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### **Upcoming Medical Meetings**

RSNA 2019 Dec. 1-6, 2019; Chicago, IL, USA www.rsna.org/annual-meeting

**AiMed 19** Dec. 11-14, 2019; Dana Point, CA, USA https://aimed.events/north-america-2019/

Sudden Cardiac Death in the Young in Ohio: The Postmortem Investigation Feb. 7, 2020; Akron, OH, USA asuncire@akronchildrens.org

CTO – Chronic Total Occlusion Summit 2020 Feb. 20-21, 2020; New York, NY, USA www.tctmd.com/node/29798

ACC.20 Together with World Congress of Cardiology Mar. 28-30, 2020; Chicago, IL, USA https://accscientificsession.acc.org/ Information-Pages/future-meetings

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# **Critical Congenital Heart Disease in Nevada: The Quest for Universal Prenatal Detection**

By William N. Evans, MD and Ruben J. Acherman, MD

### Introduction

From pregnant mothers receiving routine obstetric care, referrals to perinatologists for those with maternalfetal risk factors or suspected fetal cardiac problems create an opportunity for population-wide, nearuniversal prenatal detection of Critical Congenital Heart Disease.<sup>1</sup> Our quest is to take this opportunity and turn it into reality. This report provides details and data on our approach and success.

### **Program History and Approach**

Ruben Acherman, trained at Toronto Sick Kids and previously on the faculty at the University of Southern California's Children's Hospital Los Angeles, and Los Angeles County Hospital, established our Fetal Cardiology Program in 2002. From the beginning of the program's foundation, we expressly set out to avoid perinatalcare silos.<sup>2</sup> Rather than requesting perinatologists and obstetricians refer patients with suspected fetal heart disease to our center, we asked that referrals be to Maternal-Fetal Medicine specialists. Then, Acherman would travel to the four Southern Nevada perinatal offices and train the community's nine fetal sonographers perform comprehensive to fetal echocardiograms under his supervision at their locations. Onsite, real-time

supervision allowed for sonographerfetal cardiologist interaction and fetal cardiologist-perinatologist face-toface consultation. Further, we elected that perinatologists bill for the fetal echocardiograms, as their technicians performed the studies with their equipment, and Acherman billed for evaluation and management. This system persists; although, currently there are 11 Maternal-Fetal Medicine offices throughout Nevada, in five different perinatal groups with a total of 40 perinatal sonographers, all trained to perform comprehensive fetal echocardiograms, and with each diagnostic study under the supervision of a fetal cardiologist. Now, seven fetal cardiologists provide five days-a-week coverage for scheduled Maternal-Fetal-Medicine office patients, along with same-day consultations as needed. We also provide onsite, real-time Fetal Cardiology on-call services 24-7, 365 days-of the-year to all Nevada's 12 urban hospital maternal units for urgent or emergent fetal cardiac evaluations. Following identification of significant Fetal Congenital Heart Disease, parents receive further congenital cardiovascular surgical or interventional cardiology consultation and counseling at our congenital heart center.

In 2007, we published our program's results for Southern Nevada.<sup>3</sup> Our data demonstrated a 36% prenatal detection rate for those live-born with Critical Congenital Heart Disease from mothers receiving standard obstetric care, consistent with reports



Figure 1. The five-axial fetal-cardiac screening views

from other centers at the time.<sup>4,5</sup> We defined Critical Congenital Heart Disease patients as those that required neonatal cardiovascular surgery, neonatal interventional cardiac catheterization, or prostaglandin before surgery or interventional catheterization. We concluded that 36% was unacceptable and that we needed to improve the program.

Thus, in addition to embedding our fetal cardiologist in the Maternal-Fetal Medicine offices since 2007, we also established a state-wide system of free, ongoing education to teach multiplane, fetal echocardiographic screening to general obstetric sonographers, imaging center sonographers, and ultrasound students. Educational programs include a series of half-day didactic lectures that detail the five-axial view, fetal-echocardiographic screening method described by Simcha Yagel and associates.<sup>6-8</sup> The five-axial view protocol includes: the upper-abdominal view, four-chamber view, left-outflow view, right-outflow view, and the three-vessel-trachea view (Figure 1). The symposia for the general sonographers specifically emphasize normal findings. We show diagrammatic representations of the normal five-axial views, followed by numerous video clips of normal and a few examples of abnormal fetal echocardiograms for each of the five views. We emphasize the importance of referring patients to Maternal-Fetal Medicine specialists with abnormal or questionable findings, not necessarily making a specific diagnosis. We have given identical presentations to the Cardiac Ultrasound School of the College of Southern Nevada. We supplement visual presentations with extensive handouts that reinforce the material. Conferences for specialty perinatal sonographers include advanced topics in Fetal Echocardiography. Additionally, many general and perinatal sonographers have attended our past annual free, all-day pediatric-cardiac conferences that we developed state-wide for healthcare provider education in Congenital Heart Disease. Each annual conference has included some two-three hours of Fetal and Neonatal Cardiology instruction. Free conferences also include

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- The potential for stent fracture should be considered in all patients who undergo TPV placement. Radiographic assessment of the stent with chest radiography or fluoroscopy should be included in the routine postoperative evaluation of patients who receive a TPV.
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  performed in conjunction with clinically appropriate hemodynamic assessment.
  In patients with stent fracture and significant associated RVOT obstruction or
  regurgitation, reintervention should be considered in accordance with usual
  clinical practice.

