scan of the chest, abdomen and pelvis. People with inflammatory bowel disease (ulcerative colitis and Crohn's disease) are at increased risk of colon cancer.

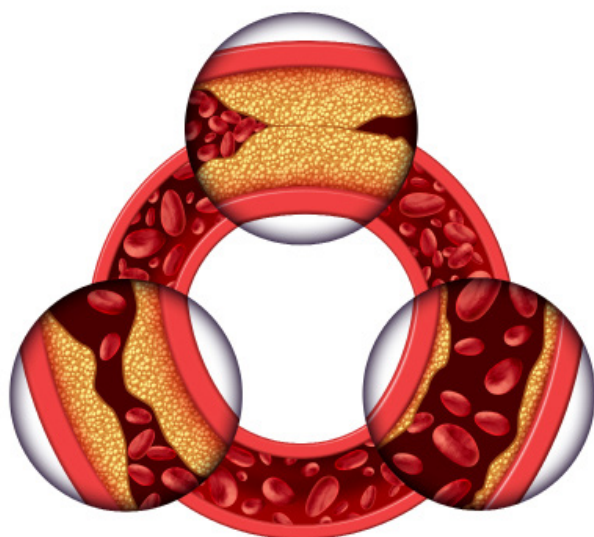
Those with a family history in two or more first-degree relatives have a two to threefold greater risk of disease and this group accounts for about 20% of all cases. A number of genetic syndromes are also associated with higher rates of colorectal cancer. The most common of these is hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome) which is present in about 3% of people with colorectal cancer. Other syndromes that are strongly associated include Gardner syndrome and familial adenomatous polyposis (FAP), in which cancer nearly always occurs and is the cause of 1% of cases. Colonoscopy is clearly preferred for high-risk people.



CORONARY HEART DISEASE

Coronary heart disease (CHD) is the narrowing or blockage of the coronary arteries, usually caused by atherosclerosis. Atherosclerosis (sometimes called “hardening” or “clogging” of the arteries) is the buildup of cholesterol and fatty deposits (called plaques) on the inner walls of the arteries. These plaques can restrict blood flow to the heart muscle by physically clogging the artery or by causing abnormal artery tone and function. According to the latest statistics released from the CDC and American Heart Association (AHA), death from CHD represents approximately 50% of all deaths related to cardiovascular disease in the U.S.

Heart attacks most often occur as a result of coronary heart disease. Without an adequate blood supply, the heart becomes starved of oxygen and the vital nutrients it needs to work properly. This can cause chest pain called angina. If blood supply to a portion of the heart muscle is cut off entirely, or if the energy demands of the heart become much greater than its blood supply, a heart attack (injury to the heart muscle) may occur. More than one million people in the United States have heart attacks each year. When a heart attack happens, delay in treatment can be deadly.



Each year, more than 225,000 people in the U.S. die from heart attacks within one hour of the onset of symptoms and before ever reaching a hospital. Somewhere between 230,000 and 325,000 people in the U.S. succumb to sudden cardiac death caused by coronary heart disease every year. Estimated deaths due to coronary heart disease total 7.1 million per year worldwide.

Coronary artery disease has a number of well determined risk factors. The most common risk factors include family history

(genetics), age, gender, smoking, hypertension, obesity, diabetes, high alcohol consumption, lack of exercise, stress, and hyperlipidemia. Smoking is associated with about 54% of cases and obesity 20%. Lack of exercise has been linked to 7–12% of cases. Job stress appears to play a minor role accounting for about 3% of cases.

Diagnosis and Preventive Actions

For symptomatic patients, stress echocardiography (ECG) can be used to make a diagnosis for obstructive coronary artery disease. However, the use of ECG is not recommended on individuals who are exhibiting no symptoms and are otherwise at low risk for developing coronary disease.



Often a person's FIRST heart attack is a fatal one! Only a minority of people who have a heart attack survive to have another one, and a very few will have multiple heart attacks before they have a fatal one. As such, it is very important that we make the right healthcare and lifestyle choices while we are young to reduce the likelihood of heart disease later in life. For those people who do not have a good chance of surviving the first heart attack, it is important to find ways to prevent that first heart attack from ever happening.

While there are many traits that are common among heart attack patients – both those who survive the event and those who die suddenly – researchers found that some traits, such as hypertension, race/ethnicity, body mass index (BMI), heart rate, and additional markers that can be identified by

CORONARY HEART DISEASE, *continued*

GCIRO14

an electrocardiogram (ECG) and large sizes of genome-wide association studies, can differentiate between dying suddenly versus living through a heart attack.

Lifestyle changes have been shown to be effective in reducing (and in the case of diet, reversing) coronary disease. Diet, weight control, smoking cessation, avoiding the consumption of trans fats (in partially hydrogenated oils) and larger amounts of alcoholic drink, and exercise like walking, jogging, or swimming, can help decrease blood pressure and the amount of blood cholesterol over time.

Statins, which reduce cholesterol, reduce risk of coronary disease. ACE inhibitors, which treat hypertension, may lower the risk of recurrent myocardial infarction. Calcium channel blockers, which are used to decrease blood pressure in patients with hypertension, have various benefits to some high risk individuals. Beta-blockers, which are used for the management of cardiac arrhythmias, protecting the heart from a second heart attack (myocardial infarction) after a first heart attack (secondary prevention), also show some beneficial effects. Consult with your doctor for medication and professional advice if you have any concerns about coronary heart disease.

High blood cholesterol can affect anyone. It's a serious condition that increases the risk for heart disease – the higher your blood cholesterol level, the greater your risk. If you have high blood cholesterol, there are steps you can take to lower it and protect your health. The National Heart, Lung and Blood Institute advocates Therapeutic Lifestyle Changes, or TLC, a three-part program that uses diet, physical activity, and weight management to lower a person's blood cholesterol level, especially the low-density lipoprotein (LDL) level to reduce risk of a heart attack or other chronic disease caused by hardening of the arteries. Sometimes, drug treatment is also needed to lower blood cholesterol enough. But even then, the TLC Program should be followed.

High blood pressure (HBP), or hypertension, is a serious condition that can lead to coronary heart disease, heart failure, stroke, kidney failure, and other health problems. About one in three adult men and women in the U.S. have HBP. The condition itself usually has no signs or symptoms. You can have it for years without knowing it. During this time, though, HBP can damage your heart, blood vessels, kidneys, and other parts of your body. Knowing your blood pressure numbers is important, even when you're feeling fine. If your blood pressure is normal, you can work with your health care team to keep it that way. If your blood pressure is too high, treatment may help prevent damage to your body's organs.

Parental history of high blood pressure can also contribute to a higher risk of heart disease in an individual. People whose parents are hypertensive have greater systolic and diastolic blood pressure numbers when compared with individuals without hypertensive parents. High blood pressure has been

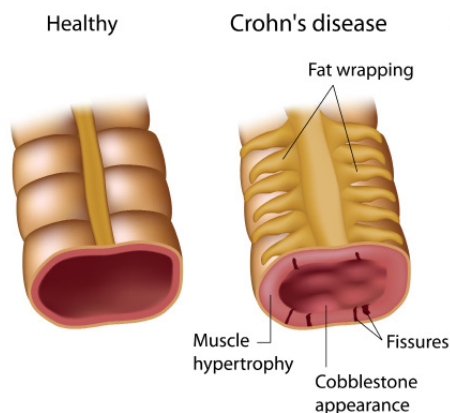


shown to be a cause of heart disease. Blood pressure tends to rise with age. Following a healthy lifestyle helps some people delay or prevent this rise in blood pressure. People who have HBP can take steps to control it and reduce their risk for related health problems. Key steps include following a healthy lifestyle, having ongoing medical care, and following your treatment plan.

CROHN'S DISEASE

GCIRO15

Crohn's disease, also known as Crohn syndrome and regional enteritis, is a type of inflammatory bowel disease that may affect any part of the gastrointestinal tract from mouth to anus, causing a wide variety of symptoms. It primarily causes abdominal pain, diarrhea (which may be bloody if inflammation is at its worst), vomiting (can be continuous), or weight loss, but may also cause complications outside the gastrointestinal tract such as skin rashes (eg, erythema nodosum), arthritis, inflammation of the eye, tiredness, and lack of concentration. Crohn's disease also increases the risk of blood clots; painful swelling of the lower legs can be a sign of deep venous thrombosis, while difficulty breathing may be a result of pulmonary embolism.



Crohn's disease is caused by interactions between environmental, immunological, and bacterial factors in genetically susceptible individuals. This results in a chronic inflammatory disorder, in which the body's immune system attacks the gastrointestinal tract possibly directed at microbial antigens. Crohn's disease has wrongly been described as an autoimmune disease in the past; recent investigations have described it as an immune deficiency state. Crohn's disease affects between 400,000 and 600,000 people in North America. Prevalence estimates for Northern Europe have ranged from 27–48 per 100,000.

Diagnosis and Preventive Actions

The diagnosis of Crohn's disease can sometimes be challenging, and a number of tests are often required to assist the physician in making the diagnosis. Even with a full battery of tests, it may not be possible to diagnose Crohn's with complete certainty; a colonoscopy is approximately 70% effective in diagnosing the disease, with further tests being less effective. Disease in the small bowel is particularly difficult to diagnose, as a traditional colonoscopy allows access to only the colon and lower portions of the small intestines.

There is a genetic association with Crohn's disease, primarily with variations of the NOD2 gene and its protein, which senses bacterial cell walls. Over thirty genes are found to be associated with the disease. Siblings of affected individuals are thirty

times more likely to have the disease. Males and females are equally affected. Smokers are two times more likely to develop Crohn's disease than nonsmokers. Therefore, individuals with an increased genetic risk can reduce their risk by cessation of cigarette smoking. Smoking increases the risk of the return of active disease (flares). The introduction of hormonal contraception in the United States in the 1960s is associated with a dramatic increase in incidence, and one hypothesis is that these drugs work on the digestive system in ways similar to smoking. Stress is sometimes claimed to exacerbate Crohn's disease.

Certain lifestyle changes can reduce symptoms, including dietary adjustments, elemental diet, proper hydration, and eating small meals. The increased incidence of Crohn's in the industrialized world indicates an environmental component. Crohn's is associated with an increased intake of animal protein, milk protein and an increased ratio of omega-6 to omega-3 polyunsaturated fatty acids. Those who consume vegetable proteins appear to have a lower incidence of Crohn's disease. Consumption of fish protein has no association. Fatigue can be helped with regular exercise, a healthy diet, and adequate sleep.



DIABETES, TYPE 1

GCIR016

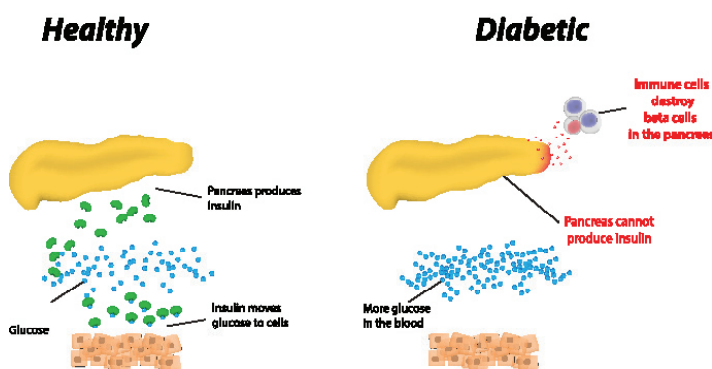
Type 1 diabetes, or insulin-dependent diabetes mellitus (IDDM), or formerly, juvenile diabetes, is a form of diabetes mellitus that results from autoimmune destruction of insulin-producing beta cells of the pancreas. The subsequent lack of insulin leads to increased blood and urine glucose. The classical symptoms are polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), and weight loss. Type 1 diabetes make up less than 10% of cases of all diabetes with the other 90% due primarily to Type 2 diabetes mellitus.

0201, which are common in North Americans of European ancestry and in Europeans. There are also variants that appear to be protective.

There is a strong genetic basis for Type 1 diabetes. The risk of a child developing Type 1 diabetes is approximately 10% if the father has it, approximately 10% if a sibling has it, approximately 4% if the mother has Type 1 diabetes and is/was aged 25 or younger when the child is/was born, and approximately 1% if the mother is/was over 25 years old when the child is/was born.

Type 1 diabetes is not currently preventable. Eventually, Type 1 diabetes is fatal unless treated with insulin. Injection is the most common method of administering insulin. Other alternatives are pancreatic transplants as well as pancreatic islet cell transplantation.

Type 1 Diabetes



Diagnosis and Preventive Actions

Diabetes mellitus is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating any one of the following:

- Fasting plasma glucose level at or above 7.0 mmol/L (126 mg/dL).
- Plasma glucose at or above 11.1 mmol/L (200 mg/dL) two hours after a 75 g oral glucose load as in a glucose tolerance test.
- Symptoms of hyperglycemia and casual plasma glucose at or above 11.1 mmol/L (200 mg/dL).
- Glycated hemoglobin (hemoglobin A1C) at or above 6.5. (This criterion was recommended by the American Diabetes Association in 2010, although it has yet to be adopted by the WHO.)

Type 1 diabetes is a polygenic disease, meaning many different genes contribute to its onset. Depending on locus or combination of loci, it can be dominant, recessive, or somewhere in-between. The strongest gene, IDDM1, is located in the MHC Class II region on chromosome 6, at staining region 6p21. Certain variants of this gene increase the risk for decreased histocompatibility characteristic of Type 1. Such variants include DRB1 0401, DRB1 0402, DRB1 0405, DQA 0301, DQB1 0302 and DQB1



DIABETES, TYPE 2

Diabetes mellitus Type 2 (formerly noninsulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes) is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency. This is in contrast to diabetes mellitus Type 1, in which there is an absolute insulin deficiency due to destruction of islet cells in the pancreas. The classic symptoms are excess thirst, frequent urination, and constant hunger. Type 2 diabetes make up about 90% of cases of diabetes with the other 10% due primarily to diabetes mellitus Type 1 and gestational diabetes. Obesity is thought to be the primary cause of Type 2 diabetes in people who are genetically predisposed to the disease.

to be called diabetes. Studies have shown that by losing weight and increasing physical activity people can prevent or delay pre-diabetes from progressing to diabetes.

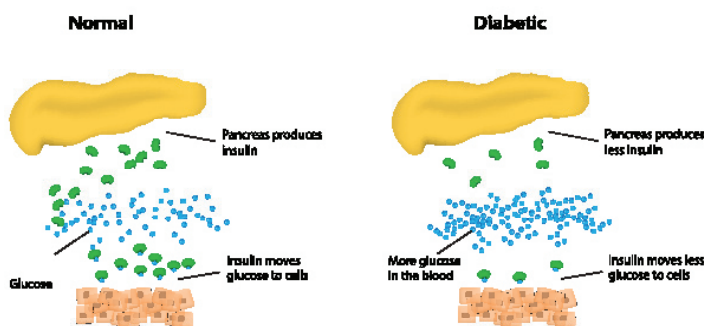
How much does diabetes cost the United States?

