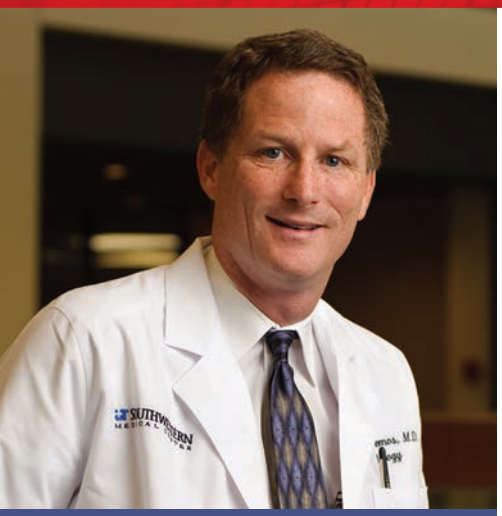
UT SOUTHWESTERN
Heart Beat

DORIS AND HARRY W. BASS JR. CLINICAL CENTER FOR HEART, LUNG AND VASCULAR DISEASE

FALL 2009



James de Lemos, M.D. Dr. James de Lemos is an Associate Professor of Internal Medicine at UT Southwestern, where he holds the J. Fred Schoelkopf Jr. Chair in Cardiology. His research interests include risk assessment and management of coronary artery disease, as well as the use of biomarkers for assessment of patients.

A graduate of Harvard Medical School, Dr. de Lemos completed his residency in internal medicine at UT Southwestern and a fellowship in cardiovascular medicine at Brigham and Women's Hospital. He sits on editorial boards of the *American Journal of Cardiology* and the *American Heart Journal*.

Dallas Heart Study: Early Results

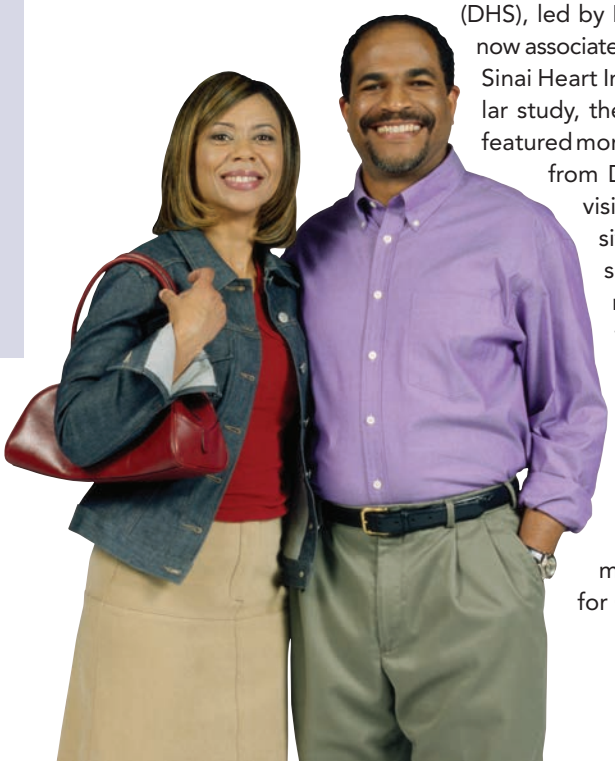
by **James de Lemos**, M.D.

Better Management, Better Care

In the medical world, a lot has happened over the past 10 years. But one of the most significant events in the Dallas/Fort Worth Metroplex, and perhaps the most far-reaching, has been the start-up and ongoing work of a major heart study conducted at UT Southwestern Medical Center (UTSW). The early results of that study are transforming cardiovascular risk factor identification and management for UTSW physicians and leading to better care for patients.

Largest Cardiovascular Study Ever in North Texas

In 1999, UTSW was selected as the first recipient of a nationally competitive award from the Donald W. Reynolds Foundation, initially receiving $24 million over four years to create broad-based programs in basic, translational, clinical, and population-based research focused on improving cardiovascular health. The grant funded, in part, the creation of the Dallas Heart Study (DHS), led by Helen Hobbs, M.D., and Ron Victor, M.D., now associate director for clinical research at the Cedars-Sinai Heart Institute. The groundbreaking cardiovascular study, the largest ever performed in North Texas, featured more than 6,000 ethnically diverse participants from Dallas County. To start, research subjects visited UTSW where they underwent extensive imaging of the heart and blood vessels using CT and MRI. Since then, UTSW researchers have focused on identifying risk factors as well as genetic and biomarker "signatures" that can detect preclinical cardiovascular disease (CVD).