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free continuing education credits for physicians, nurses, sonographers, and radiology technicians (Figure 2).

We also provide, free-of-charge, a set of cards on lanyards that detail the five-axial fetal-echocardiographic views for the general sonographers to have with them when scanning for ongoing reference for the views and the importance of each (Figure 3). Figure 4 is a blow-up of card number two, which shows the fourchamber view while the reverse side lists the important points associated with the view. Other authors have also emphasized the importance of educational programs as a method for improving prenatal detection of Congenital Heart Disease in general populations.9-11

In 2015, we published a followup study analyzing our Southern Nevada data after several years of community-wide education of general and specialty obstetric and perinatal sonographers.<sup>12</sup> That study demonstrated a highly statistically significant improvement in community detection of Critical Congenital Heart Disease from our 2007 rate of 36% to a rate of 71% for the period 2012 to 2014 (p < 0.001). Beyond education, we also attributed this significant improvement to, among others, evolving ultrasound equipment with enhanced resolution, sonographer practical experience, and the addition of outflow imaging to the guidelines for a standard obstetric ultrasound.<sup>13</sup> A third report, analyzing our statewide experience from 2016 to early 2019, is now in press.

### **Current Data**

For this article, we analyzed our current, state-wide data from January 2019 to July 2019. For this period, we identified a combined 53 patients, prenatally or postnatally detected, with critical Congenital Heart Disease. Of the 53, 47 were diagnosed prenatally. The 47 prenatal diagnoses were made from 1125 pregnant women that were referred by general obstetricians to Maternal-Fetal-Medicine specialists because of either an abnormal obstetric ultrasound or other maternal-fetal risk factors. Of the 47 prenatally diagnosed patients, one resulted in fetal demise, and one led to an elective termination. The one elective termination represented one of 25 (4%) identified by 24 weeks gestation or earlier. In some European countries, elective termination rates exceed 50% for prenatally diagnosed Congenital Heart Disease, not necessarily even Critical Congenital Heart Disease.14-16 Figure 5 is an organizational chart that breaks down the general data on the 51 live-born patients.

All patients with Critical Congenital Heart Disease born during the first seven months of 2019 had regular prenatal care; thus, the prenatal detection rate was 88% (45/51). Of the six live born patients not prenatally diagnosed, five presented with signs and symptoms before



Figure 2. Sonographer symposium in the Children's Heart Center Nevada conference room



Figure 3. Five-axial fetal-cardiac screening views as individual cards for sonographers' reference while scanning (available on request at no charge at wnevans50@aol.com)

newborn nursery discharge and before pulse-oximetry screening. The one remaining non-prenatally diagnosed patient presented late to the Emergency Room cyanotic with supracardiac total anomalous pulmonary venous return, after passing the newborn-nursery, pulseoximetry screening (false-negative result). Table 1 lists the live-born Critical Congenital Heart Diseases by diagnosis and divides the number of total live births, prenatal detection rates, those born at heart centers, those offered comfort care, and the short-term survival. Prenatal detection challenges remain, especially with some aortic arch abnormalities, total anomalous pulmonary venous return, and even simple d-transposition.



Figure 4. Blow up of fetal-cardiac screening card number 2, the 4-chamber view



Legend: DX diagnosis, POxS pulse oximetry screen, TAPVR total anomalous pulmonary venous return

Between January 2019 and July 2019. Nevada's pulse-oximetry screening program resulted in 28 that failed out of approximately 20,500 live births for the period. This number for the seven-months period is consistent with the number of failed tests per annual live births in the state.17,18 We consult on all newborns that fail pulse-oximetry screening. Of the 28 that failed pulse-oximetry screening, all 28 were false positives; thus, no patients were identified by pulseoximetry screening. Others have also shown, as prenatal detection in the population improves, the likelihood of positive pulse-oximetry screens decreasing.<sup>19</sup> Further, since Nevada's pulse-oximetry law went into effect in 2015, there have been approximately 230,000 births with approximately 230 failed pulse-oximetry screens up to the end of 2018, and of these, only two (<1%) were positive, and the 228 (>99%) others were false positives. Also, from 2015 to the end of 2018, eight patients that passed newborn nursery pulse-oximetry screening

(with false-negative results) presented late in extremis or profoundly cyanotic to hospital emergency rooms. To the best of our knowledge, no patient's parents opted out of pulse-oximetry screening for an infant later presenting with missed Critical Congenital Heart Disease. According to the Nevada Department of Health and Human Service data, only about three sets of parents, out of approximately 35,000 annual births, opt-out of testing.17,18 Finally, between January 2019 and July 2019, there were no unexpected, non-hospital deaths from Critical Congenital Heart Disease, as reported by the Clark County Coroner's Office Case Reporting System database for the state of Nevada.

