

healthpoints

ALL THE POSSIBILITIES OF MODERN MEDICINE

 COLUMBIA UNIVERSITY
MEDICAL CENTER
Department of Surgery
NewYork-Presbyterian

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Genetics and Disease

The role genes play

GENETICS IS ONE OF THE HOTTEST BUZZWORDS IN MEDICINE TODAY. With technologies in place to explore the fundamental building blocks of life, enormous resources are currently being devoted to investigating the genetic basis of diseases, developing gene-based tests to predict how people will respond to therapies, and, looking to the future, using genetic information to help determine individualized courses of therapy based on genetic predilections—and maybe even manipulating the genes themselves to prevent or reverse disease.

But just what is known so far about genes, and how well can this information be used to treat disease now?



According to **Wendy Chung, MD, PhD**, *Director of Clinical Genetics, NewYork-Presbyterian Hospital/Columbia*, much is known about so-called 'single-gene disorders.' Of the 25,000 to 30,000 genes in the human body, over 5200 genes have been identified as causing specific diseases. These powerful connections include Down syndrome, cystic fibrosis, certain types of breast cancer, certain congenital heart conditions, and others in which an aberrant or mutant single gene will very likely lead to a particular condition.

Clinical programs are in place at NewYork-Presbyterian Hospital/Columbia to screen patients for all of these conditions, such as BRCA1 and BRCA2 genes for breast cancer, and specific markers for pancreatic cancer, hereditary non-polyposis colon cancer syndrome (HNPCC), and other conditions for which genetic causes have been pinpointed.

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Human chromosomes

Such programs are particularly effective in treating diseases for which a single gene confers high risk, and early treatment can often prevent or reduce the impact of the disease. It is known that women with BRCA1 and BRCA2 mutations may face up to a 75% risk of developing breast cancer in their lifetime, and that early screening and intervention saves lives. The presence of certain genetic markers, such as whether the cancer is estrogen receptor positive or negative, further guides the treatment of patients with breast cancer for even better results.

AGGREGATION OF GENES

While the genetic basis of breast cancer is in no way simple, the role of genes in many other conditions remains even more elusive. Many diseases are known to have a familial basis, meaning that they run in families, but they likely result from a combination of genetic aberrations, environmental exposure, and lifestyle issues, rather than from a single gene mutation. In such cases, multiple genes may contribute to increasing a person's risk for a particular disease. These complexities represent a vast and largely untapped area of exploration.

"The new frontier is how to identify common genetic susceptibilities to

disease, in which the presence of multiple abnormal genes may together contribute to the development of a disease," says Dr. Chung. "The challenge ahead is to identify the composite risk of multiple contributions to diseases," she explains. Whereas the identification of single gene disorders may be considered the first phase in understanding genes, the second phase will involve learning how multiple genes act together to increase people's risk for diseases. At this time, researchers have identified approximately 300 genes that, in conjunction with other factors, are linked to common diseases.

Dr. Chung suspects that most common diseases may fall into this category. At the edge of this very complex frontier, researchers such as Dr. Chung are making early inroads. Scientists have identified the genetic contributions of four genes in causing macular degeneration, the most common cause of blindness in the elderly. Armed with this understanding, they can now more accurately predict who will go blind. The hope is to be able to use this knowledge to develop targeted therapies in the future.

The researchers also know there is a link between macular degeneration and inflammation; moreover, they have

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Genes 101

Chromosomes—structures in the cells that contain both protein and DNA. Humans have 46 chromosomes, or 23 pairs, containing the blueprint for each cell. Disruptions in the normal chromosomal number of a cell are the cause of disorders such as Down syndrome.

DNA (Deoxyribonucleic acid)—a long, double-helix (twisted ladder) shaped molecule containing the instructions for every living cell's activities.

Genes—units of heredity as encoded in long strands of DNA. Particular genes can have multiple forms, called alleles, which have different sequences of DNA.

Gene expression—The process by which a gene's coded information is converted over time into action. In some cases, studying gene expression, rather than studying the genes directly, is used during genetic research.

At NewYork-Presbyterian Hospital/Columbia, **Mario Deng, MD, FACC, FESC**, studied differences in gene expression during the process of organ rejection after heart transplantation. This led to the development of a new blood test to detect organ rejection far less invasively than the traditional method, heart biopsy, after transplantation.

Gene therapy—An experimental procedure aimed at replacing, manipulating, or supplementing nonfunctional or malfunctioning genes with healthy genes.

Genome—an organism's complete set of DNA.

RNA—A chemical that plays an important role in many activities in the cell. There are several classes of RNA molecules, including messenger RNA, transfer RNA, ribosomal RNA, and microRNAs, each serving a different purpose. Messenger RNA plays an important role in gene expression.

Sidelining Disease by Moderating Inflammation

Columbia researchers work to understand a fundamental cause of inflammation—and how to turn its associated disease process around.

