



VHVI Study Probes Stem Cell Timing



Doug Vaughan, M.D.



Antonis Hatzopoulos, Ph.D.

We hope that delivering cells to patients will improve their heart function after a heart attack, but there is not a lot of information available about the value of cell therapy more than a week or so out.

By Doug Vaughan, M.D., Director of the Division of Cardiovascular Medicine and Antonis Hatzopoulos, Ph.D., Associate Professor of Medicine

Vanderbilt Heart and Vascular Institute (VHVI) is a member of the Cardiac Cell Therapy Research Network, sponsored by the National Heart, Lung and Blood Institute (NHLBI). The network was organized in 2006, in part, to ask new questions about cell therapy.

In our quest to understand the role of stem cells in restoring cardiac function after a heart attack, we are now looking at the role timing plays and whether there is an advantage to delivering cells to the heart sooner rather than later.

This time question has not been addressed in any other major study in the world, and it's important to bring some clarity to that question.

This Phase II study, called "Time and Late-Time," will enroll patients in two groups. The first group will receive stem cell therapy within the first few days of their heart attacks. The second group will receive it within three weeks after their heart attacks. Patients will be recruited by the five centers within the network — Vanderbilt, the Cleveland Clinic, the Texas Heart Institute, the University of Minnesota and the University of Florida.

We hope that delivering cells to patients will improve their heart function after a heart attack, but there is not a lot of information available about the value of cell therapy more than a week or so out.

All of the clinical trials that have been done so far have enrolled patients within three to seven days. It's important to try to understand if there is something different about the environment of the heart immediately after a heart attack that makes it more receptive or more likely to respond to cells.

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From the Editor



Robert N. Piana, M.D.
Associate Professor of Medicine

The Vanderbilt Heart and Vascular Institute provides a unique opportunity to optimize outcomes for patients with increasingly complex cardiovascular conditions. This virtual hospital within a hospital achieves a real partnership among cardiologists, cardiac surgeons, vascular surgeons and cardiac anesthesiologists with a shared mission to provide superior health care through intensive collaborative approaches. This partnership is reflected in our team-based approaches to cardiac regeneration therapy and drug eluting stenting. Novel interdisciplinary collaborations of this type will certainly help define the future of cardiovascular care in centers of excellence.

Over the last several years, no area of cardiovascular science has been more exciting or controversial than that of stem cell biology. As part of the newly formed Cardiac Cell Therapy Research Network, we recently began testing the efficacy of bone marrow-derived cells for the treatment of patients with acute myocardial infarction and for patients with chronic left ventricular dysfunction.

In this issue, we also address the clinical benefit of using one of the latest coronary revascularization procedures — drug-eluting stents — which have been under close scrutiny and have led to a national discussion among the advisory panel for the U.S. Food and Drug Administration to help resolve the issue.

Finally, we highlight several new clinics that VHVI has opened in the past year to treat atrial fibrillation, valve disease and cardiomyopathy.



VHVI Study Probes Stem Cell Timing

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Giving stem cells to infarcted hearts may help to regenerate muscle cells that will prevent heart failure.

Will we have the luxury of time and be able to provide cell therapy weeks after someone's heart has been damaged?

Late-Time will test the hypothesis that cell therapy might reverse late defects like fibrosis and tissue remodeling.

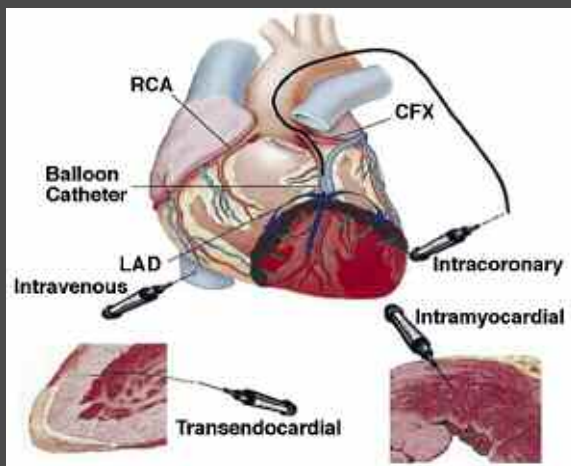
Since this phase can take weeks or months, there is a window of opportunity in both the short term and long term to see a beneficial effect of cell therapy.