### Discussion

It is a stubborn fact that Critical Congenital Heart Disease may be missed by newborn nursery discharge examinations, as desaturation may be subtle, heart murmurs may be absent, and immediate postnatal circulation

can mask critical lesions. Such realities have led states to mandate routine newborn pulse-oximetry screening.<sup>19,20</sup> Nevada's law went into full effect in 2015.21 Nevertheless, a failed pulse-oximetry screen is not specific for an exact cardiac diagnosis, pulse-oximetry and passed а screen does not rule out all forms of Critical Congenital Heart Disease.22 Alternatively, prenatal detection of Critical Congenital Heart Disease is both sensitive and specific;23,24 thus, prenatal diagnosis, in contrast to pulse-oximetry screening, is the superior evidence-based diagnostic method.

Further, prenatal diagnosis allows prenatal counseling for parental stress reduction, time to better understand the diagnosis's implications,<sup>25</sup> prenatal consultation with a care team, and directed delivery at a facility with a fully equipped and staffed congenital heart unit. Recently, Neha Purkey and associates authored a study from California on the birth location of Table 1. Data breakdown of all 51 live-born patients with critical congenital heart disease

	Total Live Births n	<b>PNC</b> n	<b>PND/PNC</b> n (%)	Heart Center Birth PND n (%)	Comfort Care LB n (%)	Alive n (%)
IAA	4	4	3 (75)	3 (100)	0	4 (100)
Ebstein	1	1	1 (100)	0	0	1 (100)
Truncus	2	2	2 (100)	1 (50)	0	2 (100)
TAPVR	2	2	1 (50)	1 (100)	0	2 (100)
нін	5	5	5 (100)	5 (100)	1 (20)	4 (80)
DTGA	3	3	1 (33)	1 (100)	0	3 (100)
DORV	5	5	5 (100)	5 (100)	0	5 (100)
Univentricle	11	11	11 (100)	11 (100)	0	10 (91)
ToF + PA/VSD	5	5	5 (100)	4 (80)	0	5 (100)
Coarctation of Ao	13	13	10 (77)	10 (100)	0	13 (100)
Total, n (%)	51	51	45 (88)	41 (91)	1 (2)	49 (96)
n/1000 LB	2.2/1000					

Legend: Ao aorta, DTGA d-transposition of the great arteries, DORV double outlet right ventricle, HLH hypoplastic left heart, IAA interrupted aortic arch, LB live-born, PNC prenatal care, PND prenatal detection, TAPVR total anomalous pulmonary venous return, ToF + PA/VSD tetralogy of Fallot and pulmonary atresia-ventricular septal defect

patients with Critical Congenital Heart Disease.<sup>26</sup> They found that only 24% of patients with Critical Congenital Heart Disease were born in a facility with a Level 4-NICU. By definition, a Level 4-NICU is in a facility capable of performing surgery for congenital cardiac malformations that require cardiopulmonary bypass.<sup>27</sup> In contrast, Nevada's high prenatal detection rate allowed directed delivery to the Congenital Heart Center for 91% of the prenatally diagnosed patients. The other 9% constituted four of the prenatallydiagnosed Reno patients whose families elected a Reno birth, followed by a neonatal transfer to the heart center. Directed delivery reduces the need for neonatal transport. Although some past studies have produced equivocal results, recent reports have shown that prenatal diagnosis of Critical Congenital Heart Disease provides advantages over postnatal diagnosis by facilitating neonatal management and reducing morbidity and mortality.<sup>28-30</sup>

### Conclusions

Achieving universal prenatal detection of Critical Congenital Heart Disease in large, general populations does not require performing a comprehensive fetal echocardiogram on every fetus.<sup>31</sup> Using our approach of sonographer education and onsite, real-time fetal cardiologyperinatal care collaboration, we have demonstrated a rising prenatal detection rate over time in Nevada. In 2019, we are now approaching a 90% (which some consider essentially universal)<sup>32</sup> detection rate for Critical Congenital Heart Disease in a geographically diffuse, state-wide, general population. The number of emergent, neonatal transports has been reduced, and a significant majority of mothers are directed to deliver at Nevada's Congenital Heart Center. In contrast, state-mandated, postnatal pulse-oximetry screening has been mostly ineffective. In our opinion, our data supports our approach, as we continue our quest to achieve universal prenatal detection of Critical Congenital Heart Disease in Nevada.

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### Pediatric Cardiologist

The Department of Pediatrics at Southern Illinois University School of Medicine is recruiting an M.D. for a fourth pediatric cardiologist at the Assistant or Associate Professor level. Faculty will join a rapidly expanding cardiology program at our Children's Hospital, an 80 bed CHA affiliated pediatric referral center for Central and Southern Illinois with a referral base of almost 2 million. The current program state-of-the-art includes noninvasive imaging in TTE, TEE, fetal echocardiogram, and advanced MRI imaging. We have developed a highly successful collaborative clinical and research program with a nationally recognized pediatric cardiology center. Opportunities exist to participate in resident and medical student education and receive an advanced degree in medical education. Candidates must be board eligible in Pediatrics and Pediatric Cardiology. Illinois licensure is required prior to official start date. Travel in central Illinois to outreach clinics is required.

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For additional information, please contact: **Ramzi Nicolas, MD** T. 217.545.9706 **rnicolas@siumed.edu**  for comprehensive cardiac evaluation. Ultrasound Obstet Gynecol. 2001;17:367-369.