CHRONIC INFLAMMATION is a major causative factor in a wide range of diseases, including atherosclerosis (hardening of the arteries), vascular complications of diabetes, macular degeneration, Alzheimer's disease, and autoimmune diseases such as multiple sclerosis and type 1 diabetes. Even the development of tumors is facilitated by chronic inflammation.

During inflammation, a complex series of events occurs in the body's cells. If one could look into the cells, one would see that certain components become highly activated when the process of inflammation is underway.

One such component, RAGE (receptor for advanced glycation end-products), has been the subject of long and thorough study because of its important

the molecule's functions in the body.

"RAGE does not appear to be critically involved in acute inflammation, such as that required to combat common bacterial infections or to heal skin wounds," says Dr. Schmidt. "Rather, RAGE is pivotal in the chronic inflammation that underpins autoimmune diseases, diabetic tissues, Alzheimer's, and other long-term conditions."

Diabetes and atherosclerosis are prototypical examples of what happens when RAGE activity is increased. RAGE activity in such inflamed tissues contributes to fundamental mechanisms that lead to tissue damage.

Dr. Schmidt is currently overseeing multiple studies to investigate what happens when RAGE is antagonized (blocked) or genetically eliminated, the

RAGE-based therapies have the potential to slow or reverse the progression of many conditions:

- ❖ Vascular disease and cardiac dysfunction that accompany diabetes and aging
- ❖ Alzheimer's disease
- ❖ Autoimmune disorders such as multiple sclerosis
- ❖ Cancer
- ❖ Autoimmune responses that occur after islet cell transplantation
- ❖ Damage after a heart attack or stroke

ing RAGE strikingly reduces the activation of a factor called early growth response-1, or EGR-1. In subjects with atherosclerosis or vascular disease, blocking RAGE dramatically inhibits the activation of another factor called NF- κ B. The reduced activity of these factors acts like a switch that shuts down the inflammatory process, which dramatically reduces or eliminates those cardiovascular diseases and their consequences.

Grants from the National Institutes of Health, the National Heart Lung and Blood Institute, and the Juvenile Diabetes Research Foundation are now advancing these discoveries closer towards clinical use. In studies led by the pharmaceutical groups testing RAGE antagonists in humans, one multi-center study is testing the safety and effectiveness of blocking RAGE in people with Alzheimer's disease. Normal volunteers and patients with Alzheimer's are receiving a therapy that tricks the RAGE receptor into inactivity. "The long-term goal is to preserve or

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contributions to many of the inflammatory conditions considered above. Since 1990, **Ann Marie Schmidt, MD**, Director, Division of Surgical Science, has made significant strides in identifying

latter in mouse models. Her laboratory has determined that in subjects with ischemic heart disease (blocked coronary arteries), stroke, deep vein thromboses (DVTs), or hypoxia, block-

Lung Cancer Screening

Navigating confusion and controversy about CT screening for lung cancer

DETECTING A DISEASE IN ITS EARLY STAGES usually leads to a better chance of successfully treating it. So should we all go out and have ourselves screened for lung cancer just to be on the safe side?

Well, not necessarily. The question is actually complex and controversial, according to **Charles A. Powell, MD**, *Medical Director, Lung Assessment Program* and *Assistant Professor of Clinical Medicine, Division of Pulmonary and Critical Care Medicine*.

The public may be confused by mixed messages regarding screening for lung cancer, as are many physicians, according to Dr. Powell. While there are strong advocates of computed tomography (CT) screening for lung cancer, the American Cancer Society does not

recommend screening as a routine test.

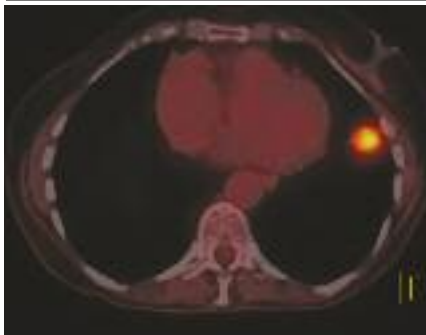
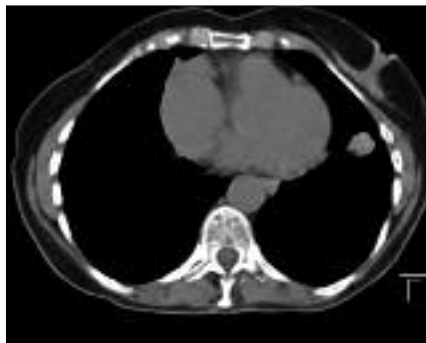
The challenge facing patients and their physicians lies in the fact that there is a good chance that a nodule will be found in the lungs, especially in patients over 55 with a history of smoking. In most cases, the nodules are eventually determined to be harmless—but many patients will experience weeks or months of anxiety until a diagnosis is established. At this time, imaging technology cannot reliably distinguish cancerous from non-cancerous nodules. In addition, differences in the ways that physicians manage the care of patients with nodules can make the follow-up process very challenging for both patients and their physicians.