Although relatively new among large epidemiology studies, the DHS has rapidly become notable due to several major discoveries and the publication of more than 80 papers that have implications for CVD prevention.

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UNIVERSITY HOSPITALS & CLINICS

John Warner, M.D., Medical Director of the Doris and Harry W. Bass Jr. Clinical Center for Heart, Lung and Vascular Disease

HeartBeat wishes to thank John Warner, M.D., for his invaluable input and guidance in the preparation of this publication.

An interventional cardiologist, Dr. Warner is Associate Professor of Internal Medicine at UT Southwestern, where he holds the Jim and Norma Smith Distinguished Chair for Interventional Cardiology and the Audre and Bernard Rapoport Chair in Cardiovascular Research. He is also the current President of the Dallas Division of the American Heart Association.

Dr. Warner is a graduate of Vanderbilt University School of Medicine. He completed fellowships in cardiology and interventional cardiology at Duke University Medical Center.

In The Next Issue
Women and Heart Disease

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RESEARCH UPDATE

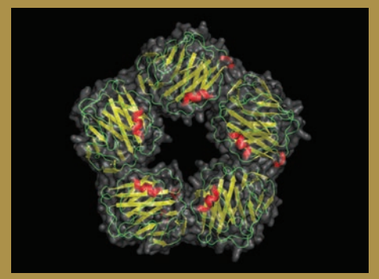
How can you mend a broken heart?

Perhaps with stem cells from the heart itself, say three UT Southwestern Medical Center researchers, who were recently awarded a $2 million grant from the American Heart Association (AHA) to study the development and mechanisms of generating new cardiac muscle cells.

The UT Southwestern researchers–Jay Schneider, M.D., Ph.D., Joseph Hill, M.D., Ph.D., and Eric Olson, Ph.D.–say their investigations could significantly help advance the understanding of stem cells' role in heart disease and repair, leading to new ways to care for patients with heart attacks or congestive heart failure by stimulating heart cell regeneration.

"The goal is to use small molecules and microRNAs as probes to understand the barriers that prevent the human heart from repairing itself after injury," says Dr. Schneider. "By doing so, we hope to develop new therapeutics that will overcome these barriers and induce the human heart to regenerate after injury."

UT Southwestern was one of only three institutions nationwide to receive the AHA grant.



Don't blame it on the C-reactive protein.

Heightened levels of C-reactive protein (CRP) in the blood help identify people with heart disease, but they are not the cause of heart problems, according to a study recently published in the *Journal of the American Medical Association* (JAMA).

"This study puts the nail in the coffin… in the question about (C-reactive protein): does it cause cardiovascular disease?" says James de Lemos, M.D., of UT Southwestern Medical Center, who co-authored an editorial in JAMA about the study. "It clearly does not."

CRP is secreted by the liver and signals tissue inflammation and a risk for heart attack or stroke.

Though the study concluded it would be "fruitless" to develop drugs aimed at lowering C-reactive protein to prevent heart disease, there still could potentially be value in testing for CRP, maintains Dr. de Lemos. "If CRP increases in response to other inflammatory triggers, it may still be a useful tool for personalizing selection of anti-inflammatory therapies, including statins," he and a colleague wrote.

Detecting Vascular Disease with Ultrasound

by **Patrick DeMuth**, B.S., R.V.T. • **Kathy Caylor**, B.A., R.V.T. • **G. Patrick Clagett**, M.D., R.V.T., R.P.V.I.

G. Patrick Clagett, M.D. Dr. Clagett is Chief of Vascular Surgery at UT Southwestern and holder of the Jan and Bob Pickens Distinguished Professorship in Medical Science. His research interests include surgical management of cerebrovascular disease, blood biomaterial interactions, the clinical utility of new anti-thrombotic agents, and vascular prosthetic infections.

He earned his undergraduate and medical degrees at the University of Virginia, finished his general surgery residency at the University of Michigan, served as a research fellow at Harvard Medical School, and completed a vascular fellowship at Walter Reed Army Medical Center.