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## **Interventional Cardiologist**

Saint Louis University, a Catholic, Jesuit institution dedicated to student learning, research, health care, and service is seeking an additional pediatric cardiologist to join an established group within the Division of Cardiology and the Department of Pediatrics at SSM Health Cardinal Glennon Children's Hospital. Applicants must be board certified/eligible in Pediatric Cardiology. General responsibilities will include clinical care, teaching, and research.

We are seeking a second invasive cardiologist at the Assistant or Associate Professor level to assist our current faculty with the growing number of cardiac catheterizations and interventional cases. The complete spectrum of pediatric interventional procedures is currently being performed. An interest in clinical research is encouraged. Academic rank will be commensurate with qualifications and experience.

The cardiology division is housed within the Dorothy and Larry Dallas Heart Center at SSM Health Cardinal Glennon Children's Hospital. The Heart Center opened in 2009 and underwent significant expansion in 2016. An active congenital heart surgery program exists, and the hospital houses state-of-the-art operating rooms, neonatal intensive care unit, pediatric intensive care unit, electrophysiology lab, and a hybrid cardiac catheterization lab/operating suite. SSM Cardinal Glennon Children's Hospital is a free-standing children's hospital, and is staffed by faculty members of Saint Louis University School of Medicine.

Interested candidates must submit a cover letter, application, and current CV to http://jobs.slu.edu.

Other correspondence regarding this position can be sent to: **Kenneth O. Schowengerdt**, **MD** 

Wieck-Sullivan Professor and Director of Pediatric Cardiology Saint Louis University School of Medicine 1465 South Grand Blvd, St. Louis, MO 63104 T. 314.577.5633 F. 314.268.4035 kenneth.schowengerdt@health.slu.edu

Saint Louis University is an Affirmative Action, Equal Opportunity Employer, and encourages nominations of and applications from women and minorities.

# **Medical News, Products & Information**

Compiled and Reviewed by Kate Baldwin and Tony Carlson

### Scientists Discover New Type of Immune Cells that are Essential for Forming Heart Valves

### UCLA Study Sheds New Light on Critical Role of Heart-Derived Macrophages

Newswise — UCLA researchers have identified for the first time the origin of an immune cell that plays a critical role in the formation of healthy heart valves. The findings could pave the way for new treatments for heart valve disorders, which can be caused by congenital defects, aging or disease.

Their study, led by Dr. Atsushi "Austin" Nakano, a UCLA Associate Professor of Molecular, Cell and Developmental Biology and member of the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA, was published in the journal Developmental Cell.

Building on previous research by Nakano, which showed that the embryonic heart tube produces blood progenitor cells, the new study found that those cells, in turn, generate specialized immune cells called macrophages. The research also revealed that these heart-derived macrophages are particularly adept at consuming excess tissue, a skill that makes them indispensable to the formation and maintenance of heart valves.

The human heart has four valves tissue-paper thin membranes that constantly open and close to control blood flow through the heart. When the valves do not function properly, blood flow to the body is disrupted, which strains the heart and can lead to heart failure, stroke or sudden death. "When valves are seriously damaged, they cannot be fixed; replacement surgery is the only option," Nakano said. "Identifying cells that contribute to valve health could reveal targets for new, less-invasive therapies."

Currently, doctors have two options for replacement valves: mechanical valves, which require lifelong use of blood-thinning medications; and biological valves, which are made from cow, pig or human heart tissue, and which usually need to be replaced every 10 to 15 years.

Because replacement valves often require replacements of their own — notably among children because they tend to outgrow their valve replacements multiple times before they reach adulthood — and because of the risks associated with any surgery that alters the heart, Nakano said new methods for treating valve disorders are urgently needed.

In a 2013 study using mice, Nakano and colleagues in his lab discovered that the

heart tube — the form the embryonic heart takes before it begins pumping blood — contributes to the production of the body's early blood cells, which are called blood progenitor cells. Just like stem cells can form any type of cell in the body, blood progenitor cells can create several different types of blood and immune cells. But unlike stem cells, blood progenitor cells are not capable of self-renewing throughout an organism's entire lifespan.

"Ever since we discovered that the heart tube produces some blood progenitor cells, we have been trying to figure out why," Nakano said. "Blood progenitor cells are generated in much greater numbers in other parts of the developing embryo. Having the heart tube produce blood progenitor cells is like having a small, not-very-productive factory just down the street from a larger, more productive factory. If both factories produce the same thing — in this case blood progenitor cells — why not just have one big factory?"



Microscopic images of a normal heart valve in a mouse, left, and a heart valve grown in a lab with heart-derived macrophages blocked, right. Without those macrophages, the valves are thick and deformed. Photo credit: Developmental Cell/UCLA Broad Stem Cell Research Center



# **Clinical Associate Professor or Clinical Professor**

The University of Washington, Department of Pediatrics, Division of Cardiology is accepting applications for a full time Clinical Associate Professor or Clinical Professor.

Responsibilities include directing our Acute Care Cardiology Program at Seattle Children's Hospital. The Acute Care Cardiology Program includes medical and surgical cardiac patients admitted to our acute care cardiology service, as well as consultative services to the cardiac, neonatal, and pediatric intensive care units. The role will also involve individual general cardiology night and weekend call and outpatient clinic.