- Total health care and related costs for the treatment of diabetes run about \$174 billion annually.
- Of this total, direct medical costs (e.g., hospitalizations, medical care, and treatment supplies) account for about \$116 billion.
- The other \$58 billion covers indirect costs such as disability payments, time lost from work, and premature death.

The development of Type 2 diabetes is caused by a combination of lifestyle and genetic factors. Rates of Type 2 diabetes have increased markedly over the last 50 years in parallel with obesity: As of 2010 there are approximately 285 million people with the disease compared to around 30 million in 1985. This is equivalent to about 6% of the world's adult population. Long-term complications from high blood sugar can include heart disease, strokes, diabetic retinopathy where eyesight is affected (blurred vision), kidney failure which may require dialysis, and poor circulation of limbs leading to amputations.

Type 2 diabetes is typically a chronic disease associated with a ten-year-shorter life expectancy. This is partly due to a number of complications with which it is associated, including two to four times the risk of cardiovascular disease which includes ischemic heart disease and stroke; a 20-fold increase in lower limb amputations, and increased rates of hospitalizations. In the developed world, and increasingly elsewhere, Type 2 diabetes is the largest cause of non-traumatic blindness and kidney failure. It has also been associated with an increased risk of cognitive dysfunction and dementia through disease processes such as Alzheimer's disease and vascular dementia. Other complications include acanthosis nigricans, sexual dysfunction, and frequent infections.

Type 2 Diabetes



How many Americans have diabetes and pre-diabetes?

- 25.8 million Americans have diabetes — 8.3% of the U.S. population. Of these, 18.8 million are diagnosed and 7 million do not know they have the disease.
- Among U.S. residents ages 65 years and older, 10.9 million, or 26.9%, had diabetes in 2010.
- In 2010, about 1.9 million new patients aged 20 or older were diagnosed with diabetes.
- The number of people diagnosed with diabetes has risen from 1.5 million in 1958 to 18.8 million in 2010, an increase of epidemic proportions.
- Gestational diabetes occurs in 2 - 10% of pregnancies. Women who have had gestational diabetes have a 35% to 60% chance of developing diabetes, mostly Type 2, in the next 10 to 20 years.
- It is estimated that 79 million adults aged 20 and older have pre-diabetes. Pre-diabetes is a condition where blood glucose levels are higher than normal but not high enough



DIABETES, TYPE 2 *continued*

GCIR017

What is the prevalence of diabetes by gender in the U.S.?

- 13.0 million men have diabetes (11.8 percent of all men ages 20 years and older).
- 12.6 million women have diabetes (10.8 percent of all women ages 20 years and older).

What are the racial and ethnic differences in diagnosed diabetes?

Compared to non-Hispanic whites, the risk of diagnosed diabetes is:

- 18% higher among Asian Americans.
- 66% higher among Hispanics/Latinos.
- 77% higher among non-Hispanic blacks.

Diagnosis and Preventive Actions

The World Health Organization (WHO) definition of diabetes (both Type 1 and Type 2) is for a single raised glucose reading with symptoms, otherwise raised values on two occasions, of either:

- Fasting plasma glucose ≥ 7.0 mmol/l (126 mg/dl); or
- With a glucose tolerance test, two hours after the oral dose of plasma glucose ≥ 11.1 mmol/l (200 mg/dl)

Most cases of diabetes involve many genes, with each being a small contributor to an increased probability of becoming a Type 2 diabetic. If one identical twin has diabetes, the chance of the other developing diabetes within his lifetime is greater than 90% while the rate for non-identical siblings is 25-50%. As of 2011, more than 36 genes have been found that contribute to the risk of Type 2 diabetes. All of these genes together still only account for 10% of the total heritable component of the disease. Thus, more research studies are being conducted in search of new genetic markers for diabetes.

Onset of Type 2 diabetes can be delayed or prevented through proper nutrition, sleep, and regular exercise. Individuals with increased genetic risks will benefit from proactive lifestyle management and regular physical exercise. Intensive lifestyle measures may reduce the risk by more than half. The benefit of exercise occurs regardless of the person's initial weight or subsequent weight loss. Evidence for the benefit of dietary changes alone, however, is limited. A number of lifestyle factors are known to be important to the development of Type 2 diabetes, including: obesity (defined by a body mass index of greater than thirty), lack of physical activity, poor diet, stress, and urbanization. A lack of sleep has been linked to Type 2 diabetes. This is believed to act through its effect on metabolism. Excess body fat is associated with 30% of cases in those of Chinese and Japanese descent, 60-80% of cases

in those of European and African descent, and 100% of Pima Indians and Pacific Islanders.

Dietary factors also influence the risk of developing Type 2 diabetes. Consumption of sugar-sweetened drinks in excess is associated with an increased risk. The type of fats in the diet are also important, with saturated fats and trans fatty acids increasing the risk and polyunsaturated and monounsaturated fat decreasing the risk. Eating lots of white rice appears to also play a role in increasing risk.



Type 2 diabetes is initially managed by increasing exercise and dietary modification. If blood glucose levels are not adequately lowered by these measures, medications such as metformin or insulin may be needed. Lifestyle interventions are more effective than taking metformin. For those on insulin, there is typically the requirement to routinely check blood sugar levels.

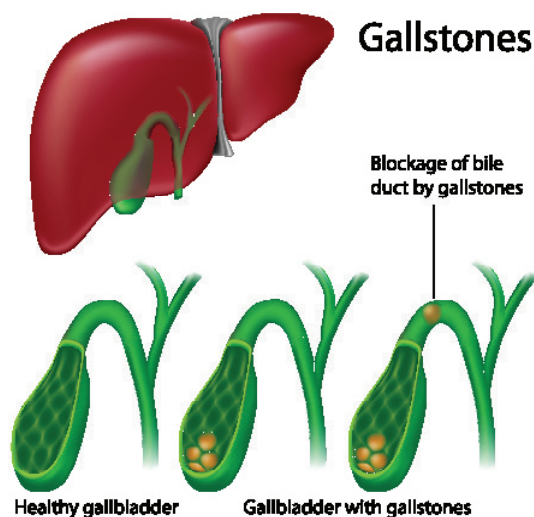
The Diabetes Prevention Program (DPP), a large prevention study of people at high risk for diabetes, showed that lifestyle intervention to lose weight and increase physical activity reduced the development of Type 2 diabetes by 58 percent during a 3-year period. Among adults ages 60 years or older, the reduction was even greater at 71%. Treatment with the drug metformin reduced the risk by 31% overall and was most effective in younger (ages 25-44 years) and in heavier (body mass index greater than or equal to 35) adults. Prevention or delay of Type 2 diabetes with either lifestyle or metformin intervention is effective in all racial and ethnic groups studied and has been shown to persist for at least 10 years. Interventions to prevent or delay Type 2 diabetes in individuals with prediabetes can be feasible and cost-effective. Research has found that lifestyle interventions are more cost-effective than medications.

GALLSTONES

GCIR018

Up to one-third of cases of painful gallstones may be related to genetic factors. A mutation in the gene *ABCG8* significantly increases a person's risk of gallstones. This gene controls a cholesterol pump that transports cholesterol from the liver to the bile duct. It appears this mutation may cause the pump to continuously work at a high rate.

Gallstone is complex and may result from the interaction between genetics and environment. Some studies suggest immune and inflammatory mediators may play key roles.



GASTRIC CANCER

GCIR019

Gastric cancer, or stomach cancer, refers to cancer arising from any part of the stomach. Gastric cancer causes about 800,000 deaths worldwide per year. Prognosis is poor (5-year survival less than 5 to 15%) because most patients present with advanced disease. Gastric cancer is often either asymptomatic (producing no noticeable symptoms) or it may cause only nonspecific symptoms (symptoms which are not specific to just stomach cancer, but also to other related or unrelated disorders) in its early stages. By the time symptoms occur, the cancer has often reached an advanced stage and may have also metastasized (spread to other, perhaps distant, parts of the body), which is one of the main reasons for its relatively poor prognosis.

Gastric cancer is the fourth most common cancer worldwide with 930,000 cases diagnosed in 2002. It is a disease with a high death rate (~800,000 per year) making it the second most common cause of cancer death worldwide after lung cancer. It is more common in men and in developing countries. It also shows a much higher rate in certain regions of the world. It is 10–20 times more prevalent in China and Korea than in Europe and the United States.

Abnormal tissue seen in a gastroscopy examination will be biopsied by the surgeon or gastroenterologist. This tissue is then sent to a pathologist for histological examination under a microscope to check for the presence of cancerous cells. A biopsy, with subsequent histological analysis, is the only sure way to confirm the presence of cancer cells.

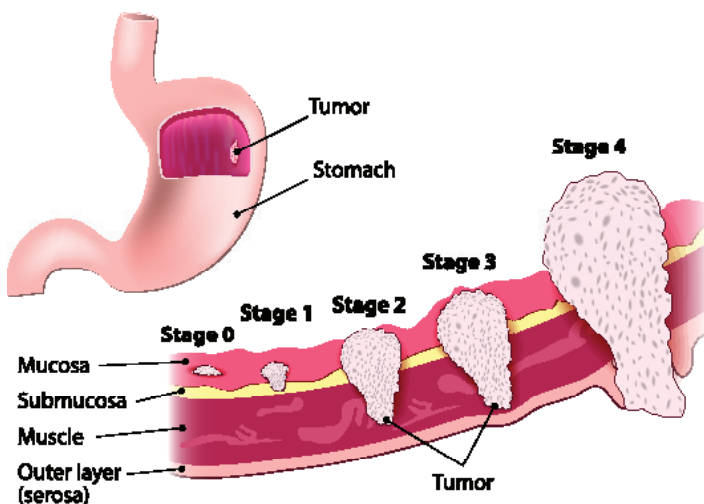
Most stomach cancer is caused by a bacterium *Helicobacter pylori* infection. Dietary factors are not proven causes, but some foods, such as smoked foods, salted fish and meat, and pickled vegetables are associated with a higher risk. Nitrates and nitrites in cured meats can be converted by certain bacteria, including *H. pylori*, into compounds that have been found to cause stomach cancer in animals.

H. pylori is the main risk factor in 65–80% of gastric cancers. On the other hand, the American Cancer Society recommends eating fresh fruits and vegetables that contain antioxidant vitamins, such as A and C, and says that they lower the risk of stomach cancer, and a Mediterranean diet is associated with lower rates of stomach cancer.

Smoking increases the risk of developing gastric cancer significantly, from 40% increased risk for current smokers to an 82% increase for heavy smokers. Gastric cancers due to smoking mostly occur in the upper part of the stomach near the esophagus. Some studies show increased risk with alcohol consumption as well.

Other factors associated with increased risk are autoimmune atrophic gastritis, intestinal metaplasia, and genetic factors. Approximately ten percent of cases show a genetic component. Gastric cancer also shows a male predominance in its incidence as up to three males are affected for every female. Individuals with an increased genetic risk can benefit by taking proactive measures to avoid smoking, eating smoked foods, salted fish and meat, and pickled vegetables.

Cancer of the stomach is difficult to cure unless it is found in an early stage (before it has begun to spread). Unfortunately, because early stomach cancer causes few symptoms, the disease is usually advanced when the diagnosis is made. Knowing your own genetic risk on the disease may help you take up proactive measurements early in your life.



Diagnosis and Preventive Actions

Diagnosis of a patient for gastric cancer may have one or all of the following exams:

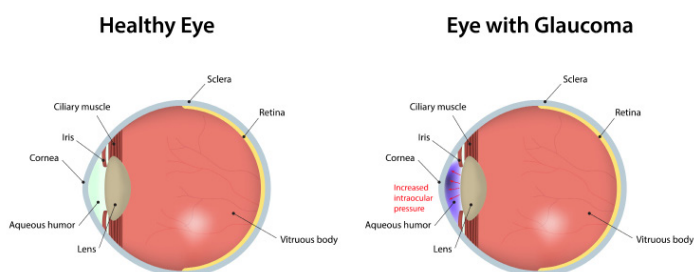
- Gastroscopic exam is the diagnostic method of choice. This involves insertion of a fiber optic camera into the stomach to visualize it.
- Upper GI series (may be called barium roentgenogram)
- Computed tomography or CT scanning of the abdomen may reveal gastric cancer, but is more useful to determine invasion into adjacent tissues, or the presence of spread to local lymph nodes.

GLAUCOMA

GCIR020

Glaucoma is a chronic disease that can damage the optic nerve and lead to a progressive loss of vision. It often occurs when liquid inside the eyeball fails to drain properly, increasing pressure on the eye. The main symptom of glaucoma is a gradual loss of peripheral vision in one or both eyes. If left untreated, vision can worsen until it seems as if one is constantly looking through a tunnel.

Glaucoma has been called the “silent thief of sight” because the loss of vision often occurs gradually over a long period of time, and symptoms only occur when the disease is quite advanced. Once lost, vision cannot normally be recovered, so treatment is aimed at preventing further loss. About one percent of the population has glaucoma. It is the second-leading cause of vision loss in the United States. It is the number one leading cause of blindness among African Americans. Worldwide, glaucoma is the second-leading cause of blindness after cataracts.



Diagnosis and Preventive Actions

Although it is mostly caused by non-genetic factors, glaucoma can also be hereditary. The proportion of risk from genetics is about 13%. Knowing from a genetic test whether you have a genetic susceptibility to the condition can help you and your doctor with early detection. Early diagnosis and proper treatment are keys to controlling glaucoma and avoiding complications.

Because the disease becomes much more prevalent as you age, experts recommend that you get your eyes screened regularly and thoroughly starting at age 40. It is the single most important step you can take to protect yourself from glaucoma. People over age 60 have the highest glaucoma rates. If the condition is detected early enough, it is possible to arrest the development or slow the progression with medical and surgical means. Experts advise people at risk of glaucoma to limit themselves to no more than two cups of coffee or caffeinated drinks a day.

GRAVES' DISEASE

GCIR021

Graves' disease is an autoimmune disease. It most commonly affects the thyroid, frequently causing it to enlarge to twice its size or more (goiter), become overactive, with related hyperthyroid symptoms such as increased heartbeat, muscle weakness, disturbed sleep, and irritability. It can also affect the eyes, causing bulging eyes (exophthalmos). It affects other systems of the body, including the skin, heart, circulation and nervous system.

It affects up to 2% of the female population, sometimes appears after childbirth, and has a female to male incidence of 5:1 to 10:1. It has a strong hereditary component; when one identical twin has Graves' disease, the other twin will have it 25% of the time. Smoking and exposure to second-hand smoke is associated with the eye manifestations but not the thyroid manifestations.