A Preventable Event

Vascular disease is one of the leading causes of disability and death in the United States, but it often goes undetected prior to the occurrence of a major medical event, such as a stroke or a ruptured aortic aneurysm. Not only are these catastrophic events potentially fatal or life-altering, more importantly, the majority of them are preventable with early detection.

Consider these facts:

- Vascular disease can cause lethal aneurysms of the aorta, the main artery of the body. More than 15,000 people die each year in the U.S. from rupture of an aortic aneurysm. More than one million people are living with an undiagnosed aneurysm; at least 95 percent of aneurysms can be successfully treated prior to rupture.
- Vascular disease can block the carotid arteries, the main arteries feeding the brain, and cause strokes. Stroke remains the third leading cause of death in the U.S., killing nearly 160,000 people each year. A large proportion of strokes are caused by plaque in the carotid arteries.
- Vascular disease can impair circulation to the legs, leading to disability, reduced mobility, and amputation. One in 20 Americans over the age of 50 has peripheral artery disease (PAD), which affects 8 to 12 million people. People with PAD suffer a five-fold increased risk of stroke and myocardial infarction and a death rate two to three times greater than individuals without PAD.

An Effective Tool

As the baby boomer generation reaches the age at highest risk for vascular disease (over 55), detecting potential problems prior to the development of symptoms is vital to their well being. Ultrasound, along with a thorough physical examination, is an effective tool to achieve that goal. A relatively quick, painless, inexpensive, noninvasive screening with ultrasound can provide crucial information regarding the presence and severity of vascular disease.

At UT Southwestern Medical Center (UTSW), the Clinical Noninvasive Vascular Laboratory provides screening exams to evaluate the most common areas of concern for vascular disease: the abdominal aorta, the carotid arteries, and the lower extremity arteries.

Evaluation of the abdominal aorta assesses the presence or absence of an aortic aneurysm, even those not palpable on physical exam. Evaluation of the carotid arteries allows detection of atherosclerotic plaque at the carotid bifurcation, one of the most common sources of ischemic stroke. And evaluation of the blood pressures in the pedal arteries in relation to the patient's systemic pressure provides assessment of the presence of PAD, which also serves as a marker for the patient's overall cardiovascular health.

Wholesale screening of everyone over the age of 55 is not recommended because it is not cost-effective. Instead, screening should be performed in patients who are most likely to have vascular disease, including those who have at least one of these risk factors: a family history of vascular disease, smoking history, hypertension, diabetes, high cholesterol, or known heart disease.

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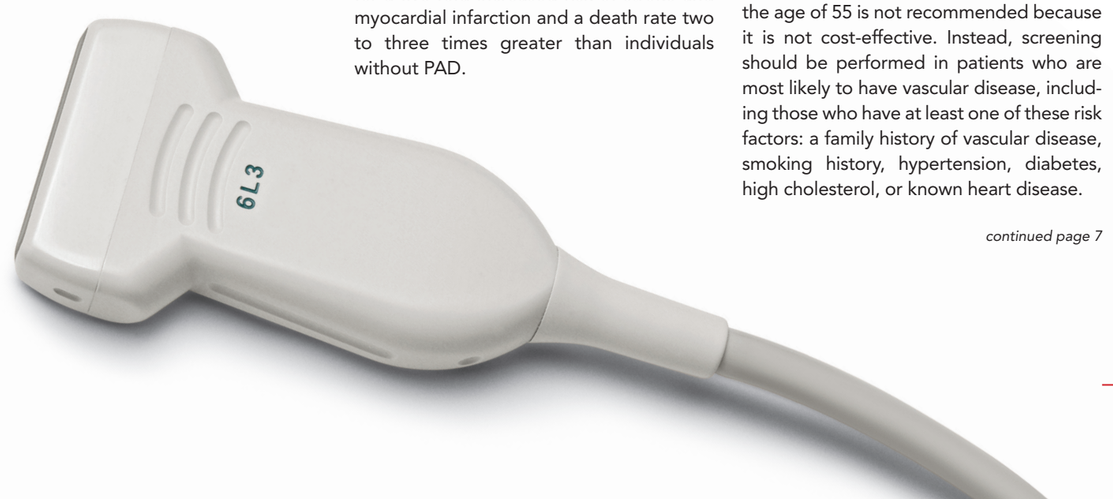

Dallas Heart Study: Early Results

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For most individuals, cardiovascular risk could be reduced by losing a few inches around the waist.