The successful candidate will have earned an MD/DO (or foreign equivalent) and be board certified/board eligible in Pediatric Cardiology.

In order to be eligible for University sponsorship for an H-1B visa, graduates of foreign (non-U.S.) medical schools must show successful completion of all three steps of the U.S. Medical Licensing Exam (USMLE), or equivalent as determined by the Secretary of Health and Human Services.

The successful candidate will be an experienced cardiologist with strong clinical skills who also has the leadership skills and the vision to direct our acute care cardiology program at Seattle Children's Hospital.

University of Washington faculty engage in teaching, research, and service.

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# Associate Professor (WOT) or Full Professor (WOT)

The University of Washington, Department of Pediatrics, Division of Cardiology is accepting applications for a full time Associate Professor (WOT) or Full Professor (WOT).

Responsibilities include directing our Acute Care Cardiology Program at Seattle Children's Hospital. The Acute Care Cardiology Program includes medical and surgical cardiac patients admitted to our acute care cardiology service, as well as consultative services to the cardiac, neonatal, and pediatric intensive care units. The role will also involve individual general cardiology night and weekend call and outpatient clinic.

The successful candidate will have earned an MD/DO (or foreign equivalent) and be board certified/board eligible in Pediatric Cardiology.

In order to be eligible for University sponsorship for an H-1B visa, graduates of foreign (non-U.S.) medical schools must show successful completion of all three steps of the U.S. Medical Licensing Exam (USMLE), or equivalent as determined by the Secretary of Health and Human Services.

The successful candidate will be an experienced cardiologist with strong clinical skills who also has the leadership skills and the vision to direct our acute care cardiology program at Seattle Children's Hospital.

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THE OHIO STATE UNIVERSITY COLLEGE OF MEDICINE

### **General Pediatric Cardiologist**

The Heart Center at Nationwide Children's Hospital in conjunction with The Ohio State University Department of Pediatrics in Columbus, Ohio seeks an academic general pediatric cardiologist to join our team. Clinical responsibilities include general outpatient cardiology, participation on our in-patient cardiology consultation service, and general cardiology night call. Other clinical interests may be explored.

The Heart Center is a dedicated hospital service-line that carries the mission of providing state-of-the-art, costeffective care to our patients with congenital and acquired heart disease regardless of age. The Heart Center has >18,000 out-patient encounters per year including multiple specialty clinics (e.g. Fontan, muscular dystrophy, preventive care, cardiogenetic). The in-patient medical discharges are 1300/yr including ~400 annual surgeries. The Heart Center has 37 cardiologists and four cardiothoracic surgeons, a dedicated 20-bed CTICU and 24-bed cardiac stepdown unit, and a dedicated administration team. Excellent services in cardiac intensive and stepdown care, catheterization and intervention, non-invasive imaging, electrophysiology, heart failure and heart/heart-lung/lung transplantation are on-site. The Heart Center has a robust adult congenital heart service. The LAUNCH program is a clinical service focused on the care of patients with single ventricle. The population served includes the regional population, a large number of referred cases for advanced intervention and surgery, an extensive state-wide outpatient network (pediatric and adult congenital) and patients managed with regional partners including the newly formed Congenital Heart Collaborative. Our program is integrated with the Center for Cardiovascular Research. Nationwide Children's Hospital is a 464 bed stand-alone children's hospital and is the pediatric teaching facility for The Ohio State University School of Medicine. Columbus is the state capital and the 14th most populous city in the US (metropolitan population just over 2 million). It is a diverse community with excellent schools, a thriving economy, and a vibrant arts/food scene.

Candidates are encouraged to submit their curriculum vitae by email to:

Robert Gajarski, MD Cardiology Section Chief RobertGajarski@nationwidechildrens.org

Catherine Krawczeski, MD Cardiology Division Chief Catherine.Krawczeski@nationwidechildrens.org

The Ohio State University is an Equal Opportunity, Affirmative Action Employer. Women, minorities, veterans, and individuals with disabilities are encouraged to apply. Answering that question was not a simple task, in part because the heart tube changes shape and begins beating within just days of its development. And with each heartbeat, blood and immune cells from all over the developing embryo flow into the heart and back out again, making it difficult to determine the origin of blood cells in the heart.

In the new study, which also used mice, the team eliminated the other blood and immune cells from the equation by removing a heart tube before it began pumping blood and continuing its growth in a lab dish. With no circulating blood to contaminate their sample, the team observed that the heartderived blood progenitor cells were producing macrophages.

Macrophages ("big eaters" in Greek) reside in tissues and travel around the body in the blood, seeking out and consuming harmful, damaged or unnecessary cells. Previous research had shown that macrophages exist in the heart valves, but Nakano's team was the first to discover their role there: eating up excess cells to make the valves paper-thin and hyper-efficient. This process begins in the developing embryo and continues after birth; the macrophages remain in the valves to help keep them in shape throughout the life cycle. "Macrophages were known to exist in heart valves, but nobody had nailed down when they arrived there and where they came from until we watched them develop in the heart tube," Nakano said.

To test just how essential heart-derived macrophages are to valve formation and remodeling, the scientists blocked their production to see if it had any effect. They found that the other macrophages in the body — those from circulating blood — traveled to the heart, but they weren't very effective at remodeling the valves. Without the heart-derived macrophages, the heart valves remained thick and unwieldy.