Moreover, adding to the confusion is research showing that detecting cancerous nodules early may or may not save lives. “CT screening may preferentially detect early stage tumors that are relatively inactive, which is analogous to the situation in prostate cancer,” says Dr. Powell. It may seem counterintuitive, but in the case of lung cancer screening, studies have found that even though

more lung cancers were detected when patients were screened (versus not screened), long-term mortality rates were not affected by the discovery of those tumors.

On the other hand, Dr. Powell notes, it is not uncommon for a patient to have a CT scan for another reason that detects a lung tumor incidentally. Because some tumors do spread and become deadly, assessment and monitoring of any suspicious lesion is critical. Abnormalities must be monitored diligently, according to Dr. Powell, so that lesions requiring intervention can be treated earlier rather than later. The High-Risk Lung Assessment Program at NewYork-Presbyterian Hospital/Columbia University Medical Center has established a highly refined process to do this in a very efficient manner.

Dr. Powell recommends consideration of CT screening for people who have a high risk of lung cancer based on family history, health, and smoking history. For those with a moderate risk, thorough discussion of the potential



The CT image (top) shows a mass in the left lung. The combined PET/CT image (below) reveals the metabolic activity of that mass, as well as its precise location in the lung.

High-Risk Lung Assessment Program

The High-Risk Lung Assessment Program uses an algorithm-driven approach to provide comprehensive, thorough care to two groups of patients. The first group, the “well at risk,” includes those at risk for pulmonary disease due to family history or environmental exposures. The program helps to define the risk each patient faces, mitigates risk factors (for example by referring smokers to innovative smoking cessation programs at Columbia), conducts further screening through lung function

tests, or orders additional CT scans or imaging tests as required. This group of “well at risk” patients includes many New York firefighters who responded to the attack on 9/11, as well as people who have been exposed to chemicals, paint, or other toxic substances.

The second group targeted by the program includes people who have begun a screening protocol, or who have been found to have an abnormality on a CT scan. For these patients, the program uses

Lung cancer most often strikes people over age 50 who have a history of smoking.



results of a scan and follow-up options is essential before deciding upon screening. He believes that it is very important to guide patients regarding screening on an individual basis, taking into account each person's health, symptoms, family history, and very importantly, how he or she would cope with the discovery of a nodule, should one be found. "Finding a nodule can affect a person's quality of life," Dr. Powell says. "Some people can handle the uncertainty associated with an undiagnosed pulmonary nodule, while others have more difficulty," he explains.

RISK FACTORS FOR LUNG CANCER

The risk factors for lung cancer are both genetic and environmental, based on

the best available evidence to manage the results of screenings and to provide comprehensive follow-up care.

For low-risk nodules, the Lung Assessment Program typically recommends follow-up imaging at algorithm-specified intervals. For intermediate lesions, the team uses other tools to try to refine the probability of malignancy. One is to follow the lesion over time, because malignant nodules tend to grow, whereas benign ones do not. Sequential CT scans at three-month inter-

Genetics and Lung Disease

Unlike breast cancer, in which the presence of BRCA1 or BRCA2 is a clear predictor of risk for cancer, specific gene mutations increasing the risk for lung cancer have not yet been identified. Ninety percent of lung cancers develop in people who have smoked tobacco.


Among the small percentage of nonsmokers who develop lung cancer, research has found significant biologic differences in their tumors compared to the tumors of smokers. This information may lead to the development of therapies that are targeted to the biologic characteristics in each group. In addition, research by Dr. Powell and colleagues, as well as other laboratories, has shown that molecular information acquired from microarray analysis of lung cancer specimens may predict tumor progression and patient survival.

Genetic causes have been linked to other lung diseases, such as alpha-1 antitrypsin deficiency for chronic obstructive pulmonary disease (COPD). The genetics program at NewYork-Presbyterian/Columbia has extensive experience in identifying individuals at risk for this and for other genetic lung diseases.

exposure to toxins and carcinogens. Lung cancer most often strikes people over age 50 who have a history of smoking. Even for smokers, however, screening for lung cancer is not a routine healthcare measure, and is not usually covered by insurance if a person has no symptoms.

Among healthy former smokers over age 55, screening will detect a nodule in 25-40% of people. When nodules are found, a process follows to distinguish which may be benign and which may be cancerous; only 1.5-2% of nodules are likely to be cancerous, according to Dr. Powell.

To determine whether a nodule is benign or cancerous, information about the nodule itself and the patient's health

history are both evaluated. Nodule properties such as size, shape, patterns of irregularity, calcification, and changes in size or shape over time are observed. Overall health factors, including general health, exposure to smoke and toxins, family history, and other factors are also considered. Together, these data are processed to determine whether the individual's nodules have a low, intermediate, or high probability of being cancerous. The determination of risk is then used to guide treatment decisions. 