Relevant Findings to Date

Lifelong Reductions in LDL Cholesterol: Employing a novel strategy in which they screened individuals from the DHS with either extremely low or extremely high LDL-C, Dr. Hobbs and her research partner, Jonathan Cohen, Ph.D., identified rare variations in a cholesterol metabolism gene called *PCSK9* that were associated with 28 percent lower LDL-C among African-American participants. These gene variants, which influence cholesterol levels over the full lifespan, were associated with an 88 percent reduction in cardiovascular events. The findings contend that moderate reduction in LDL-C (as could be obtained with a generic statin)–when applied much earlier in life–would have a much greater impact on cardiovascular disease than a typical strategy of treating cholesterol aggressively later in life after atherosclerosis has already developed.

Optimal Cardiovascular Risk: Amit Khera, M.D., has performed research in the DHS that moves beyond traditional risk factor categories and instead targets ideal levels of each of the major risk factors. He has defined optimal risk as BP <120/80 mmHg; LDL-C <100 mg/dl; fasting blood glucose <100 mg/dl; and lifetime non-smoking status. In the DHS, the optimal risk factor profile was only present in 10 percent to 12 percent of individuals. However, when present it was associated with a 90 percent reduction in atherosclerosis prevalence compared to individuals with no optimal risk factors. These findings highlight the importance of striving for ideal levels of CVD risk factors in patients and suggest that important benefits may come from lifestyle interventions that move individuals from borderline to ideal risk factor levels.

Body Size and Shape: In the DHS, we found that subclinical atherosclerosis was much more strongly associated with measures of body shape, such as waist-to-hip ratio (WHR) and waist circumference (WC), than with body mass index (BMI). An important limitation of BMI is its failure to differentiate between varied body compositions. Centrally distributed or abdominal obesity is specifically associated with adverse effects on metabolism, dyslipidemia, and insulin resistance. In addition, BMI can be falsely elevated in the presence of increased lean body mass (such as in trained athletes), and low BMI values are associated with chronic conditions leading to loss of lean body mass. The present findings suggest that WHR and WC may be preferred measures of the cardiac risk associated with obesity. From a public health standpoint, the most important implications of the DHS analyses are that the associations between WHR and WC are linear and do not demonstrate a threshold effect. This suggests that for most individuals, cardiovascular risk could be reduced by losing a few inches around the waist, even if body weight is considered "normal."

Cautions about C-reactive Protein (CRP): In Dallas County, African Americans have higher CRP than non-African Americans, and more than twice as many women as men have CRP levels above the CDC's recommended high-risk cutoff of 3 mg/L. The strongest association observed was between obesity and CRP, with a particularly notable correlation seen in women. These findings may be particularly relevant in light of the findings of the JUPITER* trial, which will lead some cardiologists to suggest that CRP levels should be used as a trigger for initiation of statin therapy. The DHS data suggest that such a strategy would lead to more statin usage among women than men, despite markedly lower cardiovascular risk in women.

**Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)*

The Future

UTSW physicians are already applying what has been learned in the DHS study as they evaluate patients who come to the Center for Heart, Lung and Vascular Disease. As a result of the DHS, both patients and referring physicians alike can look to UTSW for new ideas in cardiovascular care.

As for the future, participants from the DHS are currently returning to UTSW for a follow-up visit, in which they undergo repeat CT scanning for coronary calcium, MRI scanning to assess left ventricle structure and function, and MRI of the aorta to assess plaque and wall thickness. Several new imaging phenotypes are being collected as well, including MRI of the carotid artery and brain. The data collected in the follow-up visit will allow UTSW researchers to identify novel determinants of the progression of pre-clinical CVD and perhaps lead to even more impressive breakthroughs in cardiovascular risk factor identification and management.

Where to Find Us. The Donald W. Reynolds Cardiovascular Clinical Research Center, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-8591. Phone: 214-648-1600

Helen Hobbs, M.D.

Since its inception, the Dallas Heart Study has been spearheaded by Dr. Helen Hobbs, Chief of Clinical Genetics at UT Southwestern and Director of the Donald W. Reynolds Cardiovascular Clinical Research Center. She is also Director of the Eugene McDermott Center for Human Growth and Development at UT Southwestern, as well as an investigator for the Howard Hughes Medical Institute. She holds the Eugene McDermott Distinguished Chair for the Study of Human Growth and Development and the Dallas Heart Ball Chair in Cardiology Research.