"This showed us that the macrophages that are generated in the heart tube are particularly adept at eating up excess tissue," Nakano said. "This makes them essential not just to heart valve formation, but to heart valve maintenance throughout life."

Nakano said he hopes that the discovery will pave the way to more permanently solve heart valve conditions, perhaps by boosting or inhibiting heart-derived macrophages' activity in order to regulate heart valve formation. And, because those macrophages remain in the body throughout people's lives, it could one day be possible to target them to treat valve problems that develop later in life, he said.

The next step for Nakano's lab will be to determine if the findings can be replicated in humans.

The research was supported by the National Institutes of Health. Nakano is on the advisory board of the Japan-based

startup company Myoridge, which is developing technology to produce cardiac cells from induced pluripotent stem cells.

View the original study: www.cell.com/developmental-cell/fulltext/S1534-5807(19)30049-8

# Better Options Needed for Children at Higher Risk of Premature Heart Disease

American Heart Association Scientific Statement

Obesity and severe obesity in childhood and adolescence have been added to the list of conditions that put children and teens at increased risk for premature heart disease, according to a new scientific statement from the American Heart Association published in the association's journal Circulation.

The statement provides an overview of current scientific knowledge about managing and treating the increased risk of atherosclerosis and early heart disease, in children and teens with Type 1 or 2 Diabetes, familial high cholesterol, Congenital Heart Disease, childhood cancer survivorship and other conditions. Atherosclerosis is the slow narrowing of the arteries that underlies most heart diseases and stroke.

"Parents need to know that some medical conditions raise the chances of premature heart disease, but we are learning more every day about how lifestyle changes and medical therapies that can lower their cardiovascular risk and help these children live their healthiest lives," said Sarah de Ferranti, MD, MPH, Chair of the writing group for the statement and Chief of the Division of Cardiology Outpatient Services at the Boston Children's Hospital in Massachusetts.

For example, there are treatments for familial high cholesterol - a group of genetic disorders that affect how people process cholesterol which can lead to extremely high cholesterol levels, and that can help children and teens with this disorder live a normal lifespan.

The statement is an update of a 2006 scientific statement and adds obesity and severe obesity to the list of conditions that put children and teens at increased risk of cardiovascular diseases and reviews new treatments for previously discussed conditions.

Severe obesity and obesity are now considered moderate risk and at-risk conditions, respectively, because research shows they significantly increase chances of developing heart disease later in life. A study of almost 2.3 million individuals followed for over 40 years found the risks of



COLLEGE OF MEDICINE

### **Pediatric Electrophysiologist**

The Heart Center at Nationwide Children's Hospital in conjunction with The Ohio State University Department of Pediatrics in Columbus, Ohio seeks a board-certified/eligible, academic physician at any professorial level with advanced training in electrophysiology to join our team of two fulltime electrophysiologists, two advance practice nurses and two EP nurses. Additionally, the successful candidate will participate in a limited amount of general pediatric cardiology that includes night call and in-patient consult service.

The Heart Center is a dedicated hospital service-line that carries the mission of providing state-of-the-art, cost-effective care to our patients with congenital and acquired heart disease regardless of age. The Heart Center has >18,000 out-patient encounters per year including multiple specialty clinics (e.g. Fontan, muscular dystrophy, preventive care, cardiogenetic). The in-patient medical discharges average 1300/yr including ~400 annual surgeries. The Heart Center has 37 cardiologists and four cardiothoracic surgeons, a dedicated 20-bed CTICU and 24-bed cardiac stepdown unit, and a dedicated administration team. Excellent services in cardiac intensive and stepdown care, catheterization and intervention, non-invasive imaging, electrophysiology, heart failure and heart/heart-lung/lung transplantation are on-site. The Heart Center has a robust adult congenital heart service. The population served includes the regional population, a large number of referred cases for advanced intervention and surgery, an extensive state-wide outpatient network (pediatric and adult congenital) and patients managed with regional partners including the newly formed Congenital Heart Collaborative.

Our program is integrated with the Center for Cardiovascular Research as well as the Center for Genomic Research. Nationwide Children's Hospital is a 464 bed stand-alone children's hospital and is the pediatric teaching facility for The Ohio State University School of Medicine. Columbus is the state capital and the 14th most populous city in the US (metropolitan population just over 2 million). It is a diverse community with excellent schools, a thriving economy and a vibrant arts/food scene.

Candidates are encouraged to submit their curriculum vitae by email to:

Naomi Kertesz, MD Director of Electrophysiology and Pacing Naomi.Kertesz@nationwidechildrens.org

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### Pediatric Cardiology Medical Director Imaging

Driscoll Children's Hospital is advancing a comprehensive Heart Center to meet the healthcare needs of congenital heart patients in South Texas. The Center is recruiting a Medical Director of Imaging to guide the expansion of the imaging lab and provide oversight of all cardiac imaging. Current modalities include cardiac MRI, CT, and fetal imaging.

The ideal candidate will be board certified in Pediatric Cardiology and have 5-7 years of clinical experience with Imaging as the focused area of interest. Must have a proven history in a leadership role with vision and strategic planning.