Since Graves' disease is an autoimmune disease which appears suddenly, often quite late in life, it is thought that a viral or bacterial infection may trigger antibodies which cross-react with the human TSH receptor (a phenomenon known as antigenic mimicry, also seen in some cases of type I diabetes). Individuals with an increased genetic risk of developing Graves' disease may be able to take a proactive approach by discussing their symptoms with their physician and performing a confirmatory lab test as needed.



Diagnosis and Preventive Actions

Diagnosis is usually made on the basis of symptoms, although thyroid hormone tests may be useful, particularly to monitor treatment. Graves' disease may present clinically with one of the following characteristic signs:

- Exophthalmos (protuberance of one or both eyes)
- Fatigue, weight loss with increased appetite, and other symptoms of hyperthyroidism / thyrotoxicosis
- Rapid heart beats
- Muscular weakness

It is believed that fibroblasts in the orbital tissues may express the Thyroid Stimulating Hormone receptor (TSHr). This may explain why one autoantibody to the TSHr can cause disease in both the thyroid and the eyes. The trigger for auto-antibody production is not known. There appears to be a genetic predisposition for Graves' disease, suggesting that some people are more prone than others to develop TSHr activating antibodies due to a genetic cause.

HEREDITARY HEMOCHROMATOSIS DNA MUTATION ANALYSIS

GCIR022

Hereditary hemochromatosis (HH), the most common form of iron overload disease, is an inherited disorder that causes the body to absorb and store too much iron. Excess iron is stored throughout the body in organs and tissues including the pancreas, liver, and skin. Without detection and treatment, the iron deposits can damage these critical organs and tissues.

HH is one of the most common genetic disorders in the United States. One of every 8 to 12 people is a carrier of one abnormal gene. It is an autosomal recessive disorder caused by mutations in the HFE gene, which regulates the amount of iron absorbed from food. A person who inherits a defective gene from each parent will develop hemochromatosis. A person who inherits a defective gene from one parent and a normal gene from the other parent is a carrier but usually does not develop the disease. Carriers, however, might have a slight increase in iron absorption, and their children may inherit the disease gene from them.

Diagnosis and Preventive Actions

Patients with early hemochromatosis have no symptoms and are unaware of their condition. The disease may then be discovered when elevated iron blood levels are noted by routine blood testing. Irreversible damages to organs may have occurred by the time it is discovered. In men, symptoms may not appear until 40-50 years of age. Iron deposits in the skin cause darkening of the skin. Since females lose iron through menstrual blood loss, they develop organ damage from iron accumulation 15 to 20 years later than men on average.

Most patients with hemochromatosis are diagnosed early and have no symptoms. Their hemochromatosis is discovered when elevated levels of iron in the blood are found as part of routine blood testing; or when blood iron levels are measured as in screening studies in family members of patients with hereditary hemochromatosis family history.

Since this genetic defect is common and early detection and treatment are so effective, some researchers and education and advocacy groups have suggested that widespread screening by genetic testing for hemochromatosis would be cost-effective and should be conducted. Genetic testing provides a definitive diagnosis, but it was too expensive before our service was made available. Other testing such as blood test for transferrin saturation is widely available and relatively inexpensive, but it has limitations. It may have to be done twice with careful handling to confirm a diagnosis and show that the result is the consequence of iron overload.

The gene for hereditary hemochromatosis is referred to as the HFE gene. Hereditary hemochromatosis is associated in most patients with two mutations of the HFE gene; C282Y and H63D. Predictive genetic testing is recommended for individuals with a family history of hemochromatosis. The alleles evaluated by HFE gene analysis are evident in ~80% of patients with

hemochromatosis; a negative report for HFE gene does not rule out hemochromatosis.



Treatment is simple, inexpensive, and safe for hemochromatosis. The first step is to rid the body of excess iron. This process is called phlebotomy, which means removing blood the same way it is drawn from donors at blood banks. For those unable to tolerate routine blood draws, there is a chelating medicine available. If treatment begins before organs are damaged, associated conditions—such as liver disease, heart disease, arthritis, and diabetes—can be prevented.

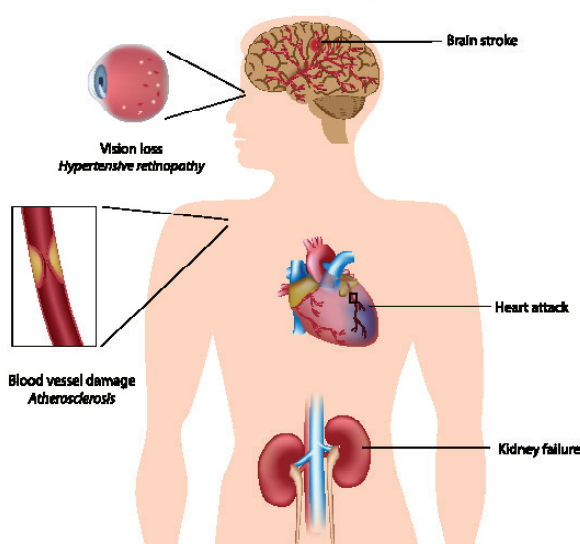
The outlook for people who already have these conditions at diagnosis depends on the degree of organ damage. For example, treating hemochromatosis can stop the progression of liver disease in its early stages, which leads to a normal life expectancy. However, if cirrhosis, or scarring of the liver, has developed, the person's risk of developing liver cancer increases.

HYPERTENSION

GCIR023

Hypertension or high blood pressure, sometimes called arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is elevated. Blood pressure is summarized by two measurements, systolic and diastolic, which depend on whether the heart muscle is contracting (systole) or relaxed between beats (diastole). This equals the maximum and minimum pressure, respectively. Normal blood pressure at rest is within the range of 100–140mmHg systolic and 60–90mmHg diastolic. High blood pressure is said to be present if it is often at or above 140/90 mmHg.

Main complications of hypertension



Hypertension is one of the most common causes for cardiovascular disease (CVD) related death in industrialized countries. It is also the most frequent treatable and preventable risk factor for premature death worldwide. It increases the risk of ischemic heart disease, strokes, peripheral vascular disease, and other cardiovascular diseases, including heart failure, aortic aneurysm, diffuse atherosclerosis, and pulmonary embolism. Hypertension is also a risk factor for cognitive impairment and dementia, and chronic kidney disease. A moderately high arterial blood pressure is associated with a shortened life expectancy.

As of 2006 hypertension affected 76 million U.S. adults (34% of the population). African American adults have among the highest rates of hypertension at 44%. It is more common in blacks, Filipinos, and Native Americans. A large clinical survey conducted in Europe and North America showed that the age- and sex-adjusted prevalence of hypertension was 28% in North American countries and 44% in European countries at the 140/90 mm Hg threshold. Data from the American Heart Association indicate that the prevalence of hypertension increases from ages 20-34 at 9.1% and 6.7 respectively for

male and female to 52% for both sexes at ages 55-64 and to 72% for male and 80% for female aged over 75. Hypertension in newborns is rare, occurring in around 0.2 to 3% of neonates, and blood pressure is not measured routinely in the healthy newborn. Hypertension is more common in high-risk newborns. A variety of factors, such as gestational age, post-conception age and birth weight needs to be taken into account when deciding if a blood pressure is normal in a neonate. Hypertension occurs quite commonly in children over the age of 3 years and adolescents (2-9% depending on age, sex and ethnicity) and is associated with long term risks of health.

Hypertension is rarely accompanied by any symptoms, and its identification is usually through screening, physical examination, or when seeking healthcare for an unrelated problem. A proportion of people with high blood pressure report headaches (particularly at the back of the head and in the morning) as well as lightheadedness.

Diagnosis and Preventive Actions

Hypertension is diagnosed on the basis of a persistent high blood pressure. Traditionally, the National Institute of Clinical Excellence recommends three separate sphygmomanometer measurements at monthly intervals. The American Heart Association recommends at least three measurements on at least two separate health care visits. An exception to this is those with very high blood pressure readings especially when there is poor organ function. Initial assessment of hypertension should include a complete history and physical examination. Once the diagnosis of hypertension has been made, physicians will attempt to identify the underlying cause based on risk factors and other symptoms, if present.

Primary or essential hypertension is more common in adolescents and has multiple risk factors, including obesity and a family history of hypertension (genetics). Secondary hypertension is more common in preadolescent children, with most cases caused by renal disease. Much of the disease burden of high blood pressure is experienced by people who are not



HYPERTENSION, *continued*

labeled as hypertensive. Consequently, population strategies in prevention are required to reduce the consequences of high blood pressure and reduce the need for antihypertensive drug therapy. Lifestyle changes are recommended to lower blood pressure, before starting drug therapy.

The 2004 British Hypertension Society guidelines proposed the following lifestyle changes consistent with those outlined by the U.S. National High BP Education Program in 2002 for the primary prevention of hypertension:

- Maintain normal body weight for adults (e.g. body mass index 20–25 kg/m²)
- Reduce dietary sodium intake to <100 mmol/ day (<6 g of sodium chloride or <2.4 g of sodium per day)
- Engage in regular aerobic physical activity such as brisk walking (≥30 min per day, most days of the week)
- Limit alcohol consumption to no more than 3 units/day in men and no more than 2 units/day in women
- Consume a diet rich in fruit and vegetables (e.g. at least five portions per day)



The first line of treatment for hypertension is identical to the recommended preventive lifestyle changes and includes dietary changes, physical exercise, and weight loss. These have all been shown to significantly reduce blood pressure in people with hypertension. Effective lifestyle modification may lower blood pressure as much as an individual antihypertensive drug. If hypertension is high enough to justify immediate use of medications, lifestyle changes are still recommended in conjunction with medication.

Dietary change such as a low sodium diet is beneficial. A long-term (more than 4 weeks) low-sodium diet is effective in reducing blood pressure, both in people with hypertension and in people with normal blood pressure. Also, the DASH diet, a diet rich in nuts, whole grains, fish, poultry, fruits and vegetables lowers blood pressure. A major feature of the plan is limiting intake of sodium, although the diet is also rich in potassium, magnesium, calcium, as well as protein.

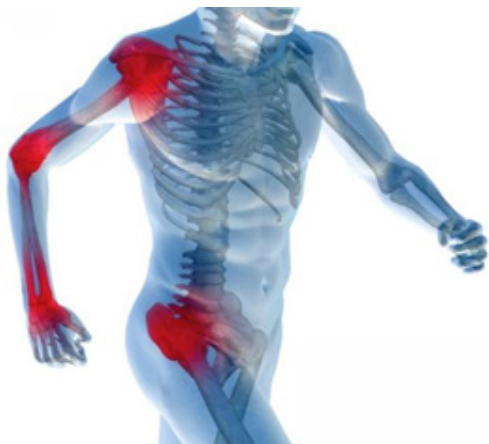
INFLAMMATION

GCIR024

Inflammation is a protective immunovascular response that involves immune cells, blood vessels, and molecular mediators.

Inflammation can be classified as either acute or chronic. Acute inflammation is the initial response of the body to harmful stimuli such as infections. Chronic inflammation may lead to a host of diseases, such as hay fever, periodontitis, atherosclerosis, rheumatoid arthritis, and even cancer (e.g., gallbladder carcinoma). Inflammation is tightly regulated by the body.

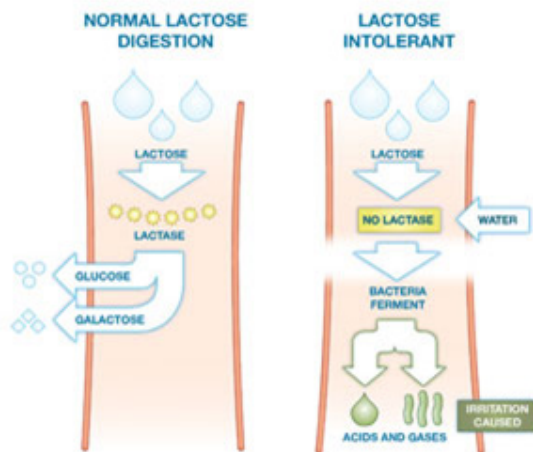
Inflammatory abnormalities are a large group of disorders that underlie a vast variety of human diseases. The immune system is often involved with inflammatory disorders, with many immune system disorders resulting in abnormal inflammation.



LACTOSE INTOLERANCE

Lactose intolerance is the inability to digest lactose, a sugar found in milk. It stems from a shortage of enzymes in the small intestine that break down milk sugar.

The condition, which causes abdominal pain, bloating, gas, and diarrhea almost immediately after you consume products that contain lactose, is very common. As many as 50 million Americans suffer from it. Lactose intolerance is different from milk allergy, which is an immune response to milk proteins.



Lactase enzyme digestive supplements such as Dairy Relief, Lactaid® and FastAct® can help prevent gas, bloating, and diarrhea by making dairy products easier to digest. If you are lactose intolerant, taking such supplements may allow you to continue to enjoy the dairy products you like.

Diagnosis and Preventative Actions

We test for genetic variants that can predict this condition, and that are particularly present in people of European descent. The genetic variation shuts down production of an enzyme, namely lactase, which is critical to the digestion of dairy products. Normally, the LCT gene, which encodes lactase, is turned on only for the first few years of a mammal's life. After this the enzyme level decreases and with it the inability to digest large quantities of milk. But some people continue to produce lactase throughout their life and can drink milk without uncomfortable side effects. In different populations around the world, the prevalence of the lactase persistent phenotype varies widely from population to population—between 0 and 100%. An SNP near the LCT gene controls whether the lactase enzyme is turned on or off as a person grows older.

Knowing from a genetic test that you are lactose intolerant can help you and your doctor manage the condition and minimize symptoms. By making changes to your diet, you can make a difference in your health and well-being. Yogurt contains less lactose than milk, since its lactose has been converted to lactic acid by bacteria. Lactose-free formula is a nutritionally complete, lactose-free infant milk formula, made from milk, designed for lactose-intolerant babies. If you have the genetic variants for long-term activity of lactase, it suggests you are not likely to be lactose intolerant because you possess the ability to produce lactase persistently throughout life.

LUNG CANCER

GCIR026

Lung cancer is a disease characterized by uncontrolled cell growth in the tissues of the lung. This growth can spread beyond the lung in a process called metastasis into nearby tissue, and eventually into other parts of the body if left untreated. Most cancers that start in lung, known as primary lung cancers, are carcinomas that derive from epithelial cells. The main types of lung cancer are small-cell lung carcinoma (SCLC), which accounts for 10-15% of all lung cancer, and non-small-cell lung carcinoma (NSCLC), which accounts for 85-90%.

The most common cause of lung cancer is long-term exposure to tobacco smoke, which causes 80–90% of lung cancers. Nonsmokers account for 10–15% of lung cancer cases, and these cases are often attributed to a combination of genetic factors, radon gas, asbestos, and air pollution including secondhand smoke.