Dr. Hobbs received her medical training at Case Western Reserve University and interned at Columbia-Presbyterian Hospital. She also has training in endocrinology and completed a postdoctoral fellowship at UT Southwestern in the laboratory of Nobel laureates Michael Brown, M.D., and Joseph Goldstein, M.D.

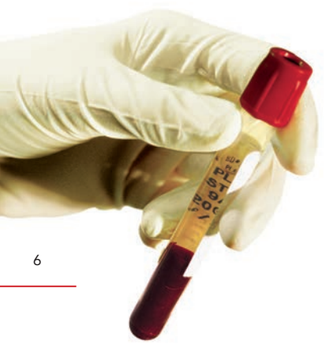
Though the landmark study that Dr. Hobbs directs remains ongoing, researchers have already identified new genetic factors that contribute to heart disease; learned that African Americans are two to three times more likely to have high blood pressure; and determined that lowering LDL cholesterol earlier in life helps protect against heart disease.

Advanced Testing for Heart Disease Risk

by **Amit Khera**, M.D.

Amit Khera, M.D. Dr. Amit Khera is an Assistant Professor of Internal Medicine at UT Southwestern, where he is also Director of Preventive Cardiology as well as Medical Director of Cardiac Rehabilitation at University Hospital–St. Paul. His research interests include risk assessment and risk factor modification in patients with premature and familial disease.

Dr. Khera earned his medical degree from Baylor College of Medicine and completed a residency in internal medicine at Brigham and Women's Hospital, followed by a cardiology fellowship at UT Southwestern. He also holds a master's degree in epidemiology from Harvard.



In recent decades there has been a marked decline in death rates from cardiovascular disease. Nevertheless, cardiovascular disease, including coronary heart disease (CHD) and stroke, remains the number one cause of death in the U.S. New therapies and more aggressive applications of conventional therapies are now being used, but one of the greatest challenges to clinicians is determining who is at highest risk. Tests are emerging which may improve our ability to do that.

Imaging Tests

One of the most widely used imaging tests for CHD risk is coronary artery calcium (CAC) scanning, which is performed in less than one minute using conventional CT scanners. Numerous studies have shown that higher CAC scores are strongly related to the risk of cardiovascular events. People with high scores (>400) have an almost ten-fold increased risk compared to those with no detectable CAC. Researchers at UT Southwestern are analyzing CAC data from the Dallas Heart Study to determine how to more effectively use these tests to screen for CHD risk.

Blood Tests

Advanced lipoprotein testing using NMR and other methods may be particularly valuable for patients with insulin resistance, high triglycerides, and low HDL levels. Other blood tests referred to as biomarkers are also promising new tools to assess CHD risk. Biomarkers that assess for low levels of inflammation including C-reactive protein (CRP) and LP-PLA2 have been shown to predict a higher likelihood of heart disease among healthy individuals. In fact, a recent study of more than 17,000 subjects demonstrated that middle-to older-aged people who had normal to low cholesterol levels–but who also had elevated levels of CRP–had a 50 percent reduction in cardiovascular events when treated with a cholesterol-lowering statin drug.

Genetic Tests

A lot of research in the area of cardiovascular risk prediction has been focused on genetic testing. Tests could be performed very early in life and provide the opportunity for early intervention. In fact, UT Southwestern researchers have shown that one genetic mutation that results in a 28 percent reduction in cholesterol levels from birth was associated with an 88 percent reduction in heart disease events. A major challenge is to discover genetic variants that consistently and reliably predict risk. One genetic variant to meet this test, the *9p21* mutation, was discovered by researchers at UT Southwestern.

Interpreting Results

Although emerging tests hold great promise, two major questions remain: Who should be tested, and what should be done with the results? Investigators from the UT Southwestern Program in Preventive Cardiology are actively studying these questions using data from the Dallas Heart Study. Current guidelines generally support using tests in intermediate-risk patients where the physician and patient are undecided about treatment, or where traditional risk factors may underestimate risk. Interpreting these tests can be complicated as results are generally not "positive" or "negative" and various tests may provide conflicting results. As such, the scientific expertise and multidisciplinary approach offered by physicians and staff at UT Southwestern give patients an advantage when trying to prevent cardiovascular disease.