The position offers a sign-on bonus, competitive compensation package, excellent benefits, generous paid time off, holiday pay, CME and retirement plans.

Driscoll Children's Hospital is a freestanding children's hospital in Corpus Christi, Texas. The Heart Center has committed substantial space for the creation of an imaging lab that can centralize studies, including telemedicine communication for outpatient studies around the region. In addition, the Driscoll Heart Center includes one electrophysiologist, two interventional cardiologists, numerous outpatient cardiologists and a team of board-certified congenital heart surgeons. Driscoll is a regional referral center for South Texas with supporting practices in Laredo, McAllen, and Brownsville.

Corpus Christi, Texas is a wonderful place to work, live and play! This is a dynamic coastal city with miles of beautiful beaches, world-class sailing and windsurfing. The mild climate allows for year-round outdoor family activities such as golf, cycling, and tennis. The cost of living is low, and there is no state income tax.

For more information, please contact: Lori Smith Director of Physician Relation and Recruitment D. 361.694.5906 M. 361.331.1311 lori.smith@dchstx.org dying from a cardiovascular disease were two to three times higher if their body weight as adolescents had been in the overweight or obese category compared to youth with normal weight. Effective treatments for obesity have proven elusive, but in general, a gradual approach to weight loss is generally required, incorporating: improvements in dietary quality, fewer calories, more physical activity, meal replacements, medical therapy and/or bariatric surgery, depending on the severity of the excess adiposity.

Other significant changes to the statement since 2006 include:

- The elevation of Type 2 diabetes to a high-risk condition because of its association with additional cardiovascular risk factors such as high blood pressure and obesity.
- The expansion of the risks of premature heart disease associated with treatments for childhood cancers.

# A Pioneering Transplant Turns a Baby's Heart Around (Literally)

Heart Surgeon Cynthia Herrington, MD, performs the Heart Institute's first dextrocardia heart transplant

Children's Hospital Los Angeles (CHLA) recently performed its first Dextrocardia Heart Transplant. The child, known as Baby Ruben, was born with dextrocardia and Complex Heterotaxy Syndrome—including a single ventricle and discontinuous pulmonary arteries, along with other defects. The child received a heart transplant at CHLA at two years of age.

An animated graphic illustrates the "before and after" of the surgery. The graphic first shows the original, preoperative heart, which was sitting backwards in his chest, pointing toward the right side of the chest instead of the left. The second image shows the same heart after CHLA Cardiothoracic Surgeons completed a Glenn procedure (the second of three HLHS palliative surgeries). The final images show the new, transplanted heart—with the misplaced blood vessels rearranged to accommodate the normal donor heart.

"I tell my trainees all the time, 'You don't get to complain about complex anatomy," says Dr. Cynthia Herrington, Surgical Director of the Heart Transplant Program at CHLA. "Because that's what we do. This is what we thrive on here."

"It was all doable," says Dr. Herrington, who had performed one other dextrocardia transplant earlier in her career. "We just took the steps and walked through."



Photo credit: Children's Hospital Los Angeles



Photo credit: Children's Hospital Los Angeles



Photo credit: Children's Hospital Los Angeles



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Photo credit: Children's Hospital Los Angeles



Baby Ruben today with his new heart. The transplant took place in August 2018. Photo credit: Children's Hospital Los Angeles

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Dr. Sarah Badran, one of Ruben's CHLA cardiologists, watched much of the surgery and describes it differently. "It was a massive reconstruction to fit a normal-shaped heart in a backwards space," she says. "The way she brought the liver and inferior vena cava veins over, the amount of extensions she had to use to make things connect and not be twisted—it was amazing. I don't know of a lot of surgeons who could have done that."

www.youtube.com/watch?v=mFLssyoaEzE&feature=youtu.be

### 'Broken Heart' Syndrome May Originate in the Brain

### European Society of Cardiology

Scientists have shown for the first time that the brain is involved in the development of a heart condition called Takotsubo Syndrome (TTS). They found that regions of the brain responsible for processing emotions and controlling the unconscious workings of the body, such as heart beat, breathing and digestion, do not communicate with each other as well in TTS patients as in healthy people.

The study is published in the European Heart Journal<sup>1</sup> and the researchers say that although, at this stage, they cannot show that the reduced brain functions definitely cause TTS, their findings suggest that these alterations in the central nervous system may be part of the mechanism involved and they are linked with the onset of TTS in response to stressful or emotional triggers.

TTS is known as "Broken Heart" Syndrome and is characterized by a sudden temporary weakening of the heart muscles that causes the left ventricle of the heart to balloon out at the bottom while the neck remains narrow, creating a shape resembling a Japanese octopus trap, from which it gets its name. Since this relatively rare condition was first described in 1990, evidence has suggested that it is typically triggered by episodes of severe emotional distress, such as grief, anger or fear, or reactions to happy or joyful events. Patients develop chest pains and breathlessness, and it can lead to heart attacks and death. TTS is more common in women with only 10% of cases occurring in men<sup>2</sup>.



This is a Takotsubo Heart, showing the typical shape resembling a Japanese octopus trap.