Worldwide, lung cancer is the third most common cancer in terms of incidence and the number one cancer in terms of mortality. In 2008, there were 1.61 million new cases, and 1.38 million deaths due to lung cancer. The highest rates are in Europe and North America. On January 1, 2010, in the United States, there were approximately 399,431 men and women alive who had a history of cancer of the lung and bronchus. The National Cancer Institute estimated that 228,190 men and women (118,080 men and 110,110 women) will be diagnosed with and 159,480 men and women will die of cancer of the lung and bronchus in the United States in 2013. The population segment most likely to develop lung cancer is people over 50 who have a history of smoking. In contrast to the mortality rate in men, which began declining more than 20 years ago, women's lung cancer mortality rates have been rising over the last decades, and are just recently beginning to stabilize.

In the U.S., the lifetime risk of developing lung cancer is about 1 in 13 (8%) in men and 1 in 16 (6%) in women. These numbers include both smokers and non-smokers. For smokers the risk is much higher, while for non-smokers the risk is lower.

Eastern Europe has the highest lung cancer mortality among men, while northern Europe and the U.S. have the highest mortality among women. In the United States, black men and women have a higher incidence. Lung cancer incidence is currently less common in developing countries. With increased smoking in developing countries, the incidence of lung cancer has risen significantly in the past few decades, notably in China and India.

Diagnosis and Preventive Actions

Some people have a genetic predisposition to lung cancer. In relatives of people with lung cancer, the risk is increased 2.4 times. This may be due to genetic factor. Large sizes of genome-wide association studies were conducted to identify genetic risk markers. We use the clinically validated genetic markers to estimate your genetic risk for this disease. Performing a chest radiograph is one of the first investigative steps if a patient reports symptoms that may suggest lung cancer.

Prevention is the most cost-effective means of mitigating lung cancer development. While in most countries, industrial and domestic carcinogens have been identified and banned, tobacco smoking is still widespread. Eliminating tobacco smoking is a primary goal in the prevention of lung cancer, and smoking cessation is an important preventive tool in this process. People with an increased genetic risk for lung cancer are more susceptible to smoking and other carcinogens in the environment.



LUPUS

Systemic lupus erythematosus (SLE), or lupus, is a systemic autoimmune disease (or autoimmune connective tissue disease) that can affect any part of the body. As occurs in other autoimmune diseases, the immune system attacks the body's cells and tissue, resulting in inflammation and tissue damage. SLE most often harms the heart, joints, skin, lungs, blood vessels, liver, kidneys, and nervous system. The course of the disease is unpredictable, with periods of illness (called flares) alternating with remissions. The disease occurs nine times more often in women than in men, especially in women in child-bearing years ages 15 to 35.

Symptoms vary from person to person, and may come and go. The "malar rash," also known as the "butterfly rash", is typically seen in lupus. It appears across the nose and cheeks in a butterfly-shape, it has no itching or pain, and is generally reddish in color. The rash is not scaly, and has sharp definition. Almost everyone with lupus has joint pain and swelling. Some develop arthritis. Frequently affected joints are the fingers, hands, wrists, and knees. Patients with systemic lupus erythematosus experience skin symptoms such as rash after sunlight exposure (photosensitivity). The disease from lupus ranges from mild to fatally severe. Extreme cases of lupus are responsible for thousands of deaths in America every year. To the credit of medical advances, earlier diagnoses, and improvement in treatments, lupus is usually not fatal, and the majority of patients with lupus can lead normal lives.

Diagnosis and Preventive Actions

Systemic lupus is difficult to diagnose because there is no single diagnostic test for lupus. In fact, many people may have positive lupus tests-particularly the anti-nuclear antibody test-and yet NOT have the disease. Physicians have to gather information from a variety of sources: past medical history, lab tests, and current symptoms. They use a list of 11 criteria to help diagnose SLE. A person needs to satisfy at least 4 out of the 11 criteria before the diagnosis can be pinpointed. Some criteria, such as a biopsy diagnosis of lupus, can carry more weight.

Of the 11 criteria, 7 relate to symptoms, and 4 have to do with lab tests. The ANA test is used as a screening test for systemic lupus. We know that 95 % of people with SLE have a positive ANA. Therefore, if a person has many symptoms of systemic lupus and their ANA test is negative, that's generally regarded as pretty good evidence against lupus being the explanation for the symptoms they are having.

If on the other hand, the ANA comes back positive, that is NOT proof of lupus. The positive ANA is only an indicator, it is not diagnostic. A positive ANA can be found in a number of illnesses and conditions.

We do not yet fully understand what causes lupus. Lupus is a genetically complex disease. Research indicates that SLE has a genetic link. SLE does run in families, but no single causal



gene has been identified. Instead, multiple genes appear to influence a person's chance of developing lupus when triggered by environmental factors. The most important genes are located in the HLA region on chromosome 6, where mutations may occur randomly (de novo) or may be inherited. HLA class I, class II, and class III are associated with SLE, but only classes I and II contribute independently to increased risk of SLE. Other genes which contain risk variants for SLE are IRF5, PTPN22, STAT4, CDKN1A, ITGAM, BLK, TNFSF4 and BANK1. Some of the susceptibility genes may be population specific. Conventional lab testing is not advisable in individuals who do not have symptoms.

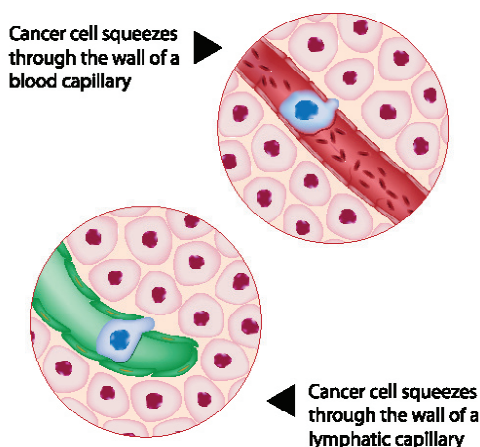
LYMPHOMA

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Lymphoma is a group of blood cell tumors that develop from lymphocytes, a type of white blood cells. Symptoms may include enlarged lymph nodes that are not generally painful, fevers, night sweats, itchiness, weight loss and feeling tired among others.

There are two main types of lymphoma: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Non-Hodgkin lymphoma makes up about 90% of cases and includes a large number of sub-types. Risk factors for HL include infection with Epstein-Barr virus and having other relatives in the family with the disease. Risk factors for NHL include autoimmune diseases such as Celiac disease, lupus, and rheumatoid arthritis, HIV/AIDS, infection with human T-lymphotropic virus, eating a large amount of meat and fat, as well as immunosuppressant medications, radiation and some pesticides.

Lymphoma is the most common form of hematological malignancy, or “blood cancer”, in the developed world. Lymphomas represent 5.3% of all cancers (excluding simple basal cell and squamous cell skin cancers) in the United States and 55.6% of all blood cancers. According to the U.S. National Institutes of Health, lymphomas account for about five percent of all cases of cancer in the United States. Patients with a weakened immune system such as from HIV infection or from certain drugs or medication also have a higher incidence of lymphoma.



The overall five-year survival rates in the United States are 85% and 69% for HL and NHL, respectively. Lymphomas developed in 566,000 people in 2012 and caused 305,000 deaths. As a group, lymphomas rank the 7th most common cancer in adults and the 3rd most common in children.

Diagnosis and Preventive Actions

Lymphoma can be definitively diagnosed by a lymph node biopsy, meaning a partial or total excision of a lymph node that is then examined under the microscope. This examination reveals histopathological features that may indicate lymphoma. After lymphoma is diagnosed, a variety of tests may be carried out to look for specific features characteristic of different types of lymphoma.



Maintaining a healthy immune system is important in prevention of the disease. Lifestyle is an important risk factor. Harsh working conditions, lack of sleep, exposure to radiation and/or harmful chemicals and certain viral infections may increase your odds to develop the disease. Lowering the amount of fat and meat in meals can help as these foods tend to produce a more acidic systemic environment which appears to be found often in cancerous tissues. Regular physical exercise can help boost your body's immune system. Finally, cigarette smoking significantly increases the risk of lymphoma.

MIGRAINE

Migraine is a chronic neurological disorder characterized by recurrent moderate to severe headaches often in association with a number of autonomic nervous system symptoms. Typically the headache is unilateral (affecting one half of the head) and pulsating in nature, lasting from 2 to 72 hours. Associated symptoms may include nausea, vomiting, photophobia (increased sensitivity to light), phonophobia (increased sensitivity to sound) and the pain is generally aggravated by physical activity. Up to one-third of people with migraine headaches perceive an aura: a transient visual, sensory, language, or motor disturbance which signals that the headache will soon occur. Occasionally an aura can occur with little or no headache following it.



Migraines are believed to be due to a mixture of environmental and genetic factors. About two-thirds of cases run in families. Fluctuating hormone levels may also play a role. Migraines affect slightly more boys than girls before puberty, but about two to three times more women than men. Propensity for migraines usually decreases during pregnancy. The exact mechanisms of migraine are not known. It is, however, believed to be a neurovascular disorder.

Diagnosis and Preventive Actions

The diagnosis of a migraine is based on signs and symptoms. Imaging tests are occasionally performed to exclude other causes of headaches. It is believed that a substantial number of people with the condition have not been diagnosed.

The diagnosis of migraine without aura, according to the International Headache Society, can be made according to the following criteria; The “5, 4, 3, 2, 1 Criteria”:

- Five or more attacks—for migraine with aura, two attacks are sufficient for diagnosis
- Four hours to three days in duration
- Two or more of the following:
 - Unilateral (affecting half the head)
 - Pulsating
 - Moderate or severe pain intensity

- Aggravation by or causing avoidance of routine physical activity
- One or more of the following:
 - Nausea and/or vomiting
 - Sensitivity to both light (photophobia) and sound (phonophobia)

If someone experiences two of the following: photophobia, nausea, or inability to work/study for a day the diagnosis is more likely. The underlying causes of migraines are unknown. However, they are believed to be related to a mix of environmental and genetic factors. They run in families in about two-thirds of cases and rarely occur due to a single gene defect. A number of psychological conditions are associated including: depression, anxiety, and bipolar disorder, as are many biological events or triggers.

Studies of twins indicate a 34 to 51% genetic influence of likelihood to develop migraine headaches. This genetic relationship is stronger for migraines with aura than for migraines without aura. A number of specific variants of genes increase the risk by a small to moderate amount.

Single gene disorders that result in migraines are rare. One of these is known as familial hemiplegic migraine, a type of migraine with aura, which is inherited in an autosomal dominant fashion. Four genes have been shown to be involved in familial hemiplegic migraine. Three of these genes are involved in ion transport. The fourth is an axonal protein associated with the exocytosis complex. Another genetic disorder associated with migraine is CADASIL syndrome or cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

Preventive treatments of migraines include: medications, nutritional supplements, lifestyle alterations, and surgery. Prevention is recommended in those who have headaches more than two days a week, cannot tolerate the medications used to treat acute attacks, or those with severe attacks that are not easily controlled. The goal is to reduce the frequency, painfulness, and/or duration of migraines, and to increase the effectiveness of abortive therapy. Another reason for prevention is to avoid medication overuse headache. This is a common problem and can result in chronic daily headache.

Preventive migraine medications are considered effective if they reduce the frequency or severity of the migraine attacks by at least 50%. Guidelines are fairly consistent in rating topiramate, divalproex/sodium valproate, propranolol, and metoprolol as having the highest level of evidence for first-line use. There is some tentative evidence of benefit for magnesium, coenzyme Q10, riboflavin, vitamin B12, and feverfew, although data is limited and better quality trials must be conducted to reach more definitive conclusions.

Many physicians believe that exercise for 15–20 minutes per

MIGRAINE, *continued*

GCIR029

day is helpful for reducing the frequency of migraines. Sleep is often a good solution if a migraine is not so severe as to prevent it, as when a person awakes the symptoms will have most likely subsided. Diet, visualization, and self-hypnosis are also alternative treatments and prevention approaches. Sexual activity has been reported by a proportion of male and female migraine sufferers to relieve migraine pain significantly in some cases.

Some individuals have a condition called celiac disease (or “gluten intolerance”) that results in the body incorrectly processing gluten. Studies have suggested that 4% of migraine sufferers have celiac disease, and for those who do, decreasing gluten intake may significantly reduce migraine frequency. Please refer to the Celiac disease section of this report for more information about celiac disease.



Methylenetetrahydrofolate reductase (MTHFR) DNA mutation analysis tests for the presence or absence of two mutations in the MTHFR gene: 677C>T (677T) and 1298A>C (1298C). Testing for these mutations helps assess whether an individual is at increased risk for hyperhomocysteinemia and thus increased risk for vascular diseases, venous thrombosis, and neural tube defects.

We all have some homocysteine in our blood. Elevated homocysteine levels (also called hyperhomocysteinemia) may cause irritation of the blood vessels. Elevated levels of homocysteine show an increased risk for hardening of the arteries (atherosclerosis), which could eventually result in a heart attack and/or stroke, and blood clots in the veins, referred to as venous thrombosis.

There are certain implications of having elevated homocysteine that are specifically relevant for women. Elevated homocysteine levels have been observed more frequently among women with certain pregnancy complications, including preeclampsia (elevated blood pressure that can lead to dangerous consequences), placental abruption (where the placenta detaches from the uterus), recurrent pregnancy loss, and giving birth to a small, low birth-weight baby (called intrauterine growth restriction). However, medical research suggests that elevated homocysteine levels may be a consequence of these complications, rather than the cause.

Diagnosis and Actionable Information to Physicians

An individual with MTHFR mutations should develop a plan with his/her physician to check homocysteine levels periodically and adjust treatment accordingly. Women with elevated homocysteine levels should also be aware of the possible implications that this may have for pregnancy complications and should discuss this with a knowledgeable healthcare provider. Homocysteine is measured through a routine blood test. Most of the time, no fasting is needed before blood testing as short-term dietary factors will not likely influence test results. Avoid taking multivitamin supplements a few days before the blood test. Occasionally, a practitioner may order a test called the methionine-load test. This test measures homocysteine levels before and after the intake of 100 mg/kg of methionine (dissolved in orange juice). The test is most commonly used to diagnose abnormal homocysteine metabolism in people who have a high risk for cardiovascular disease but who have normal baseline homocysteine levels. This test can be used to make decisions about therapy, as people with abnormal "load" tests may respond better to vitamin B6 supplementation compared with folic acid.

Typically, a homocysteine level less than 13 µmol/L is considered normal. A level between 13 and 60µmol/L is considered moderately elevated, and a value greater than 60 to 100 µmol/L is severely elevated.

FAQs for MTHFR mutations

Question 1: Can a patient be tested while he/she is on an anticoagulant such as heparin or warfarin? Yes. This genetic test is performed by testing DNA from the patient for the mutations. Heparin and warfarin treatment will not affect this testing methodology.