"Giving stem cells to infarcted hearts may help to regenerate muscle cells that will prevent heart failure," said David Zhao, M.D., director of the Cardiac Catheterization Laboratory and Interventional Cardiology.

In addition, the delayed cell delivery time holds the potential for extending cell-based therapies to a broader population.

Specifically, it will permit patient transfer to tertiary sites for cell delivery and inclusion of sicker patients with cardiogenic shock who would be too ill to receive cell therapy soon after a heart attack.

Multiple Approaches for Transplanting Cells to Heart



Advanced treatments, including stem-cell based therapies, have proved to restore injured and/or lost cardiac tissue to improve heart function.

A person who elects to participate in the trial will undergo a bone marrow aspiration, which is done under local anesthesia. The cells are removed, filtered and processed to concentrate endothelial progenitor cells.

The cells are then infused via a catheter directly into the coronary artery during the patient's return visit to the cath lab.

Using echocardiography and cardiac MRI, researchers will obtain baseline and follow-up measures of the patient's heart structure and function to see how the cell therapy has impacted cardiac function.

"Time and Late-Time" is currently enrolling patients. To find out more, please call 1-800-767-9192.

Drug Eluting Stents in 2008

Realizing the Promise and Overcoming the Hurdles

By Robert Piana, M.D.
Associate Professor of Medicine

Recent scrutiny of long-term patients has somewhat tempered early unbridled enthusiasm. Stent placement effectively treats angina (chest pain due to obstructed coronary arteries), but it does not reduce myocardial infarction (MI) or death, emphasizing the critical importance of secondary prevention with lipid lowering, smoking cessation and other measures.

Drug eluting stents (DES) have dramatically transformed the treatment of coronary artery disease. Treatment of coronary artery blockages with balloon angioplasty has been plagued by early renarrowing rates of 30 percent to 60 percent causing recurrent symptoms.¹ Bare metal stents (BMS) reduce restenosis to 24 percent to 37 percent by minimizing recoil.²⁻⁴

DES combine this scaffolding effect with profound inhibition of the cellular proliferative response at the treatment site due to slow elution of drugs embedded in the stent. (Figure 1). As a result, restenosis rates with DES have plummeted to 7 percent in relatively simple lesions.^{1, 4}

This dramatic achievement is tempered by the recognition that prevention of restenosis does not reduce myocardial infarction (MI) or death. Importantly, stent placement also introduces a persisting small risk of blood clot formation within the device: stent thrombosis (ST). Standard treatment to prevent ST after BMS includes dual antiplatelet therapy with aspirin plus ticlopidine or clopiogrel for two to four weeks. This reduces ST to a very low rate of ~1%, usually occurring within the first month. However, the consequences of this rare occurrence are dramatic, with mortality rates of ~20%.⁵ For DES, dual antiplatelet therapy was originally recommended for three to six months based on the presumption that reduced cellular proliferation within the stents might extend the window of risk for ST.

In 2006 limited data emerged suggesting that DES might have an increased risk of late ST. The Food and Drug Administration therefore convened an expert panel which had the following conclusions regarding DES when they are used in accordance with their approved indications⁵:

- DES are associated with a small increase in stent thrombosis compared to BMS that emerges one-year post-stent implantation.
- However, this increased risk of stent thrombosis is not associated with an increased risk of death or myocardial infarction (MI) compared to BMS.
- When compared to bare metal stents, DES are not associated with an increased rate of all-cause mortality.
- The concerns about thrombosis do not outweigh the benefits of DES compared to BMS when DES are implanted within the limits of their approved indications for use.

Cardiologists have since faced the challenge of synthesizing these data and translating the FDA observations into clinical practice. Particularly challenging has been the recognition that ~60% of DES procedures are "off-label," and these more complex patients sustain increased rates of adverse clinical outcomes after DES.^{6,7} The critical question has been whether long-term death/MI is paradoxically increased after DES compared to BMS due to