Please visit www.columbiathoracic.org and click on the Lung Assessment Program box.

vals may be recommended to monitor for signs of change. Another strategy is to use PET/CT scanning to determine whether a nodule may be metabolically active, because malignant lesions tend to be metabolically active while benign nodules do not.

If a lesion is highly likely to be cancerous, the program may recommend biopsy or removal of the lesion. In most cases, the program uses minimally invasive surgical methods. For those patients with lung cancer, the program uses endobronchial

ultrasound, which provides sophisticated staging of the lesions. A new device called opto-electronic plethysmography now allows the program to very easily and non-invasively evaluate lung function in each portion of the lung. In addition, the program includes thoracic oncology evaluation for consideration of chemotherapy when appropriate.

Patients may be referred by a primary care physician or pulmonologist, or they may seek evaluation on their own.

Emphysema Research

Columbia's Center for Chest Disease tests new devices to treat advanced emphysema.

EMPHYSEMA occurs when the small air sacs of the lung break down. The collapse of these sacs leads to trapped gas and hyperinflation (overfilling of the chest with air). Breathing becomes increasingly difficult, causing shortness of breath, fatigue, and diminished exercise capacity.

Lung Volume Reduction Surgery (LVRS) is the gold standard in treating advanced emphysema, and in addition to oxygen therapy, the only treatment shown to prolong survival. By removing the damaged portions of lung tissue, the procedure enables the remaining lung tissue to function more effectively. After the procedure, patients experience an increase in ability to exercise, improved survival, and an overall improvement in quality of life.

NewYork-Presbyterian Hospital/Columbia University Medical Center has been a leader in LVRS since 1994, with

and these devices are currently in late clinical trials. The lead investigators are **Mark E. Ginsburg, MD**, *Surgical Director of the LeBuhn Center for Chest Disease and Respiratory Failure at NewYork-Presbyterian Hospital/Columbia University Medical Center*, and **Roger Maxfield, MD**, *Associate Clinical Professor of Medicine at Columbia University College of Physicians and Surgeons*.

INVESTIGATIONAL DEVICES

Exhale Airway Stents for Emphysema (EASE): this trial is testing the safety and effectiveness of implanting a tiny drug-eluting stent to keep the airway open. Placement of up to six stents (wire mesh devices smaller than the size of a pencil eraser) is performed through a bronchoscope inserted through the mouth. Once placed, the stents create new pathways for the air to flow, bypassing the damaged lung tissue.

Endobronchial Valve for Emphysema Palliation Trial (VENT): this multicenter trial is testing an implantable, one-way valve called Emphasys Endobronchial Valve (EBV™). The valve is designed to redirect airflow to healthier lung tissue by blocking inhaled air to the diseased lung tissue. EBV is most appropriate for a subset of patients with hyperinflation of the lungs and severe emphysema, according to Dr. Ginsburg. [👑](#)

Learn more about emphysema, lung volume reduction surgery, and clinical trials at www.columbiathoracic.org.

Emphysema and Genetics

As is the case with lung cancer, the highest risk for emphysema results from heavy smoking. Of all patients who smoke heavily, only some develop emphysema, and genetic researchers believe that genes are likely involved in determining why some develop the disease and some do not. Research is currently underway to identify which genes may play a role in predisposing people to the disease.

About one out of 50 people with emphysema has an inherited disorder called Alpha-1 antitrypsin deficiency. In these patients, replacement of the insufficient protein, Alpha-1 antitrypsin, can be achieved through medical therapy. This can prevent the development of emphysema, liver disease, and other problems in people with this inherited condition.



Deployment of the one-way Emphasys Endobronchial Valve™ in a blocked airway

success rates of over 90%. In most cases, surgeons at the center perform LVRS using video-assisted thoracoscopic techniques through minimally invasive incisions. The procedure is very safe and effective, with no procedure-related deaths occurring at the center in over twelve years.

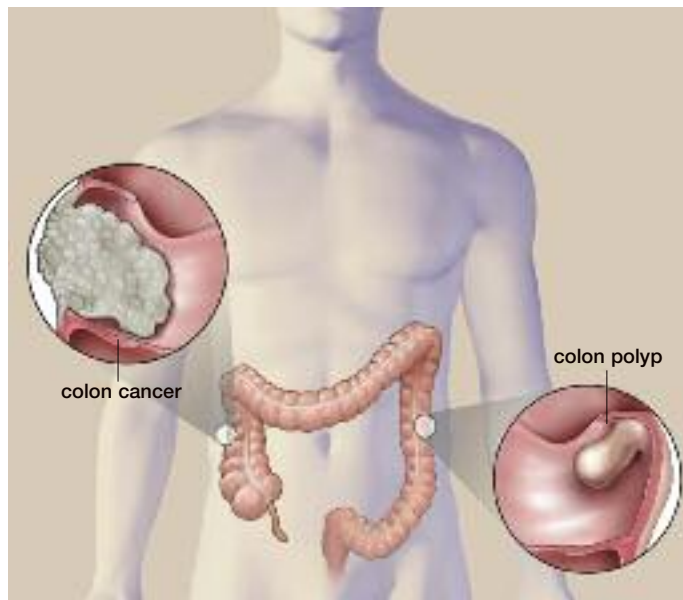
To expand treatment options for more patients, the Center for Chest Disease is currently investigating two devices that could achieve LVRS-like results without surgery. The investigational devices are inserted through the windpipe into the lungs,

Genetic Testing for Colorectal Cancer

For a Broadway performer in her 40's, knowing about her genetic risk gave her the opportunity to choose her path and be proactive about her care.