Question 2: My patient has had recurrent miscarriages. How do I interpret the result of this test in that context? The role of MTHFR mutations in miscarriage is controversial. Most evidence shows that MTHFR mutation status does not predict thrombophilia or pregnancy loss in pregnant women. Consider investigating the presence or absence of other risk factors.

Question 3: What is the clinical significance of 677C>T mutations? Patients who are heterozygous for the 677T mutation are unlikely to have hyperhomocysteinemia and are thus unlikely to need any medical treatment based on this single test result. However, patients who are homozygous, i.e. those with two copies of the 677T mutation, are at greater risk for hyperhomocysteinemia. Measuring the patient's blood homocysteine level is the best way to assess clinical status to determine if your patient needs treatment.

Question 4: What is the significance of my patient being heterozygous for the 1298A>C mutation? Patients who are heterozygous for the 1298C mutation are not at risk for hyperhomocysteinemia. However, patients who are compound heterozygotes (ie, those who have inherited one copy of 1298C from one parent and one copy of 677T from the other parent) may be at risk for hyperhomocysteinemia. Measuring the patient's blood homocysteine level is the best way to assess clinical status and determine if your patient needs treatment.

Question 5: Are treatments different for people with a hereditary predisposition to elevated homocysteine? Regardless of whether one has an MTHFR mutation in both genes or not, the treatment for elevated homocysteine is the same—dietary intervention and supplementation with folic acid and vitamins B6 and B12.

Elevated homocysteine levels can be lowered. We know that folic acid, vitamin B6, and vitamin B12 are all involved in breaking down homocysteine in the blood. Therefore, increasing your intake of folic acid and B vitamins may lower your homocysteine level. A good source of folate can be found in fruits and vegetables (especially green leafy vegetables). Other good sources of folate include fortified breads and cereals, lentils, chickpeas, asparagus, spinach, and most beans.

MULTIPLE SCLEROSIS (MS)

GCI031

Multiple sclerosis (MS), also known as “disseminated sclerosis” or “encephalomyelitis disseminata”, is an inflammatory disease in which the fatty myelin sheaths around the axons of the brain and spinal cord are damaged, leading to demyelination and scarring as well as a broad spectrum of signs and symptoms. Disease onset usually occurs in young adults, and it is more common in women. It has a prevalence that ranges between 2 and 150 per 100,000.

MS affects the ability of nerve cells in the brain and spinal cord to communicate with each other effectively. Nerve cells communicate by sending electrical signals called action potentials down long fibers called axons, which are contained within an insulating substance called myelin. In MS, the body’s own immune system attacks and damages the myelin. When myelin is lost, the axons can no longer effectively conduct signals. The name multiple sclerosis refers to scars (sclera—better known as plaques or lesions) particularly in the white matter of the brain and spinal cord, which is mainly composed of myelin. Although much is known about the mechanisms involved in the disease process, the cause remains unknown. Theories include genetics or infections. Different environmental risk factors have also been found.

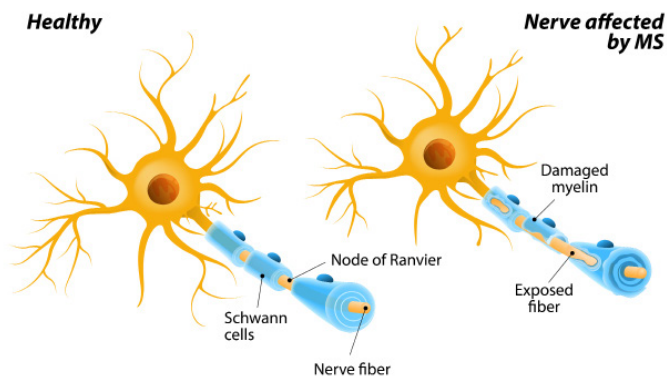


Diagnosis and Preventive Actions

Multiple sclerosis can be difficult to diagnose since its signs and symptoms may be similar to other medical problems. Medical organizations have created diagnostic criteria to ease and standardize the diagnostic process especially in the first stages of the disease. Historically, the Schumacher and Poser criteria were both popular. Clinical data alone may be sufficient for a diagnosis of MS if an individual has suffered separate episodes of neurologic symptoms characteristic of MS. The most commonly used diagnostic tools are neuroimaging, analysis of cerebrospinal fluid and evoked potentials. Magnetic resonance imaging (MRI) of the brain and spine shows areas of demyelination (lesions or plaques).

It is not yet clear in clinical practice how to prevent MS, since its causes are not fully understood. Most likely MS occurs as a result of some combination of genetic, environmental and infectious factors, and possibly other factors like vascular problems. Epidemiological studies of MS have provided hints on possible causes for the disease. The search for new biomarkers of the disease may aid diagnosis.

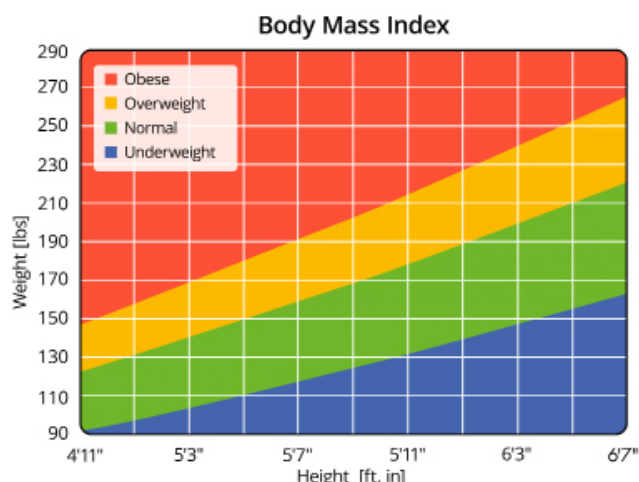
MS is not considered a hereditary disease. However, a number of genetic variations have been shown to increase the risk of developing the disease. Changes in several genes including the HLA region of chromosome 6 increase the probability of suffering MS. The risk of acquiring MS is higher in relatives of a person with the disease than in the general population, especially in the case of first degree relative such as siblings, parents, and children. The disease has an overall familial recurrence rate of 20%.



Almost any neurological symptom can appear with the disease, and the disease often progresses to physical and cognitive disability, including transient loss of vision and mobility, weakness of the legs, clumsiness of the hands, numbness, dizziness, bladder disturbances, and erectile dysfunction. MS takes several forms, with new symptoms occurring either in discrete attacks (relapsing forms) or accumulating over time (progressive forms). Between attacks, symptoms may go away completely, but permanent neurological deficits often occur, especially as the disease advances.

OBESITY

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems. People are considered obese when their body mass index (BMI), a measurement obtained by dividing a person's weight in kilograms by the square of the person's height in meters, exceeds 30 kg/m².



Obesity increases the likelihood of various diseases, particularly heart disease, Type 2 diabetes, obstructive sleep apnea, certain types of cancer, and osteoarthritis. Obesity is most commonly caused by a combination of excessive food energy intake, lack of physical activity, and genetic susceptibility. Although a few cases are caused primarily by genes, endocrine disorders, medications or psychiatric illness.

Obesity is a leading preventable cause of death worldwide, with increasing prevalence in adults and children, and it is considered to be one of the most serious public health problems of the 21st century. The estimated prevalence of overweight and obesity in U.S. adults (over 20 years of age) is 154.7 million, which represented 68.2% of this group in 2010. Nearly 35% U.S. adults are obese. Men and women of all ethnic groups in the nation are affected by the epidemic of overweight and obesity. Among children 2 to 19 years of age, 31.8% are overweight and obese.

Preventative Actions

Obesity is preventable even for individuals with an increased genetic risk for obesity. Dieting and physical exercise are the mainstays of treatment for obesity. Diet quality can be improved by reducing the consumption of energy-dense (high calorie) foods such as those high in fat and sugars, and by increasing the intake of dietary fiber and water. Excessive input of calories from food is one of the main causes for obesity. Eating small meals instead of big meals and drinking plenty of water helps

control weight and appetite. Regular physical exercise is another effective way to prevent obesity. Anti-obesity drugs may be taken to reduce appetite or inhibit fat absorption together with a suitable diet.

Like many other medical conditions, obesity is the result of an interplay between genetic and environmental factors. Polymorphisms in various genes controlling appetite and metabolism predispose to obesity when sufficient food energy is present. More than 40 of these sites on the human genome have been linked to the development of obesity when a favorable food/energy environment is present. We test these genetic markers to provide you an assessment on your genetic predisposition to obesity, but you are in control to prevent it.

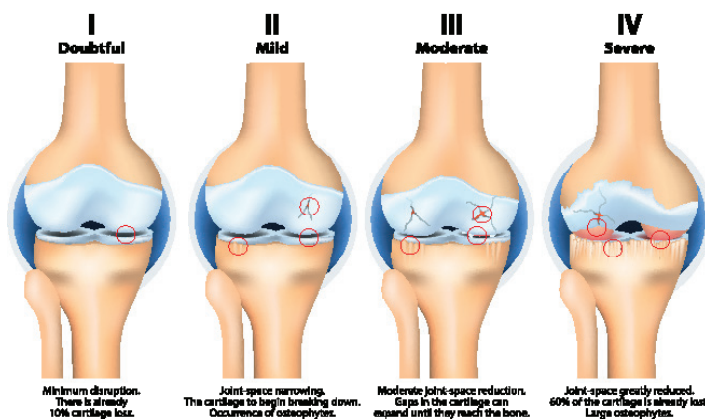


OSTEOARTHRITIS

GCIR032

Osteoarthritis (OA), also known as degenerative arthritis or degenerative joint disease, is a group of mechanical abnormalities involving degradation of joints, including articular cartilage and subchondral bone. Symptoms may include joint pain, tenderness, stiffness, locking, and sometimes an effusion. A variety of causes—hereditary, developmental, metabolic, and mechanical—may initiate processes leading to loss of cartilage. When bone surfaces become less well protected by cartilage, bone may be exposed and damaged. As a result of decreased movement secondary to pain, regional muscles may become atrophy, and ligaments may become more lax.

STAGE OF KNEE OSTEOARTHRITIS



The main symptom is pain, causing loss of ability and often stiffness. Pain is generally described as a sharp ache, or a burning sensation in the associate muscles and tendons. OA can cause a crackling noise (called “crepitus”) when the affected joint is moved or touched, and patients may experience muscle spasm and contractions in the tendons. Occasionally, the joints may also be filled with fluid. Humid and cold weather increases the pain in many patients.

OA commonly affects the hands, feet, spine, and the large weight bearing joints, such as the hips and knees, although in theory, any joint in the body can be affected. As OA progresses, the affected joints appear larger, are stiff and painful, and usually feel better with gentle use but worse with excessive or prolonged use, thus distinguishing it from rheumatoid arthritis.

The development of OA is correlated with a history of previous joint injury and with obesity, especially with respect to knees. Since the correlation with obesity has been observed not only for knees but also for non-weight bearing joints and the loss of body fat is more closely related to symptom relief than the loss of body weight, it has been suggested that there may be a metabolic link to body fat as opposed to just mechanical loading. Exercise, including running in the absence of injury, has not been found to increase one’s risk of developing OA.

Diagnosis and Preventive Actions

Diagnosis is made with reasonable certainty based on history and clinical examination. X-rays may confirm the diagnosis. The typical changes seen on X-ray include: joint space narrowing, subchondral sclerosis (increased bone formation around the joint), subchondral cyst formation, and osteophytes.

A number of studies have shown that there is a greater prevalence of the disease among siblings and especially identical twins, indicating a hereditary basis. Although a single factor is not generally sufficient to cause the disease, about half of the variation in susceptibility has been assigned to genetic factors. Changes in sex hormone levels may play a role in the development of OA as it is more prevalent among post-menopausal women than among men of the same age.

OA affects nearly 27 million people in the United States and about eight million people in the United Kingdom, accounting for 25% of visits to primary care physicians and half of all NSAID prescriptions.

Treatment generally involves a combination of exercise, lifestyle modification, and analgesics. If pain becomes debilitating, joint replacement surgery may be used to improve the quality of life. OA is the most common form of arthritis, and the leading cause of chronic disability in the United States. Joint supplement glucosamine is reported to reduce pain in some OA patients.

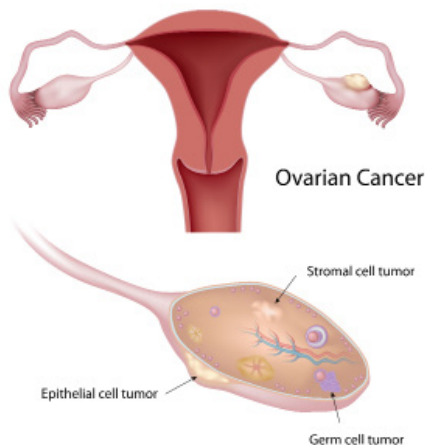


OVARIAN CANCER

Ovarian cancer is a cancerous growth arising from the ovary. Symptoms are frequently very subtle early on and may include: bloating, pelvic pain, difficulty eating and frequent urination, and are easily confused with other illnesses. More than 90% of ovarian cancers are classified as “epithelial” and are believed to arise from the surface (epithelium) of the ovary. However, some evidence suggests that the fallopian tube could also be the source of some ovarian cancers. Other types may arise from the egg cells (germ cell tumor) or supporting cells. Ovarian cancers are included in the category gynecologic cancer.

Ovarian cancer is the fifth leading cause of death from cancer in women and the leading cause of death from gynecological cancer. In the United States, females have a 1.4% to 2.5% (one out of 40-60 women) lifetime chance of developing ovarian cancer. Older women are at highest risk. More than half of the deaths from ovarian cancer occur in women between 55 and 74 years of age and approximately one quarter of ovarian cancer deaths occur in women between 35 and 54 years of age. It is estimated that there were 21,880 new cases and 13,850 deaths of ovarian cancer in the United States in 2010.

Ovarian cancer is called a “silent killer” because most symptoms of ovarian cancer at its early stages (I/II) are non-specific and thus of little use in diagnosis. As a result, most newly-diagnosed ovarian cancer patients (60%-75%) have stage III or IV tumors, where the disease is advanced and the chance of cure or remission is poor, with 5-year survival rates of 45% or less.



Diagnosis and Preventive Actions

Signs and symptoms of ovarian cancer are frequently absent early on and when they exist they may be subtle. In most cases, the symptoms persist for several months before being recognized and diagnosed. Most typical symptoms include: bloating, abdominal or pelvic pain, difficulty eating, and possibly urinary symptoms. If these symptoms recently started and occur more than 12 times per month, then diagnosis should be considered.

Diagnosis of ovarian cancer starts with a physical examination (including a pelvic examination), a blood test (for CA-125 and sometimes other markers), and transvaginal ultrasound. The diagnosis must be confirmed with surgery to inspect the abdominal cavity, take biopsies of tissue samples for microscopic analysis and look for cancer cells in the abdominal fluid.