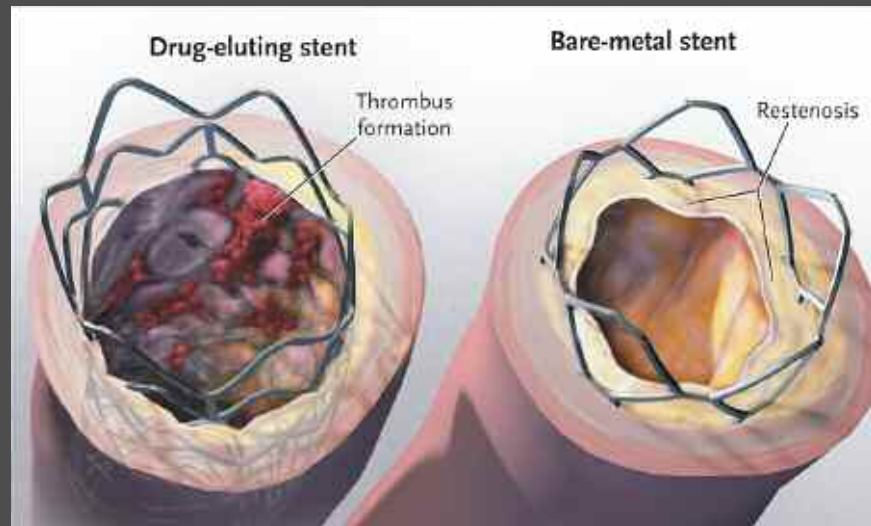
a persisting risk of ST. Fortunately, new data from several registries now suggest that long-term rates of death/MI in off-label procedures are similar for DES and BMS, while repeat revascularization procedures are reduced with DES.⁹⁻¹¹

At Vanderbilt, we have established a very proactive approach to ensuring the benefits of DES.

- A dedicated team of nurse practitioners ensures pre-procedural dual antiplatelet therapy and provides specific orders on discharge stipulating no discontinuation of clopidogrel without approval of the physician who implanted the DES.
- Optimal stent deployment is ensured with a combination of state of the art angiographic imaging and intravascular ultrasound.
- BMS may be used if a true advantage of DES is not evident for an individual patient.
- We recommend a minimum of one year of dual antiplatelet therapy after DES for all patients without contraindications.^{12, 4-5}
- Premature discontinuation of dual antiplatelet therapy emerges in multiple trials as the biggest risk factor for ST. We screen each patient for medical and social ability to comply with long-term therapy, recommending medical therapy, BMS or angioplasty for those who cannot. We also advocate a non-DES strategy whenever possible for patients with impending noncardiac surgery as surgeons generally stop antiplatelet therapy to reduce bleeding complications. We advise surgeons and dentists to delay elective procedures beyond one year after DES if possible and to minimize any interruption of dual antiplatelet therapy for urgent procedures.

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Risks Associated with Drug-Eluting Stents and Bare-Metal Stents



Ingrowth of tissue may cause bare-metal stents to become obstructed, resulting in the need for a second procedure. Drug-eluting stents inhibit this process, but uncovered struts may be prone to thrombosis after the discontinuation of antiplatelet therapy.

Drug Eluting Stents in 2008 Realizing the Promise and Overcoming the Hurdles

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It is imperative that interventional cardiologists focus on optimizing patient outcomes with careful case selection, vigorous education of both patients and referring physicians regarding appropriate antiplatelet therapy, and rigorous application of secondary prevention measures.

- Our unique alliance between Cardiology and Cardiac Surgery facilitates a collaborative approach in which bypass surgery is utilized in situations where this is likely to offer superior outcomes.

DES offer a tremendous reduction in the need for repeat revascularization procedures after PCI. If this can be successfully coupled with a very low risk of ST long term, patient outcomes could be dramatically enhanced.

New research efforts are under way to study the optimal duration of antiplatelet therapy and to examine rigorously the long-term clinical results of DES. In the interim, it is imperative that interventional cardiologists focus on optimizing patient outcomes with careful case selection, vigorous education of both patients and referring physicians regarding appropriate antiplatelet therapy, and rigorous application of secondary prevention measures.

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EMPiRE Clinical Study Tests GORE Neuro Protection System



Jeffery Dattilo, M.D.



Charles Ross, M.D.

*By Jeffery Dattilo, M.D., Assistant Professor of Surgery and Principal Investigator;
Charles Ross, M.D., Assistant Professor of Surgery and Co-Investigator*

Vanderbilt vascular surgeons are participating in the EMPiRE (Embolic Protection with Flow Reversal) clinical study, designed to test the safety and efficacy of the GORE Neuro Protection System for carotid artery stenting (CAS).

The system has been used abroad with great success and is now being studied in selected centers in the United States. Vanderbilt Heart and Vascular Institute is one of 30 sites offering the procedure.