“L” COULD BE CONSIDERED VERY LUCKY. At age 40, the Broadway performer, singer, and voice coach had a colonoscopy and some precancerous polyps removed. The following year, her colonoscopy was clean. Two years later, when she became anemic, she should have had another colonoscopy, but put it off.

It was the illness of a close cousin, a 49 year old cardiologist, that soon set the wheels of life-altering discovery in motion.



Nancy Heim

Otherwise very healthy, L's cousin was suddenly diagnosed with advanced colon cancer. Genetic tests identified the presence of a mutation in a gene called MSH2, linking his illness to hereditary non-polyposis colon cancer (HNPCC), or Lynch syndrome. His father (L's uncle) was found positive for the gene as well. The family quickly began putting the pieces together. L's mother had died in 1985 from what had initially been labeled cancer of the gall bladder, but her pathology samples, not yet discarded, were now reanalyzed: they tested positive for MSH2 as well. It was remembered that L's maternal grandmother died of endometrial cancer. L soon sought genetic testing and counseling with **Wendy Chung, MD, PhD, Director of Clinical Genetics at NewYork-Presbyterian/Columbia**.

From the genetic tests, analysis of L's mother's samples, and family history emerged a picture of a strong line of the inherited Lynch syndrome, in this case caused by MSH2 abnormalities. L and her youngest sister tested positive for the mutation of MSH2, while their middle sister was negative. Some doctors urged L and

A small percentage of colon cancers are caused by a rare inherited disease called Lynch Syndrome, or Hereditary Nonpolyposis Colon Cancer (HNPCC). The syndrome, caused by mutations of certain genes (MSH2, MLH1, MSH6, PMS1, or PMS2), causes carriers to have about an 80% lifetime risk of developing colon cancer, as well as an increased risk of endometrial, ovarian, gastrointestinal, hepatobiliary, and other cancers. While people *without* the syndrome who develop colorectal cancer are typically diagnosed during their mid-sixties, those with HNPCC are diagnosed at an average age of 44. Children of those with HNPCC have a 50% chance of inheriting the gene from a parent who carries it.

her youngest sister to undergo hysterectomies to prevent the development of ovarian and endometrial cancer.

At this juncture, L and her sister chose quite different paths. Her sister, married with two children, opted to undergo the hysterectomy. She would still need to be regularly screened for colorectal cancer. L, on the other hand, worked with the genetic counselors at NewYork-Presbyterian/Columbia and decided upon the path of continuous monitoring rather than surgery. Every six months she has a thorough checkup, with more intensive yearly testing, including colonoscopy, endoscopy, sonogram, and blood tests, to detect the early signs of cancer that will remain a threat for the rest of her life. So far, L remains cancer free, and is satisfied that she made the right decision for herself.

Not all patients are as ready as L to undergo genetic testing or to share such information with their families. Another of Dr. Chung's patients, a Russian woman in her 50's, also learned that she carries a genetic mutation for HNPCC. She has had multiple surgeries to remove cancerous polyps and lesions, and she knows that her risk of other cancers is higher because of her genetic disposition. But her family is currently dealing with her husband's prostate cancer, and she does not want her adult daughters to worry about their risk of cancer. So for now, she has not divulged her test results, or shared that they have a 50% chance of carrying the same mutation.

L is glad she made the decisions she did, and she remains open to the possibility of a hysterectomy when she reaches menopause. “My sister and I are very supportive of each other's unique decisions,” she says. “There are many different paths you

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Acute care surgery

New surgical division provides superior accessibility and safety.

TO ENSURE THE BEST CARE possible for patients who require immediate surgery due to acute surgical problems or trauma, the Department of Surgery at NewYork-Presbyterian Hospital/Columbia University Medical Center has established a new Division of Acute Care Surgery.

One of the first such divisions in the nation, and the first in the New York metropolitan area, the Acute Care Surgery Division staffs ‘surgeons of the day’ who are devoted exclusively to per-


hernias, and more. Advanced monitoring and diagnostic technology allow the division to perform bedside procedures in critically ill patients.