Ovarian cancer at its early stages (I/II) is difficult to diagnose until it spreads and advances to later stages (III/IV). This is because most symptoms are non-specific and thus of little use in diagnosis. In most cases, the exact cause of ovarian cancer remains unknown. The risk of developing ovarian cancer appears to be affected by several factors:

- Older women who have never given birth, and those who have a first or second degree relative with the disease, have an increased risk.
- Hereditary forms of ovarian cancer can be caused by mutations in specific genes (most notably BRCA1 and BRCA2, but also in genes for hereditary nonpolyposis colorectal cancer).
- Infertile women and those with a condition called endometriosis, and those who use postmenopausal estrogen replacement therapy are at increased risk.
- Ovarian cancer is associated with age, and family history of ovarian cancer (9.8-fold higher risk).

One of the preventative measures for high risk individuals is genetic testing for certain “cancer genes”. Carriers of certain BRCA mutations are notably at risk. The BRCA1 and BRCA2 genes account for 10%–15% of ovarian cancers and certain populations (e.g. Ashkenazi Jewish women) are at a higher risk of both breast cancer and ovarian cancer, often at an earlier age than the general population. Patients with a personal history of breast cancer or a family history of breast and/or ovarian cancer, especially if diagnosed at a young age, may have an elevated risk, and should be tested for the “cancer genes”.

In the United States, 10 to 20 percent of women with ovarian cancer have a first- or second-degree relative with either breast or ovarian cancer. Mutations in either of two major susceptibility genes, breast cancer susceptibility gene 1 (BRCA1) and breast cancer susceptibility gene 2 (BRCA2), confer a lifetime risk of breast cancer of between 60- and 85-percent and a lifetime risk of ovarian cancer of between 15- and 40-percent.

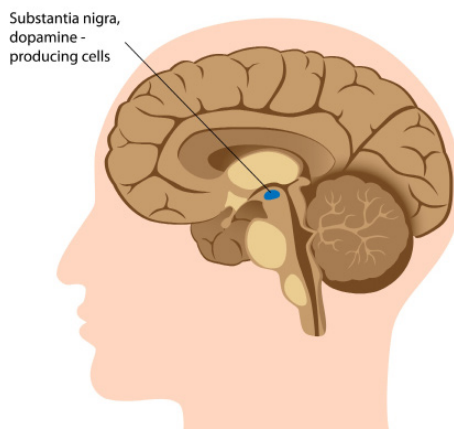
Hereditary breast-ovarian cancer syndromes (HBOC) produce higher than normal levels of breast cancer and ovarian cancer in genetically related families (either one individual suffered from both, or several individuals in the families suffered from one or the other disease). The hereditary factors may be proven or suspected to cause the pattern of breast and ovarian cancer occurrences in the family.



Women who have had children are less likely to develop ovarian cancer than women who have not, and breastfeeding may also reduce the risk of certain types of ovarian cancer. Tubal ligation and hysterectomy reduce the risk and removal of both tubes and ovaries (bilateral salpingo-oophorectomy) dramatically reduces the risk of not only ovarian cancer but breast cancer also. A hysterectomy that does not include the removal of the ovaries has a one-third reduced risk of developing ovarian cancer. It also has no higher risk of developing other types of cancer, heart disease, or hip fractures. A double mastectomy that does not include the removal of the ovaries may reduce the risk of ovary cancer by more than one-half.

PARKINSON'S DISEASE (PD)

Parkinson's disease (PD) is a degenerative disorder of the central nervous system. PD is the second most common neurodegenerative disorder after Alzheimer's disease and affects approximately seven million people globally and one million people in the United States. The motor symptoms of Parkinson's disease result from the death of dopamine-generating cells in the substantia nigra, a region of the midbrain; the cause of this cell death is unknown. Early in the course of the disease, the most obvious symptoms are movement-related; these include shaking, rigidity, slowness of movement and difficulty with walking. Later, thinking and behavioral problems may arise, with dementia commonly occurring in the advanced stages of the disease, whereas depression is the most common psychiatric symptom. Other symptoms include sensory, sleep and emotional problems. PD is more common in the elderly, with most cases occurring after the age of 50, although 5–10% of cases, classified as young onset, begin between the ages of 20 and 50.



Notable cases include famous boxing athlete Muhammad Ali who was diagnosed at 42 although he showed signs of Parkinson's when he was 38. Actor Michael J. Fox has PD and has greatly increased the public awareness of the disease. Fox was diagnosed in 1991 when he was 30, but kept his condition secret from the public for seven years. He has written two autobiographies in which his fight against the disease plays a major role. He has appeared before the United States Congress without medication to illustrate the effects of the disease. The Michael J. Fox Foundation aims to develop a cure for Parkinson's disease and it has raised and provided hundreds of millions of dollars funding for PD research. Recently, one of Google's founders, billionaire Sergey Brin, announced that he and his mother (who has Parkinson's disease) both carry the G2019S mutation. Mr. Brin was 35 years old at the time of the announcement, and in his blog, he comments that "I now have the opportunity to adjust my life to reduce those odds".

Diagnosis and Preventive Actions

A physician will diagnose Parkinson's disease from the medical history and a neurological examination. There is no lab test that will clearly identify the disease, but brain scans are sometimes used to rule out disorders that could give rise to similar symptoms. Patients may be given levodopa and resulting relief of motor impairment tends to confirm diagnosis. Parkinson's disease affects movement-producing motor symptoms. Non-motor symptoms, which include autonomic dysfunction, neuropsychiatric problems (mood, cognition, behavior or thought alterations), and sensory and sleep difficulties, are also common. Some of these non-motor symptoms are often present at the time of diagnosis and can precede motor symptoms.

Mutations in specific genes have been conclusively shown to cause PD. Genetic factors are also seen in early onset Parkinson's disease. The heritability of PD is relatively low but a recent study estimated it to be about 27% in European populations. A fraction of Parkinson's cases are attributed to rare mutations in a small number of genes, including the G2019S mutation in the LRRK2 gene. This mutation has been associated with PD at varying frequencies in Asian, European, North American, North African, and Ashkenazi Jewish populations, with the North African population showing the highest prevalence. The odds for G2019S carriers were estimated to be 15% at 60 years, and they increase approximately 40% between ages 60 and 70, and double to 32% at 80 years or older.

A number of environmental factors have been associated with an increased risk of Parkinson's including: pesticide exposure, head injuries, and living in the country or farming. Rural environments and the drinking of well water may be risks as they are an indirect measures of exposure to pesticides and herbicides.

Caffeine consumption appears protective against Parkinson's disease with a greater decrease in risk occurring with a larger intake of caffeinated beverages such as coffee. Although tobacco smoke decreases life expectancy and quality of life, it may reduce the risk of PD by a third when compared to non-smokers. The basis for this effect is not known, but possibilities include an effect of nicotine as a dopamine stimulant.

Antioxidants, such as vitamins C and D, have been proposed to protect against the disease but results of studies have been contradictory and no positive effect has been proven. The results regarding fat and fatty acids have been contradictory, with various studies reporting protective effects, risk-increasing effects or no effects. Finally there have been preliminary indications of a possible protective role of estrogens and anti-inflammatory drugs.

PERIPHERAL VASCULAR DISEASE (PVD)

GCIR036

Peripheral vascular disease (PVD), commonly referred to as peripheral arterial disease (PAD) or peripheral artery occlusive disease (PAOD), refers to the obstruction of large arteries not within the coronary, aortic arch vasculature, or brain. PAD can result from atherosclerosis, inflammatory processes leading to stenosis, an embolism, or thrombus formation. It causes either acute or chronic ischemia (lack of blood supply). Often PAD is a term used to refer to atherosclerotic blockages found in the lower extremity (eg, feet). PAD also includes a subset of diseases classified as microvascular diseases resulting from episodic narrowing of the arteries (Raynaud's phenomenon), or widening thereof (erythromelalgia), i.e. vascular spasms.

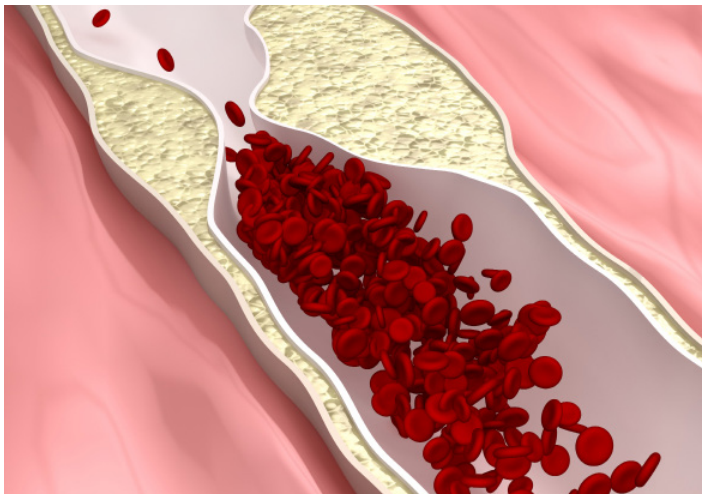
The prevalence of peripheral vascular disease in the general population is 12–14%, affecting up to 20% of those over 70; 70%–80% of affected individuals are asymptomatic; only a minority ever require revascularization or amputation. Peripheral vascular disease affects 1 in 3 diabetics over the age of 50. In the U.S., peripheral arterial disease affects 12–20 percent of Americans age 65 and older. Approximately ten million Americans have PAD. About 20% of patients with mild PAD may be asymptomatic.



to angiography. CT provides complete evaluation of the aorta and lower limb arteries without the need for an angiogram's arterial injection of contrast agent. Magnetic resonance angiography (MRA) is a noninvasive diagnostic procedure that uses the combination of a large magnet, radio frequencies, and a computer to produce detailed images to provide pictures of blood vessels inside the body. The advantages of MRA include its safety and ability to provide high-resolution three-dimensional (3D) imaging of the entire abdomen, pelvis and lower extremities in one setting.

Risk factors contributing to PAD are the same as those for atherosclerosis:

- Smoking - tobacco use in any form is the single most important modifiable cause of PAD internationally. Smokers have up to a tenfold increase in relative risk for PAD in a dose-related effect. Exposure to second-hand smoke has also been shown to promote changes in blood vessel lining (endothelium) which is a precursor to atherosclerosis. Smokers are 2 to 3 times more likely to cause lower extremity peripheral arterial disease than coronary artery disease. More than 80%-90% of patients with lower extremity peripheral arterial disease are current or former smokers. The risk of PAD increases with the number of cigarettes smoked per day and the number of years smoked.
- Genetic factors - PAD has a genetic basis like other cardiovascular disease and diabetes. Recent medical research has identified a number of mutations/genetic markers associated with PAD.
- Diabetes mellitus - causes between two and four times increased risk of PAD by creating endothelial and smooth muscle cell dysfunction in peripheral arteries. The risk of developing lower extremity peripheral arterial disease is proportional to the severity and duration of diabetes. Diabetics account for up to 70% of non-traumatic



Diagnosis and Preventive Actions

Upon suspicion of PAD, the first-line study is the ankle brachial pressure index (ABPI/ABI). When the blood pressure reading in the ankles is lower than that in the arms, blockages in the arteries which provide blood from the heart to the ankle are suspected. Normal ABI range of 1.00 to 1.40. The patient is diagnosed with PAD when the ABI is ≤ 0.90 . ABI values of 0.91 to 0.99 are considered borderline, and values >1.40 indicate non-compressible arteries. PAD is graded as mild to moderate if the ABI is between 0.41 and 0.90, and an ABI less than 0.40 is suggestive of severe PAD.

Modern multisided computerized tomography (CT) scanners provide direct imaging of the arterial system as an alternative

PERIPHERAL VASCULAR DISEASE, *continued*

GCIR037

amputations performed, and a known diabetic who smokes runs an approximately 30% risk of amputation within 5 years.

- Dyslipidemia (high low density lipoprotein [LDL] cholesterol, low high density lipoprotein [HDL] cholesterol) - elevation of total cholesterol, LDL cholesterol, and triglyceride levels each have been correlated with accelerated PAD. Correction of dyslipidemia by diet and/or medication is associated with a major improvement in rates of heart attack and stroke. This benefit is gained even though current evidence does not demonstrate a major reversal of peripheral and/or coronary atherosclerosis.
- Hypertension - elevated blood pressure is correlated with an increase in the risk of developing PAD, as well as in associated coronary and cerebrovascular events (heart attack and stroke). Hypertension increased the risk of intermittent claudication 2.5-fold and 4-fold in men and women, respectively.



- Risk of PAD also increases in individuals who are over the age of 50, male, obese, heart attack, or stroke, or with a family history of vascular disease.

Dependent on the severity of the disease, the following steps can be taken:

- Smoking cessation (cigarettes promote PAD and are a risk factor for cardiovascular disease)
- Management of diabetes
- Management of hypertension
- Management of cholesterol, and medication with anti-platelet drugs. Medication with aspirin, clopidogrel and statins, which reduce clot formation and cholesterol levels, respectively, can help with disease progression and address the other cardiovascular risks that the patient is likely to have

PROSTATE CANCER

GCIR038

Prostate cancer is a form of cancer that develops in the prostate, a gland in the male reproductive system. Most prostate cancers are slow growing, however, there are some cases of aggressive prostate cancers. The cancer cells may metastasize (spread) from the prostate to other parts of the body, particularly the bones and lymph nodes. Prostate cancer may cause pain, difficulty in urinating, problems during sexual intercourse, or erectile dysfunction. Other symptoms can potentially develop during later stages of the disease.

Rates of detection of prostate cancers vary widely across the world, with South and East Asia detecting less frequently than in Europe, and especially the United States. Prostate cancer tends to develop in men over the age of fifty. Globally, it is the sixth leading cause of cancer-related death in men (in the United States it is the second). Prostate cancer is most common in the developed world with increasing rates in the developing world. However, many men with prostate cancer never have symptoms, undergo no therapy, and eventually die of other unrelated causes. Many factors, including genetics and diet, have been implicated in the development of prostate cancer.

The presence of prostate cancer may be indicated by symptoms, physical examination, prostate-specific antigen (PSA), or biopsy. Prostate-specific antigen testing increases cancer detection but does not decrease mortality.

A complete understanding of the causes of prostate cancer remains elusive. The primary risk factors are obesity, age, genetics and family history. Prostate cancer is very uncommon in men younger than 45, but becomes more common with advancing age. The average age at the time of diagnosis is 70. However, many men never know they have prostate cancer. Autopsy studies of Chinese, German, Israeli, Jamaican, Swedish, and Ugandan men who died of other causes have found prostate cancer in thirty percent of men in their 50s, and in eighty percent of men in their 70s.

Men who have first-degree family members with prostate cancer appear to have double the risk of getting the disease compared to men without prostate cancer in the family. This risk appears to be greater for men with an affected brother than for men with an affected father. In 2005, there were an estimated 230,000 new cases of prostate cancer and 30,000 deaths due to prostate cancer in the United States.