We operated on our first EMPiRE patient in March. The patient had a critical blockage of his carotid artery. About 30 percent of strokes are caused by atherosclerotic carotid artery disease. Correction of carotid blockage represents one of the ways to significantly reduce the risk of first-time and recurrent strokes.

To correct the blockage, we inserted a catheter sheath-balloon system from the patient's femoral artery in the groin into his common carotid artery and external carotid artery. The system was connected, through a filtration system, to the patient's femoral vein. The carotid balloons were then

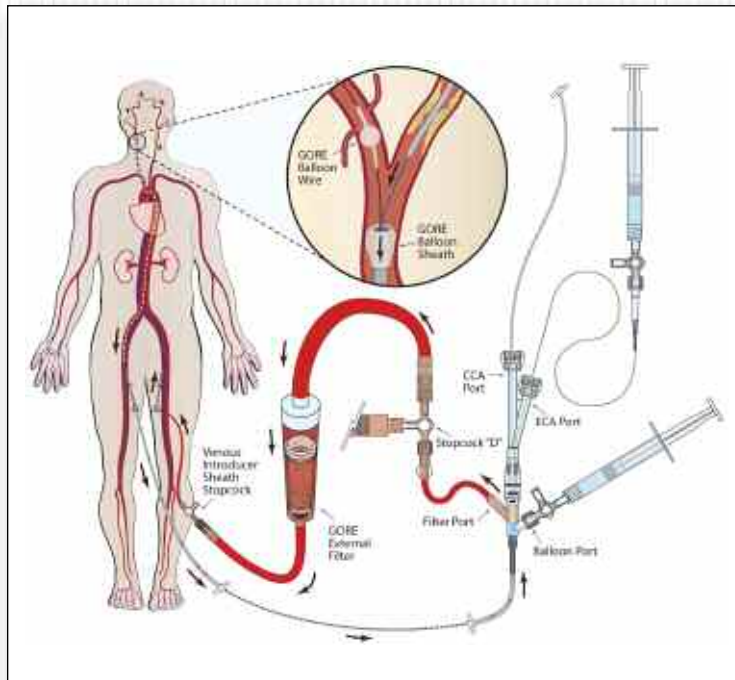
inflated, thus reversing flow from the carotid system to the low pressure venous system – away from the severely diseased internal carotid artery. We treated the blockage with balloon angioplasty and stenting, with blood running to the filtered vein instead of the brain. If any plaque were to break loose, it would flow “downhill” and get trapped in the filter.

This system simply and elegantly takes advantage of the physiology and hemodynamics of most people and is a novel way of protecting the brain from dislodged plaque, or embolization, during carotid artery stenting. It represents another step forward in our quest to improve the safety of carotid artery stenting.

Until this technique became an option for use in CAS, vascular surgeons or other

vascular interventionalists most commonly threaded a minuscule basket above the blockage to function as a filter. Crossing the lesion itself, however, carried the risk of causing some particles to break free before the basket could be opened. Additionally, in some cases, so much plaque could loosen during balloon inflation that it could completely clog a basket.

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EMPiRE Clinical Study Tests GORE Neuro Protection System

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With the new device, blood flow is reversed before the lesion is crossed. This system can also handle large volumes of plaque and debris, thereby reducing the risk of stroke to a minimum.

Carotid endarterectomy, an open procedure in which the surgeon removes the plaque surgically, is the “gold standard” treatment for significant carotid artery blockage. It is the second most common vascular operation performed in the country behind coronary artery bypass.

CAS is an evolving alternative to carotid endarterectomy. Patients who may benefit from CAS include those at high risk for complications due to co-morbid illness and those at anatomic “high risk” for local complications from surgery.

Anatomic Risk

- Lesions located above the level of C2 or below the clavicle
- Restenosis after a prior carotid endarterectomy
- Previous radiation therapy and/or neck dissection
- Spinal immobility of the neck
- Tracheostomy stoma
- Previous laryngectomy
- Contralateral laryngeal nerve palsy/vocal cord paralysis

Co-Morbid Medical High Risk

- Advanced age, greater than 80 years
- Contralateral internal carotid occlusion
- Congestive heart failure (NYHA Class III or IV)
- Left ventricular ejection fraction $\leq 35\%$
- Unstable angina
- Recent MI, within 30 days of need for CAS
- Planned CABG or valve replacement
- Coronary artery disease
- 2 coronary arteries with $> 70\%$ stenosis

For carotid artery stenting to be performed safely, a number of systems have been developed to prevent stroke, and Vanderbilt Heart and Vascular Institute offers all of them, in addition to optimal medical management and standard open carotid surgery.