- ❖ **Surgical Critical Care:** unexpected or supplemental surgical intervention for critically ill hospital patients. For such patients, the Acute Care Division provides continuous monitoring and consultation with other specialists.
- ❖ **Trauma Surgery:** NewYork-Presbyterian/Columbia cares for about 1,800

dental visits to New York City, the papal visit, the United Nations General Assembly, and other diplomatic events.

Maurizio A. Miglietta, DO, Chief, Division of Acute Care Surgery, says that the division is able to provide superior care because it ensures timely surgical assessment and operative management. “If a patient needs surgery in the middle of the night, we are there 24-7. Patients receive care faster, and I believe this will lead to better outcomes.”

The division may also help patients in less direct, but nonetheless important ways. “Our presence frees up other specialists and allows them to concentrate on what they do best,” he says. In many cases, Dr. Miglietta says, he acts as something of a puppet master, coordinating patients’ care with multiple other services. “With many physicians becoming more and more specialized, the need for general surgeons has become great,” he adds.

Tracey D. Arnell, MD, Vice Chair, Medical Education, and Assistant Professor of Surgery, concurs that the 24/7 availability of the new division improves the quality of medical care in the hospital. “This accessibility provides an increased safety net to patients because they do not need to wait for specialists to arrive – we are readily available.” While people sometimes expect to be treated by a resident at teaching hospitals such as NewYork-Presbyterian Hospital, patients receiving care from the Acute Care Surgery Division receive treatment by a Board-certified surgeon. 

For more information, visit columbiasurgery.org.



Maurizio Miglietta, DO, Tracey Arnell, MD, and colleagues treating patients in the new Division of Acute Care Surgery.

forming emergency general surgery, trauma surgery, and surgical critical care. Sometimes called Surgical Hospitalists or Surgicalists, these in-house surgeons provide rapid assessment and interventions for hospitalized patients with time-sensitive problems. Because acute care surgeons face tremendous variety in the patients they treat, they draw from many disciplines and are adept at a great range of surgical procedures.

The new division provides three main types of care:

- ❖ **Emergency General Surgery:** emergency surgery to treat a wide range of acute problems, such as appendicitis, cholecystitis, intestinal obstructions,

adults each year with serious injuries to the neck, chest, abdomen, and extremities. Care is coordinated with other surgical specialists, including neurosurgeons, orthopedic surgeons, plastic surgeons, and interventional radiologists.

The division also has a one-of-a-kind mobile trauma unit (MTU) which provides advanced operative services and other care at the site of accidents, including treatment of people trapped by collapsed buildings, industrial or subway accidents, or in areas inaccessible due to high-level security. This on-call team provides emergency services during national security events such as presi-

Pancreatic Cancer Genetics

Inherited gene mutations play a role in up to 25% of cases of pancreatic cancer. There is up to a 20-fold increase in the risk of pancreatic cancer in individuals with a family history of the disease. At least five distinct cancer syndromes account for a number of inherited pancreatic cancers:

- ❖ Familial atypical multiple mole melanoma syndrome (FAMMM);
- ❖ Peutz-Jeghers syndrome (PJS);
- ❖ Early-onset familial breast cancer syndrome due to BRCA1 or BRCA2 mutations;
- ❖ Hereditary non-polyposis colorectal cancer syndrome (HNPCC); and
- ❖ Hereditary pancreatitis.

The Muzzi Mirza Pancreatic Cancer Prevention and Genetics Program of the Pancreas Center at Columbia University, under the leadership of **Harold Frucht, MD**, *Program Director*, analyzes family and personal medical



Cross-sectional view in a fused PET/CT scan shows a cancerous “hotspot” in the pancreas of a patient with jaundice.

history and provides recommendations for pancreatic cancer screening, genetic counseling, and testing as appropriate. If there is a significant genetic risk, the center provides guidance and recommends an ongoing testing regimen so that patients may ultimately avoid the disease. This testing regimen involves imaging the pancreas with sensitive instruments to detect pre-cancerous abnormalities or small cancers that are surgically curable.

Genetics and Disease


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begun to understand the importance of inflammation in heart disease, diabetes, and other conditions, and they have preliminary leads from genetic research about what might be the genetic culprits – but the full causes and mechanisms still remain far from clear.