Where to Find Us. Doris and Harry W. Bass Jr. Clinical Center for Heart, Lung and Vascular Disease, 5939 Harry Hines Blvd., Dallas, TX 75390-9047. To schedule an appointment, call 214-645-8000. To learn more about UT Southwestern's heart, lung and vascular program, visit: utsouthwestern.org/heartlungvascular

Detecting Vascular Disease with Ultrasound

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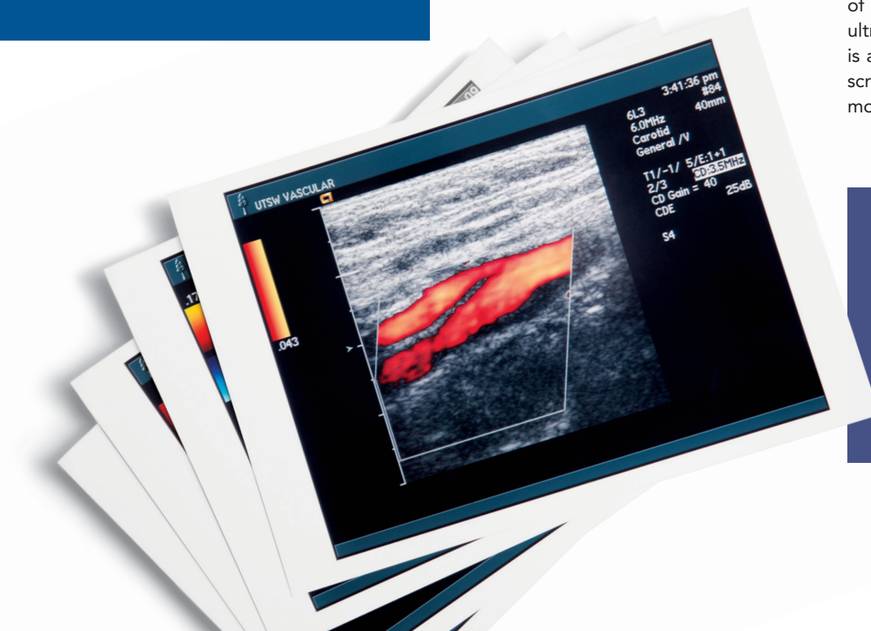
A relatively quick, painless, inexpensive, noninvasive screening with ultrasound can provide crucial information regarding the presence and severity of vascular disease.



Accredited Technologists

The accuracy and reliability of ultrasound to detect vascular disease are well documented. However, ultrasound is recognized to be highly operator-dependent. The UT Southwestern Clinical Noninvasive Vascular Laboratory uses state-of-the-art, dedicated vascular equipment, and the lab is fully accredited by the Intersocietal Commission on Accreditation of Vascular Laboratories (ICAVL), an accrediting body that serves as the national standard for quality vascular testing. In addition, each of our technologists is a credentialed diagnostic vascular technologist (RVT). Our interpreting physicians have earned the Registered Physician in Vascular Interpretation (RPVI) credential, verifying expertise in the interpretation of vascular ultrasound examinations.

Affordable Screening

The out-of-pocket cost to the patient for each vascular screening at UTSW's vascular lab is $50, which is comparably priced to other screening programs in the community. Generally, patients do not need a physician referral for a vascular screening; however, a final report of the findings will be sent to their primary care physician upon request. When screening is performed due to a referral, a preliminary report is prepared by the examining technologist and expedited to the referring physician. The examination is then read by a board-certified vascular surgeon, who provides a final interpretation of the screening. The decision to perform further testing remains in the hands of the primary care physician.

Some screenings may require a physician referral, particularly if the screening is performed on a new Medicare enrollee. Since 2006, Medicare has included the abdominal aortic ultrasound screening as part of the "Welcome to Medicare" physical examination to qualified individuals. When a patient enrolls in Medicare and has a history of smoking, or a family history of aortic aneurysm, an aortic screening ultrasound to evaluate the aortic diameter is a covered expense. Otherwise, vascular screenings are generally not covered by most insurance companies.

Where to Find Us. The Clinical Noninvasive Vascular Laboratory is located at 5939 Harry Hines Blvd., Dallas, TX 75390-9047. Screenings may be scheduled by calling 214-645-0545, or by faxing a physician's order to 214-645-0536. Vascular physicians are also available for consultation with any physician whose patient is referred for vascular disease.

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