Vanderbilt Heart Lebanon Clinic



Henry S. Jennings III, M.D.

Because our Lebanon practice is part of the most comprehensive heart program in the area, the patients who come through our doors can expect to receive the same innovative and high quality treatments for heart disease that we offer in Nashville.

From the desk of Henry S. Jennings III, M.D., Medical Director, Network Development

The Vanderbilt Heart and Vascular Institute is taking heart care to the community with its new cardiology clinic in Lebanon.

The clinic is located at 1420 W. Baddour Pkwy., across the street from University Medical Center. David Hansen, M.D., associate professor of Medicine, sees patients on Tuesdays, Wednesdays and Thursdays from 8 a.m. to 4:30 p.m.

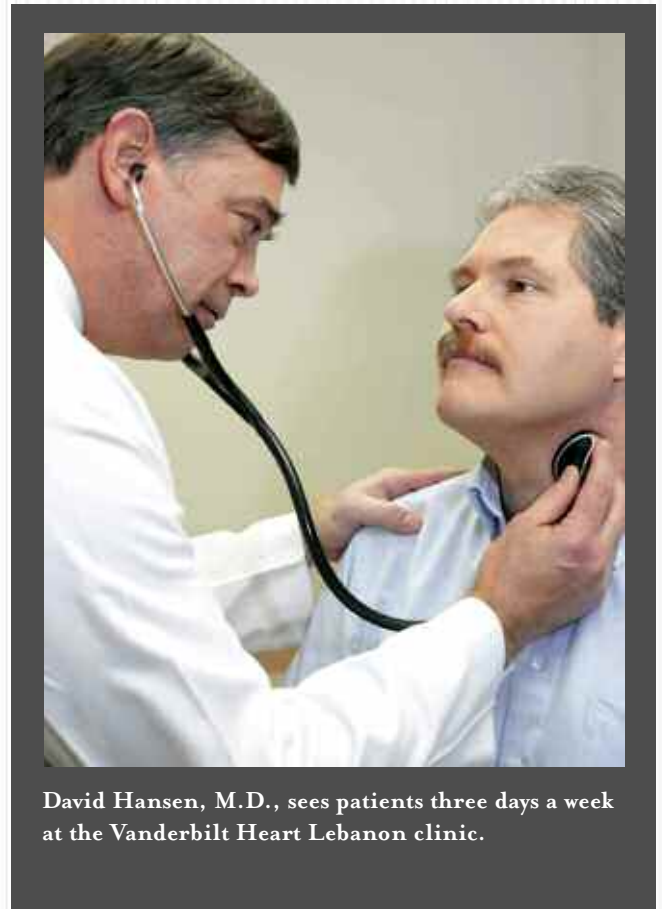
Hansen brings more than 20 years of experience as a Vanderbilt cardiologist to the Lebanon community.

“This practice brings a comprehensive, yet individualized, approach to care to the residents of Lebanon,” Hansen said.

Diagnostic options include stress tests, electrocardiograms, nuclear imaging, radiographic tests and ultrasound. Treatment can include recommendations for lifestyle modifications, medications and various non-surgical and surgical procedures.

“Because our Lebanon practice is part of the most comprehensive heart program in the area, the patients who come through our doors can expect to receive the same innovative and high quality treatments for heart disease that we offer in Nashville,” Hansen said.

The phone number for Vanderbilt Heart Lebanon is (615) 547-7778.



David Hansen, M.D., sees patients three days a week at the Vanderbilt Heart Lebanon clinic.

Vanderbilt Heart Center for Atrial Fibrillation



Dawood Darbar, M.D.

By Dawood Darbar, M.D., Director of the Vanderbilt Arrhythmia Service

Atrial fibrillation, an irregular rhythm of the upper chambers of the heart, affects more than 2 million people in the United States and is a major cause of symptoms like palpitations, shortness of breath, lightheadedness and even stroke.

The Vanderbilt Heart Center for Atrial Fibrillation opened in February and offers a multidisciplinary approach to treating this very common condition.

The center brings together clinicians, researchers and nurses to better understand the causes of arrhythmia, apply state of the art therapies and use genetics to identify and tailor therapies in susceptible individuals.