Genetic background may contribute to prostate cancer risk, as suggested by associations with race, family, and specific gene variants. Men who have a first-degree relative (father or brother) with prostate cancer have twice the risk of developing prostate cancer, and those with two first-degree relatives affected have a fivefold greater risk compared with men with no family history. In the United States, prostate cancer more commonly affects black men than white or Hispanic men, and is also more deadly in black men. In contrast, the incidence and mortality rates for Hispanic men are one third lower than for non-Hispanic whites.

Studies of twins in Scandinavia suggest that forty percent of prostate cancer risk can be explained by inherited factors. Many different genes have been implicated in prostate cancer. Mutations in BRCA1 and BRCA2, important risk factors for ovarian cancer and breast cancer in women, have also been implicated in prostate cancer. Other linked genes include the Hereditary Prostate Cancer gene 1 (HPC1), the androgen receptor, and the vitamin D receptor. Loss of function of certain cancer suppressor genes early in the prostatic carcinogenesis has been reported.

Diagnosis and Preventive Actions

The presence of prostate cancer may be indicated by symptoms, physical examination, prostate-specific antigen (PSA), or biopsy. Prostate-specific antigen testing increases cancer detection but does not decrease mortality. The only test that can fully confirm the diagnosis of prostate cancer is a biopsy, the removal of small pieces of the prostate for microscopic examination. However, prior to a biopsy, less invasive testing can be conducted. The American Cancer Society believes that men should not be tested without learning about what we know and don't know about the risks and possible benefits of testing and treatment. Starting at age 50, (45 if African American, or if a brother or father suffered from the condition before age 65) talk to your doctor about the pros and cons of testing so you can decide if testing is the right choice for you.

Early prostate cancer usually causes no symptoms. However, when it does, they are often similar to those of diseases such as benign prostatic hyperplasia. These include frequent urination, nocturia (increased urination at night), difficulty starting and maintaining a steady stream of urine, hematuria (blood in the urine), and dysuria (painful urination). About a third of patients diagnosed with prostate cancer have one or more such symptoms, while two thirds have no symptoms.

While some dietary factors have been associated with prostate cancer the evidence is still tentative. Evidence supports little role for dietary fruits and vegetables in prostate cancer occurrence. Red meat and processed meat also appear to have little effect in human studies. Higher meat consumption has been associated with a higher risk in some studies. Lower blood levels of vitamin D may increase the risk of developing prostate cancer. Taking multivitamins more than seven times a week may increase the risk of developing the disease. Men with high blood pressure are more likely to develop prostate cancer. There is a small increased risk of prostate cancer associated with lack of exercise.

PSORIASIS

Psoriasis is a common skin disease that causes itchy or sore patches of thick, red skin with silvery scales. It can last a long time, even a lifetime. Psoriasis is very common. Anyone can get it, but it most commonly begins between ages 15 and 35. The cause of psoriasis is not fully understood, but it is believed to have a genetic component.

You cannot catch psoriasis or spread it to others. Doctors think it may be an autoimmune condition. This occurs when the immune system mistakenly attacks and destroys healthy body tissue. Psoriatic arthritis (also called arthritis psoriatica, arthropathic psoriasis or psoriatic arthropathy) is a type of inflammatory arthritis that will develop in up to 30 percent of people who have the chronic skin condition psoriasis. Individuals suffering from the advanced effects of HIV often exhibit psoriasis.

Psoriasis has a large hereditary component, and many genes are associated with it, but it is not clear how those genes work together. Most of them involve the immune system, particularly the major histocompatibility complex (MHC) and T cells. The main value of genetic studies is that they identify molecular mechanisms and pathways for further study and potential drug targets.

Classic genome-wide linkage analysis has identified nine locations (loci) on different chromosomes associated with psoriasis. They are called psoriasis susceptibility 1 through 9 (PSORS1 through PSORS9). Within those loci are genes. Many of those genes are on pathways that lead to inflammation. Certain variations (mutations) of those genes are commonly found in psoriasis.

The major determinant is PSORS1, which probably accounts for 35–50% of its heritability. It controls genes that affect the immune system or encode proteins that are found in the skin in greater amounts in psoriasis. PSORS1 is located on chromosome 6 in the MHC, which controls important immune functions. Three genes in the PSORS1 locus have a strong association with psoriasis vulgaris: HLA-C variant HLA-Cw6, which encodes a MHC class I protein; CCHCR1, variant WWC, which encodes a coiled protein that is overexpressed in psoriatic epidermis; and CDSM, variant allele 5, which encodes corneodesmosin, which is expressed in the granular and cornified layers of the epidermis and upregulated in psoriasis.

Genome-wide association studies have identified other genes which are altered to characteristic variants in psoriasis. Some of these genes express inflammatory signal proteins, which affect cells in the immune system that are also involved in psoriasis. Some of these genes are also involved in other autoimmune diseases.



Diagnosis and Preventive Actions

A diagnosis of psoriasis is usually based on the appearance of the skin with a dermatologist; there are no special blood tests or diagnostic procedures. Sometimes, a skin biopsy, or scraping, may be needed to rule out other disorders and to confirm the diagnosis.

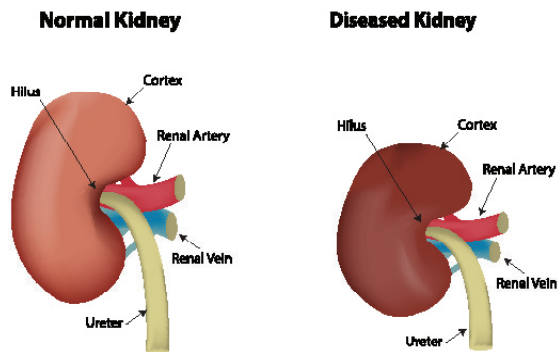
Psoriasis occurs more likely in dry skin than oily or well-moisturized skin, and specifically after an external skin injury such as a scratch or cut, known as the Koebner phenomenon. This is believed to be caused by an infection, in which the infecting organism thrives under dry skin conditions with minimal skin oil, which otherwise protects skin from infections.

Prevalence across different racial groups is similar; race does not appear to be a risk factor. The prevalence of psoriasis in Western populations is estimated to be around 2–3%. Psoriasis affects both sexes equally, and can occur at any age, although it most commonly appears for the first time between the ages of 15 and 25 years. Onset before age 40 usually indicates a greater genetic susceptibility and a more severe or recurrent course of psoriasis.

RENAL DISEASE

GCIR040

Most cases of renal disease have an autosomal dominant pattern of inheritance. People with this condition are born with one mutated copy of the PKD1 or PKD2 gene in each cell. In about 90 percent of these cases, an affected person inherits the mutation from one affected parent. The other 10 percent of cases result from new mutations in one of the genes and occur in people with no history of the disorder in their family.



RESTLESS LEGS SYNDROME

GCIR041

Restless legs syndrome is a neurological condition in which your legs feel extremely uncomfortable while you're sitting or lying down. Some refer to it as a "creepy crawly" feeling. Symptoms occur at rest, but are usually absent during daytime work, labor, or exercise. Fortunately, while the problem can affect sleep and wellbeing, it does not cause dire health problems.

An estimated eight million Americans have restless legs syndrome, which may stem from an imbalance of the brain chemical dopamine, which sends messages to control muscle movement. The health condition affects both men and women, can begin at any age and may worsen as you get older.

Restless legs syndrome runs in families, with heredity accounting for more than half your chance of getting the health condition. Knowing from a genetic test whether you have a genetic susceptibility to the disorder can enable you to work with your physician to make lifestyle changes. Some treatments are also effective at controlling restless legs syndrome.

Getting an adequate amount of sleep, limiting alcohol and caffeine consumption and paying attention to improve low iron levels may help prevent restless legs syndrome, or at least reduce your risk.

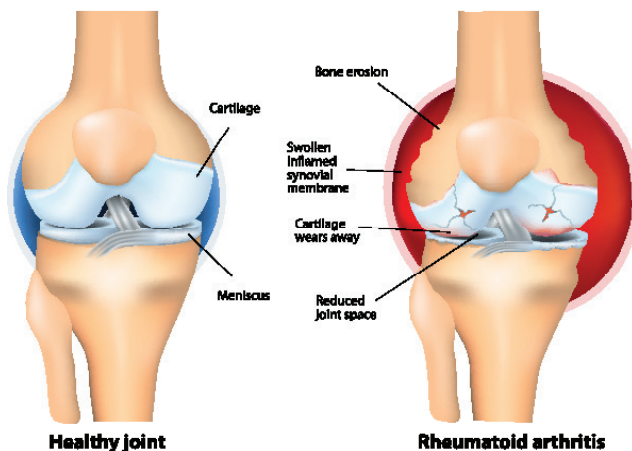


RHEUMATOID ARTHRITIS (RA)

GCIR042

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks flexible (synovial) joints. It can be a disabling and painful condition, which can lead to substantial loss of functioning and mobility if not adequately treated.

Rheumatoid arthritis is a form of autoimmunity, the causes of which are still not completely known. It is a systemic (whole body) disorder principally affecting synovial tissues. There is no evidence that physical and emotional effects or stress could be a trigger for the disease. The many negative findings suggest that either the trigger varies, or that it might in fact be a chance event inherent with the immune response.



Inheritance of RA is recessive in males and is nearly recessive in females. It is strongly associated with the inherited tissue type major histocompatibility complex (MHC) antigen HLA-DR4, and the genes PTPN22 and PADI4—hence family history is an important risk factor. Inheriting the PTPN22 gene variant has been shown to double a person's susceptibility to RA. PADI4 has been identified as a major risk factor in people of Asian descent, but not in those of European descent.

Diagnosis and Preventive Actions

X-rays of the hands and feet are generally performed in people with polyarthritis. In RA, there may be no changes in the early stages of the disease, or the x-ray may demonstrate juxta-articular osteopenia, soft tissue swelling and loss of joint space. As the disease advances, there may be bony erosions and subluxation. X-rays of other joints may be taken if symptoms of pain or swelling occur in those joints. Other medical imaging techniques such as magnetic resonance imaging (MRI) and ultrasound are also used in RA.

When RA is clinically suspected, immunological studies are required, such as blood testing for the presence of rheumatoid factor (RF, a non-specific antibody). A negative RF does not rule out RA; rather, the arthritis is called seronegative. This is the

case in about 15% of patients. During the first year of illness, rheumatoid factor is more likely to be negative with some individuals converting to seropositive status over time. RF is also seen in other illnesses, for example Sjögren's syndrome, Hepatitis C, chronic infections and in approximately 10% of the healthy population, therefore the test is not very specific. Several other blood tests are usually done, including test for the presence of the anti-citrullinated protein antibodies (ACPAs). Recently a serological point-of-care test for the early detection of RA has been developed. This assay combines the detection of rheumatoid factor and anti-MCV (detection of autoantibodies against Mutated Citrullinated Vimentin) for diagnosis of RA.

Lifestyle and environment can have an impact on the development of RA. Regular exercise is recommended as both safe and useful to maintain muscles strength and overall physical function. It is uncertain if specific dietary measures have an effect. There is no cure for RA, but treatments can improve symptoms and slow the progress of the disease. Disease-modifying treatment has the best results when it is started early and aggressively. The goals of treatment are to minimize symptoms such as pain and swelling, to prevent bone deformity, and to maintain day-to-day functioning.

There is no known prevention for the contraction. Reduction of risk factors and aggressive treatment after diagnosis are recommended actions. The evidence of the benefit in applying acupuncture as alternative therapy for RA is inconclusive, with it appearing to be equivalent to sham acupuncture. The American College of Rheumatology has stated, "There are no herbal medicines whose health claims are supported by sound scientific evidence" and "the use of herbal remedies is not recommended." Some evidence supports omega-3 fatty acids and gamma-linolenic acid in RA. The benefit from omega-3 appears modest but consistent, though the current evidence is not strong enough to determine that supplementation with omega-3 polyunsaturated fatty acids (found in fish oil) is an effective treatment for RA. Gamma-linoleic acid, which may reduce pain, tender joint count and stiffness, is generally safe. Joint supplement glucosamine is also reported to reduce pain in some RA patients.





Large genome wide association studies span several types of cancer with large number of patients (together with over 30,000 cases and 45,000 controls) have identified a number of genetic variants that are associated with increased risk of skin cancer and other types of cancer. We test for these variants and provide you with an assessment of your genetic predisposition for two common forms of skin cancer: basal cell carcinoma and melanoma.

Basal cell carcinoma (BCC)

Basal cell carcinoma (BCC) is a form of non-melanoma skin cancer that arises from the cells of the lower (i.e. basal) part of the outer layer of the skin (the epidermis). BCC is the most common cancer in the world, but is rarely fatal, as the cancer's ability to invade other tissues and organs is limited. It does, however, cause considerable morbidity in afflicted individuals and places a huge burden on healthcare systems around the world. Moreover, individuals afflicted with BCC have an increased risk of further developing BCC and other malignancies.



BCC is the most common form of skin cancer, accounting for around 75% of skin cancers. Australia has the highest rate of BCC incidence in the world. It is estimated that 295,000 Australians (about 1 in 14 individuals) will be diagnosed with BCC each year. Over 96% of afflicted individuals were 40 years of age or older. The incidence of younger Australians with BCC is increasing, however, and this has been attributed to increased sun exposure.

Melanoma

Melanomas are malignant tumors, usually found on the skin, which can grow to invade surrounding tissue. They arise from damaged melanocytes, cells of the lower epidermis which, under physiologic conditions, produce pigment, melanin, in skin. Damage to the DNA within melanocytes leads to proliferation of the cells and unbridled growth into melanoma. Melanomas are a major cause of premature cancer death, and even though they account for only 4 percent of all dermatologic cancer, they are responsible for 80 percent of deaths from skin cancer. Only 14 percent of individuals diagnosed with metastatic melanoma survive beyond 5 years, therefore it is critical to diagnose melanoma in its early stages of development. Despite this, when detected early and treated appropriately there is a high survival rate for superficial spreading melanoma.



Most melanomas originate on the skin's surface as a pigmented lesion; in this case, the disease is called cutaneous melanoma. However, they can occur all over the body, including the eye (ocular melanoma or intraocular melanoma), mouth, nose, vulva, anus, digestive tract and under finger or toe nails. They can also present both on sites that are constantly, or never, exposed to solar radiation, with the most common areas of the body being women's legs and men's backs.