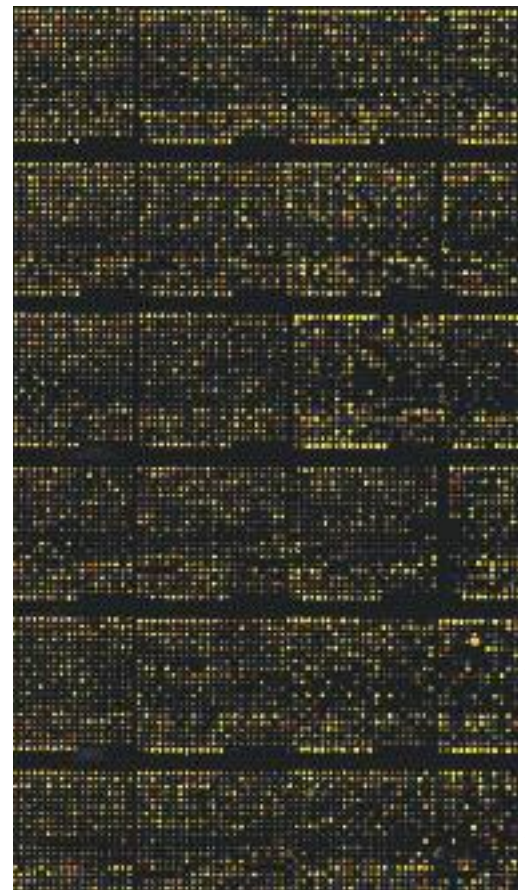
Even more difficult, says Dr. Chung, is understanding the complex dance between genetics and the environment. “This is incredibly important,” she says. While genes cannot be altered at this time, we can modify other risk factors (such as diet, smoking, exercise, etc.) in an effort to prevent or treat disease.”

Gene therapy, which involves manipulation or replacement of faulty genes with different or healthy genes, may some day offer hope for curing genetic

illnesses. Although some promising results have been achieved in research to date, gene therapy is still in its early infancy. According to Dr. Chung, the first widespread clinical applications of gene therapy will likely be as a method of drug delivery, such as targeting therapeutic proteins to cancerous tissues to kill the tumor or repair heart tissue after a heart attack.

In the meantime, genetic counseling is a vital component of each of NewYork-Presbyterian/Columbia’s centers of excellence. Through testing, education, and evaluation of treatment options, patients and family members of those with inherited diseases can significantly improve their likelihood of preempting those diseases. 

For more information, visit www.columbiasurgery.org, or call 800.227.2762.




National Human Genome Research Institute

Microarrays, also called gene chips, provide snapshots of all the genes that are active in a cell at a particular time.

Genetic Testing for Colorectal Cancer

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can take – some are better for some people.” But for L, the choice to undergo genetic testing was never in doubt. “I had always suspected something, and it’s good to know (about the genetic risk) so I can be proactive. Everyone is predisposed to something – there is no harm in finding out. The more we share information, the better we can treat things. Colon cancer is easy to discover and take care of, if it is found early,” says L. 

Fetal Cardiology

Genetic screening provides opportunities to give newborns optimum care.

FOR PARENTS-TO-BE, perhaps nothing is more frightening than the prospect of giving birth to a child with a genetic defect – especially something as serious as a defect of the heart. Despite the relative rarity of such problems (about 8 in every 1000 births), congenital heart disease represents the most common potentially life-threatening birth defect. Pregnant women are increasingly subject to in-depth ultrasound screening for evidence of congenital malformations, especially since the average age of motherhood has been increasing during the past several years. Prenatal screening ultrasound can reveal previously undetectable problems before birth, providing families and physicians with the best opportunity to create expedient treatment plans for newborns with genetic anomalies.

Fetal medicine specialists may order detailed fetal cardiac examination in otherwise low-risk pregnancies if they can not be certain from screening ultrasound examination that the cardiac structure and function of a fetus is normal. According to **Charles S. Kleinman, MD**, *Professor of Pediatrics in Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons, and Chief, Fetal Cardiology, Morgan Stanley Children's Hospital of New York-Presbyterian* the development of detailed ultrasound examination of the fetus has led to an important evolutionary change in the care of fetuses and newborns with congenital malformations. Close interaction of obstetricians, genetic counselors, clinical geneticists, neonatologists, cardiologists, pediatric surgeons, and other subspecialists now constitutes the new field of “prenatal pediatrics.”

Down syndrome is among the best known genetic syndromes because it is a single gene anomaly that was identified in the earliest days of genetic research. But according to Dr. Kleinman, clinical scientists have now come to understand the genetic basis of many other heart problems. In collaboration with basic scientists, researchers at Columbia University are feverishly working to learn how specific genetic abnormalities

children with Down syndrome) having a specific malformation called atrioventricular septal or “canal” defect. According to Dr. Kleinman, “We now know that if a previously undiagnosed fetus is found to have atrioventricular septal defect during a screening exam, that genetic testing is indicated, since over 50% of patients with this specific heart disease have Down syndrome.”

Another well understood genetic



affect the developing heart, says Dr. Kleinman.

If a newborn infant has physical characteristics consistent with Down syndrome, he or she will undergo genetic testing in order to confirm the abnormal presence of trisomy of chromosome number 21. Cardiology evaluation is included as a routine aspect of the evaluation of such infants, since congenital heart disease is commonly found in association with Down syndrome (about 50%), with 50% of those children (about 25% of all

syndrome stems from abnormalities on chromosome 22. “We know that children with a missing portion of chromosome 22 (22 q11 deletion) are at high risk for DiGeorge syndrome,” says Dr. Kleinman. This syndrome includes heart defects, immune deficiency due to absence of the thymus gland, abnormal calcium metabolism due to absence of the parathyroid glands, abnormalities such as submucosal clefts of the palate, as well as learning disabilities and psychological problems. Tetralogy of Fallot, a common cardiovascular malfor-

mation associated with cyanosis (blueness related to deficient oxygen content of arterial blood), is frequently associated (25%) with the DiGeorge syndrome. Babies with tetralogy of Fallot typically have a ventricular septal defect (hole in the wall between the ventricles) immediately below the aorta and pulmonary artery (the great arteries emerging, respectively, from the left and right ventricles) and obstruction to blood flow from the right ventricle into the pulmonary artery (pulmonary stenosis).