While drug therapy still remains the principal means of treating atrial fibrillation, non-pharmacologic management of cardiac arrhythmias has evolved dramatically over the past two decades.

The application of radiofrequency catheter ablation techniques has had a dramatic impact on the approach to the treatment of a variety of cardiac arrhythmias, particularly on the management of atrial fibrillation.

Ablation can be performed in conjunction with other heart operations such as valve surgery or bypass surgery, or as a stand-alone procedure. Data suggests that ablation is potentially a curative treatment for atrial fibrillation.

While drug therapy still remains the principal means of treating AF, non-pharmacologic management of cardiac arrhythmias has evolved dramatically over the past two decades.

The availability of new devices and techniques means that ablations can be performed with minimally invasive surgery.

Instead of opening the heart, surgeons can perform ablation through a mini-thoracotomy, which limits length of stay and complications and gets the patient back to a normal life within five days of surgery.

For more information on the Vanderbilt Heart Center for Atrial Fibrillation, please call (615) 322-2318.



Vanderbilt's David Bearden, here working out at Health Plus, found renewed energy after receiving treatment for his irregular heart rhythm.

(photo by Dana Johnson)

Vanderbilt Heart Valve Clinic



John G. Byrne, M.D.

Valve disease consists of often complex conditions, and the proper treatment sometimes can encompass the entire spectrum of medical care, interventional procedures and surgery.

By John Byrne, M.D., Chair of the Department of Cardiac Surgery

The Vanderbilt Heart Valve Clinic, which opened in February, is held on Wednesday afternoons on the fifth floor of Medical Center East.

When patients arrive at the Valve Clinic, they see a cardiologist and a cardiac surgeon to determine if their valve disease should be treated medically, minimally invasively or surgically. They undergo appropriate imaging studies, if needed. Their cases, where appropriate, are then presented at the Vanderbilt Valve Conference, which is held on Thursday mornings, and reviewed by the entire team of cardiologists and surgeons in attendance.

We call the patient and referring physician on Thursday afternoon with the opinion of the group.

Valve disease consists of often complex conditions, and the proper treatment sometimes can encompass the entire spectrum of medical care, interventional procedures and surgery. As patient conditions become more complex, a multidisciplinary approach is needed to arrive at an optimal treatment plan for each patient.

Typically, valve conditions can be managed medically with follow-up for a period of time. Eventually, however, they most likely will require surgical correction.

Most valve surgery is performed on the aortic and mitral valves and involves either valve replacement or valve repair. Damaged valves are removed and replaced with an artificial valve made of either mechanical parts or biological tissues. During valve repair surgeons use the patient's own native valve tissue to reconstruct the valve. Valve repair has been referred to as "plastic surgery of the valve."

We utilize a hybrid OR suite where patients undergo image-guided open heart procedures. An angiogram can be performed immediately after surgery in the same suite. We are one of the select few hospitals in the region to offer percutaneous valvuloplasty to treat mitral stenosis, aortic valve stenosis and pulmonary valve stenosis.

For more information on the Vanderbilt Heart Valve Clinic, please call (615) 343-9195.

Center for Inherited Heart Disease



Rebecca Hung, M.D.

By Rebecca Hung, M.D., Co-Director of the Center and Assistant Professor of Medicine

Dilated cardiomyopathy (DCM) has plagued three generations of Christy Woodard's family, and with Vanderbilt's help, she is hoping to alter the fate of its youngest members.

Woodard, her children and grandchildren are enrolled in Vanderbilt's newly established Center for Inherited Heart Disease, trying to piece together their genetic puzzle in order to change their family picture.

Testing has confirmed that Woodard and her sons have a large deletion in the dystrophin gene, which is often associated with mild cases of Becker muscular dystrophy and the DCM that may accompany it. Woodard's sisters are also suffering from heart failure.

The Woodards obviously have a long family history. Although they knew heart trouble ran in their family, they didn't know what gene caused it. Without knowing what gene, it's hard to predict who is going to be affected.

About 20 percent to 30 percent of young adults with DCM have a relative with the disease although they may not have been diagnosed or have symptoms.

The clinic will offer patients and their families clinical and genetic screening, education about their specific disorder, and counseling about their risks of progressing to symptomatic disease.

In addition, we hope to build a large database to preserve clinical and biological data in hopes of altering the natural history of the disorder for future patients and their offspring.

For more information, please call (615) 322-2318.

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