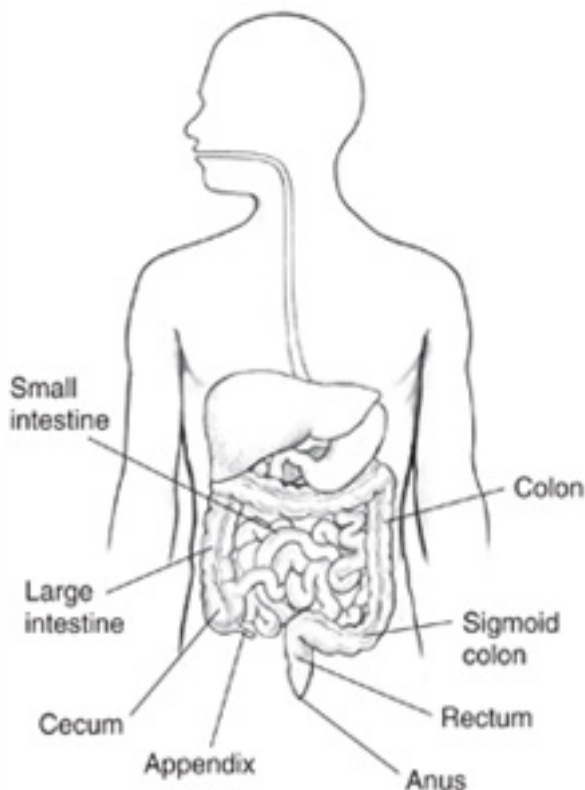
The incidence of melanoma varies geographically and by latitude. Australia has the highest incidence, with 1 in 25 people succumbing to the disease in their lifetime, compared to 1 in 5000 in the USA and European countries. Over ten thousand new cases of melanoma are diagnosed in Australia every year, causing approximately 1,250 deaths each year. The prevalence of malignant melanoma has doubled in the last ten years, together making up 10% of all cancers. The incidence of melanoma continues to rise in the United States, Australia, Sweden, Puerto Rico, Italy, Canada and Japan.

As with all types of skin cancer, the incidence of melanoma increases with age, though it is disproportionately high in young people, with nearly one third appearing in people under 50. In Australia melanoma is the most common type of cancer for those aged 15 to 44.

ULCERATIVE COLITIS

GCIR044

Ulcerative colitis is a chronic disease of the large intestine, also known as the colon, in which the lining of the colon becomes inflamed and develops tiny open sores, or ulcers, that produce pus and mucous. The combination of inflammation and ulceration can cause abdominal discomfort and frequent emptying of the colon. Ulcerative colitis is the result of an abnormal response by your body's immune system. It is an autoimmune disease characterized by T-cells infiltrating the colon.



The exact cause of ulcerative colitis is unknown. Researchers believe the following factors may play a role in causing ulcerative colitis:

- overactive intestinal immune system
- genetics
- environment

Scientists believe that one cause of ulcerative colitis may be an abnormal immune reaction in the intestine. Researchers believe bacteria or viruses can mistakenly trigger the immune system to attack the inner lining of the large intestine. This immune system response causes the inflammation, leading to symptoms.

Ulcerative colitis sometimes runs in families. Research studies have shown that certain abnormal genes may appear in people

with ulcerative colitis.

Some studies suggest that certain things in the environment may increase the chance of a person getting ulcerative colitis, although the overall chance is low.

Some people believe eating certain foods, stress, or emotional distress can cause ulcerative colitis. Emotional distress does not seem to cause ulcerative colitis. A few studies suggest that stress may increase a person's chance of having a flare-up of ulcerative colitis. Also, some people may find that certain foods can trigger or worsen symptoms.

Ulcerative colitis can occur in people of any age. However, it is more likely to develop in people

- between the ages of 15 and 30
- older than 60
- who have a family member with IBD
- of Jewish descent

It's important to understand the difference between ulcerative colitis and Crohn's disease. Crohn's disease can affect any part of the gastrointestinal (GI) tract, but ulcerative colitis affects only the colon. Additionally, while Crohn's disease can affect all layers of the bowel wall, ulcerative colitis only affects the lining of the colon.

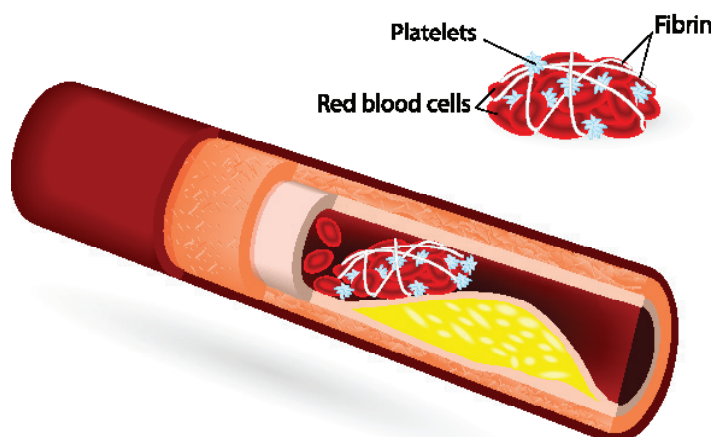
While both ulcerative colitis and Crohn's disease are types of Inflammatory Bowel Diseases (IBD), they should not be confused with Irritable Bowel Syndrome (IBS), a disorder that affects the muscle contractions of the colon. IBS is not characterized by intestinal inflammation.

VENOUS THROMBOEMBOLISM (VTE)

A venous thrombosis or phlebothrombosis is a blood clot (thrombus) that forms within a vein. Thrombosis is a term for a blood clot occurring inside a blood vessel. A classical venous thrombosis is deep vein thrombosis (DVT), which can break off (embolize), and become a life-threatening pulmonary embolism (PE). The disease process venous thromboembolism can refer to DVT and/or VTE. An inflammatory reaction is usually present, mainly in the superficial veins and, for this reason this pathology is often called thrombophlebitis.

As with heart attacks, and in contrast to the understanding for how arterial thromboses occur, venous thrombosis formation is not well understood. Venous thrombi are caused mainly by a combination of venous stasis and hypercoagulability—but to a lesser extent endothelial damage and activation. Various risk factors, including genetic factor, increase the likelihood of any one individual developing a thrombosis.

The valves of veins are a recognized site of VTE initiation. Due to the blood flow pattern, the base of the valve sinus is particularly deprived of oxygen (hypoxic). Stasis exacerbates hypoxia, and this state is linked to the activation of white blood cells (leukocytes) and the endothelium. Specifically, the two pathways of hypoxia-inducible factor-1 (HIF-1) and early growth response 1 (EGR-1) are activated by hypoxia, and they contribute to leukocyte and endothelial activation.



Physicians (ACP) gave three strong recommendations with moderate quality evidence on VTE prevention in non-surgical patients: that hospitalized patients be assessed for their risk of thromboembolism and bleeding before prophylaxis; that heparin or a related drug is used if potential benefits are thought to outweigh potential harms; and that graduated compression stockings not be used. As an ACP policy implication, the guideline stated a lack of support for any performance measures that incentivize physicians to apply universal prophylaxis without regard to the risks. Unfortunately, despite development of various practice guidelines for prevention of VTE, they remain underused in most countries.

Preventive Actions

Evidence supports the use of heparin in surgical patients who have a high risk of thrombosis to reduce the risk of DVTs; however, the effect on PEs or overall mortality is not known. In hospitalized non-surgical patients, heparin results in an almost statistically significant decrease in mortality and may decrease the risk of PE and DVT. However, it increases major bleeding events thus yielding little or no overall clinical benefit. It does not appear however to decrease the rate of symptomatic DVTs.

A 2011 clinical guideline from the American College of

Pharmacogenomics is the study of the relationship between individual genetic variation and drug response. One of the major goals is to use an individual's genomic information in conjunction with other demographic and environmental covariates to personalize a previously uniform treatment regimen to optimize treatment efficacy and minimize side-effects. Pharmacogenomics is used to derive a genotype-to-phenotype correlation of a drug dosage, efficacy, toxicity, or a variable indicating response/non-response or adverse-event/no-adverse-event, to the genotype of a patient.

PDX™ pharmacogenomic test is designed to determine the genotypes of a number of drug metabolizing enzymes (DME) in a person. Based on the results of these genotypes and their combinations, this report displays your likely response to a number of drugs. There may be differences in the likelihood or severity of side effects, or differences in disease risk tied to use of a drug. Only a medical professional can determine whether a drug is right for a particular patient. The information contained in this report should not be used to independently establish a drug regimen, or abolish or adjust an existing course of treatment without the supervision of a physician.

The U.S. Food and Drug Administration recommends that physicians obtain genotype information for the administration of two prescription drugs, clopidogrel (Plavix®) and warfarin (Coumadin).



CYP2C19 Genotyping

The cytochrome P450 proteins are monooxygenases that catalyze many reactions involved in drug metabolism. Cytochrome P450 2C19 (CYP2C19) testing is appropriate for any patient taking or considering using clopidogrel (under the brand name of Plavix®). Clopidogrel is an oral antiplatelet agent used to inhibit blood clots in coronary artery disease, peripheral vascular disease, and cerebrovascular disease (including

stroke). Approximately 700,000 (i.e., 30%) clopidogrel patients are 2C19 Intermediate or Poor Metabolizers. Intermediate or Poor 2C19 Metabolizers have a 3.58 times greater risk for major adverse cardiovascular events such as death, heart attack, and stroke. It has been suggested that clopidogrel may be less effective in reducing the rate of cardiovascular events among persons who are carriers of certain CYP2C19 alleles that are associated with reduced conversion of clopidogrel to its active metabolite. Testing the genotype of 2C19 to clopidogrel can substantially improve treatment responses. Please note that 2C19 metabolizes many other drugs and taking additional medications in addition to clopidogrel may affect a person's response to these drugs. These other drugs include:

- Anticonvulsants: mephenytoin, diazepam, phenytoin, primidone
- Antidepressants: amitriptyline, citalopram, S-citalopram, clomipramine
- Antineoplastics: cyclophosphamide
- Antiretrovirals: nelfinavir, Protease inhibitors: lansoprazole, omeprazole, pantoprazole
- Miscellaneous drugs: progesterone, propranolol, R-warfarin, proguanil

This test detects poor metabolizer CYP2C19 alleles *2, *3, *4, *5, *6, *7, and *8, as well as the ultra rapid metabolizer allele, *17. CYP2C19 *1 is for the normal allele with extensive metabolism. Since a person has two alleles (one from each parent) for each gene, he or she will have either two identical alleles (homozygous) or two different alleles (heterozygous) for the 2C19 genotype. If you carry two poor metabolizer alleles, you would have poor metabolic activities for drugs that require CYP2C19 to metabolize. You would not benefit from the drugs, instead, you would be at a higher risk of developing adverse effects from taking these drugs. If you carry a normal allele and an ultra rapid metabolizer allele *17, you would expect to be a rapid metabolizer for the same type of drugs. Your doctor will be able to use such information to prescribe the right medicines with the right doses for you.

VKORC1 and CYP2C9 Genotyping

Warfarin (also under the brand name of Coumadin) is an anticoagulant commonly used in the prevention of thrombosis and thromboembolism - the formation of blood clots in the blood vessels, and their migration elsewhere in the body, respectively. However, due to its narrow therapeutic index and the large inter-individual variability in its maintenance dose, warfarin is not easy to dose. To determine the effective therapeutic dose, frequent monitoring of the international normalized ratio (INR) followed by careful dose adjustments is required for each individual. It often takes 30–60 days to find out the maintenance dose. Warfarin activity is determined partially by genetic factors. In

2007 the U.S. Food and Drug Administration approved updated labeling for warfarin suggesting the opportunity for healthcare providers to use genetic tests to improve their initial estimate of what is a reasonable warfarin dose for individual patients.

Polymorphisms in two genes (VKORC1 and CYP2C9) are particularly important for the use of warfarin. Vitamin K epoxide reductase complex subunit 1 is an enzyme encoded by the VKORC1 gene. VKORC1 polymorphisms explain 30% of the dose variation between patients. Particular mutations make VKORC1 less susceptible to suppression by warfarin. There are two main haplotypes that explain 25% of variation: low-dose haplotype group (A) and a high-dose haplotype group (B). VKORC1 polymorphisms explain why African Americans are on average relatively resistant to warfarin (higher proportion of group B haplotypes), while Asian Americans are generally more sensitive (higher proportion of group A haplotypes). Group A VKORC1 polymorphisms lead to a more rapid achievement of a therapeutic effect, but also a shorter time to reach an overdose, which is associated with bleeding.

CYP2C9 polymorphisms explain 10% of the dose variation between patients, mainly among Caucasian patients as these variants are rare in African American and most Asian populations. These CYP2C9 polymorphisms do not influence time to effective as opposed to VKORC1, but does shorten the time to reach an overdose.

Clopidogrel inhibits CYP2C9 at high enough doses. This may therefore interfere with the metabolism of drugs processed by CYP2C9, and individuals with CYP2C9 variants that encode lower metabolizers would presumably be at greater risk for such side-effects when taking clopidogrel at the same time with drugs metabolized by CYP2C9.

This test detects poor metabolizer CYP2C9 alleles *2, *3, *4, *5, *6, *8, *11, *13, *15 and *25, as well as the normal allele CYP2C9 *1.

CYP2D6 Genotyping

Cytochrome P450 2D6 (CYP2D6) is one of the most important enzymes involved in the metabolism of xenobiotics in the body. In fact, almost 25% of all drugs are metabolized by CYP2D6, including dextromethorphan (a key ingredient in products such as Nyquil), beta-blockers, antiarrhythmics, and antidepressants. Also, many substances are bioactivated by CYP2D6 to form their active compounds, including tamoxifen (a popular drug used to treat / prevent breast cancer). CYP2D6 shows the largest phenotypical variability among the CYPs, largely due to genetic polymorphism. The genotype accounts for normal, reduced, and non-existent CYP2D6 function in patients.

The type of CYP2D6 function of an individual may influence the person's response to different doses of drugs that CYP2D6 metabolizes. The nature of the effect on the drug response depends not only on the type of CYP2D6 function, but also on

the extent to which processing of the drug by CYP2D6 results in a chemical that has an effect that is similar, stronger, or weaker than the original drug, or no effect at all.

Ethnicity is a factor in the occurrence of CYP2D6 variability. The prevalence of CYP2D6 poor metabolizers is approximately 6–10% in white populations, but is lower in most other ethnic groups such as Asians (2%). In blacks, the frequency of poor metabolizers is greater than for whites. The occurrence of CYP2D6 ultra rapid metabolizers appears to be greater among Middle Eastern and North African populations.

This variability is accounted for by the differences in the prevalence of various CYP2D6 alleles among the populations—approximately 10% of whites appear to have the non-functional CYP2D6*4 allele, while approximately 50% of Asians possess the CYP2D6*10 allele, which produces decreased CYP2D6 function as intermediate metabolizers. Those with normal function are considered extensive metabolizers.

Knowing your DME genotype can help explain why you are more sensitive to the side-effects of some drugs while getting less from their benefits, and why your drug reactions are different from those of your parents or your children. You may be able to choose better medications by sharing the information with your doctor.