At Morgan Stanley Children's Hospital/Columbia University Medical Center, pediatric cardiologists work hand in hand with specialists from maternal-fetal medicine, genetics, pediatric surgery, and pediatric cardiac surgery. Of all newborns at the hospital diagnosed during 2007 with congenital heart problems, 67% were diagnosed before birth. About half of congenital heart defects require corrective surgery, while the other half are not serious enough to require surgical intervention. "We have reached a level of success with reconstructive neonatal cardiac surgery where, with rare exception, survival is almost a given," states Dr. Kleinman. The focus now, he explains, is on optimizing quality of life for young patients as they grow.

"If tetralogy of Fallot is diagnosed in a fetus, we know that genetic screening is advisable. Through such testing, we can determine whether other abnormalities requiring treatment during the newborn period or early childhood are likely to be encountered," says Dr. Kleinman. "This enables us to deal with potential problems proactively, before

they become serious, such as providing treatments to enhance thymic function for patients with deficiencies in cellular immunity, or providing early interventions for learning disabilities. This greatly enhances a child's health and overall quality of life, and can have dramatic lifelong effect," he explains.


Advances in genetics play an increasing role in this care, says Dr. Kleinman, primarily because genetic testing can diagnose so many more problems early, whereas in the past, such problems would often remain hidden until they became fully expressed in a critical fashion. The ability to detect diseases through genetic testing is moving so rapidly that Dr. Kleinman consults the geneticists at Columbia University Medical Center on almost a weekly basis to ascertain the current status of genetic testing for specific abnormalities.

In some instances, **Wendy Chung, MD, PhD**, *Director of Clinical Genetics*, may detect a genetic problem, and then refer a patient to Dr. Kleinman and his colleagues to determine whether the child has an associated heart problem as well, and if so, to determine the severity of the problem. "The presence of one congenital malformation means we need to look for another," says Dr. Kleinman. "If we find two, then we look for a third, and so on. The objective is to best manage the child's care, because we may need to choreograph management among multiple specialists by determining which anomaly needs to be treated first," he says.

Prenatal care across the country is beginning to adapt to the knowledge gained by genetic insights. If it is not possible during ultrasound to confirm

that the four chambers of the heart are normal, then additional testing is indicated. If there is a family history of certain heart diseases, Dr. Kleinman and colleagues now begin looking for fetal abnormalities at just 12 weeks, using a vaginal ultrasound probe. By 14 weeks, says Dr. Kleinman, the heart can frequently be viewed through the abdominal wall. "At a minimum, we advocate genetic screening when there is any abnormality significant enough to require intervention," he says.

Dr. Kleinman recommends genetic screening whenever a baby has a congenital heart defect "in order to answer questions that the parents may not know they will have at some point, down the road." In his experience, parents often begin to ask questions later, such as how likely they will be to have another child with a congenital defect, whether there is anything they could have done to avoid the problem, or if the child will experience additional problems later in life, including when they face parenthood themselves.

At Morgan Stanley Children's Hospital/ NewYork-Presbyterian, patients with congenital heart disease are treated by a multidisciplinary team including high-risk obstetrics, neonatology, cardiology, cardiac surgery, and human genetics. Depending on the presence of additional abnormalities, other specialists may participate in a child's care, including pediatric general surgeons, neurosurgeons, plastic surgeons, ear-nose-throat specialists, and others. 

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improve cognitive function in those with the disease,” Dr. Schmidt explains. “If proven safe and effective, a RAGE-based therapy would have enormous potential to help millions of people with Alzheimer’s disease.” In another trial, the researchers are studying the impact of RAGE inhibition on the progression of diabetes-associated kidney disease. The goal in these early studies is to determine if blocking RAGE stops or reverses the abnormal leakage of proteins into the urine that typifies diabetic complications in the kidney.

While mediating the RAGE molecule has the potential to open new treatment avenues for

many complex diseases, Dr. Schmidt cautions that it is still necessary to clarify how much RAGE can be blocked without causing detrimental effects. “Much research remains to be done before RAGE-based approaches will be translated into new therapies,” she says. But Dr. Schmidt is extremely optimistic about its future, and believes “this work holds tremendous promise for alleviating major causes of human disease.” 

Learn more about research on RAGE and inflammation at columbiasurgery.org in the Surgical Science Division.



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