In an unusual example of collaboration between neuroscientists and cardiologists, researchers carried out MRI brain scans in 15 TTS patients taken from the InterTAK Registry, established at the University Hospital Zurich, Switzerland, in 2011<sup>3</sup>. They compared the scans with those from 39 healthy people. The scans were performed between July 2013 and July 2014 and the average time between TTS diagnosis and the MRI scans was about a year.

Professor Christian Templin, Principle Investigator at the Registry and Professor of Cardiology at University Hospital Zurich, said: "We were interested in four specific brain regions that are spatially separate from one another but functionally connected, meaning they share information. We found that TTS patients had decreased communication between brain regions associated with emotional processing and the autonomic nervous system, which controls the unconscious workings of the body, compared to the healthy people."

"For the first time, we have identified a correlation between alterations to the functional activity of specific brain regions and TTS, which strongly supports the idea that the brain is involved in the underlying mechanism of TTS. Emotional and



physical stress are strongly associated with TTS, and it has been hypothesized that the overstimulation of the autonomic nervous system may lead to TTS events."

The regions of the brain that the researchers looked at included the amygdala, hippocampus and cingulate gyrus, which control emotions, motivation, learning and memory. The amygdala and cingulate gyrus are also involved in the control of the autonomic nervous system and regulating heart function. In addition, the cingulate gyrus is involved in depression and other mood disorders that are common among TTS patients.

"Importantly, the regions we've identified as communicating less with one another in TTS patients are the same brain regions that are thought to control our response to stress. Therefore, this decrease in communication could negatively affect the way patients respond to stress and make them more susceptible to developing TTS," said Professor Templin.

A limitation of the study is that the researchers did not have MRI scans of patients' brains before or at the time they developed TTS, so cannot say for certain that the decreased communication between brain regions caused the TTS or vice versa.

Co-author, Jelena Ghadri, MD, a senior research associate at the University Hospital Zurich and co-principle investigator of the InterTAK Registry, said: "Our results suggest that additional studies should be conducted to determine whether this is a causal relationship. We hope this study offers new starting points for studying TTS in terms of understanding that it is much more than 'Broken Heart' Syndrome and clearly involves interactions between the brain and the heart, which are still not fully understood. We are at the beginning of learning more about this complex disorder. Hopefully, one day new findings can be translated into developments in preventive, therapeutic and diagnostic strategies to improve patient care."

"Of note, this study presents the results of a collaboration between neuroscientists and cardiologists. One problem in TTS research is that usually cardiologists only focus on the heart; we believe that approaching TTS in a multidisciplinary way might help to uncover the real nature and causes of this disease. The methods we used are mainly neuroscientific in nature, but the findings we uncovered are, in our view, of major importance for cardiologists in understanding TTS."

### References

- "Fast track brief communication: altered limbic and autonomic processing supports brain-heart axis in Takotsubo syndrome", by Christian Templin et al. European Heart Journal. doi:10.1093/eurheartj/ehz068
- 2. TTS affects less than 3% of people who suffer a heart attack and tends to occur between the ages of 60-75.

### **Congenital Cardiologist** with Focus on Adult Congenital Cardiology

Congenital Heart has been the premier Congenital Cardiology Practice in the state of Maine for over 50 years. We are excited to announce that Congenital Heart has partnered with Maine Medical Partners and MaineHealth to continue providing state-of-the-art care for children and adults with congenital heart disease. This partnership will form the new Division of Pediatric Cardiology and Congenital Heart Care at Maine Medical Center. Commensurate with this partnership is the opportunity to formalize an Adult with Congenital Heart Disease (ACHD) program to serve the burgeoning population of ACHD in Maine.

The candidate would be BE/BC in Pediatric Cardiology and BE/BC in ACHD with appropriate academic appointments. Responsibilities would include developing and directing an ACHD service that would provide both inpatient consultative services and outpatient care through multidisciplinary clinics with the expectation of having the program accredited. There would be close collaboration with the Adult Cardiology Service as well as with comprehensive subspecialty services both in Pediatrics and Adult Medicine at Maine Medical Center. This program has been deemed a priority by the institution with proforma data to support additional hires for the service as needed.

A research interest is encouraged with opportunities for collaboration with established research institutes like the Maine Medical Cardiovascular Research Institute (MMCRI). Call responsibilities would be 1:5 nights and include being a congenital consultant in the post-operative PICU, caring for service patients on the ward, and fielding calls from outpatients in our practice and from ER's throughout the state.

The candidate will join 6 other Pediatric Cardiologists, who have established the only comprehensive Congenital Heart program in the state of Maine. The program has recently hired an experienced surgeon to serve as the Director of Congenital Cardiac Surgery. After providing comprehensive congenital surgical care in the state for the past 25 years, the new Director has ensured that the infrastructure is in place to continue providing excellent surgical care. Comprehensive interventional services have been provided for over 20 years with all FDA-approved devices and procedures, including transcatheter pulmonary valve insertion being performed. The program also performs state-of-the-art imaging including fetal, TTE, TEE, CMRI and CTA.

Maine Medical Center (MMC) has 637 licensed beds and is the state's leading tertiary care hospital and Level One Trauma Center, with a full complement of Residencies and Fellowships and an integral part of Tufts University Medical School.

Situated on the Maine coast, Portland offers the best of urban sophistication combined with seaside charm. The Old Port area receives tourists from around the world with nationally recognized restaurants, breweries, and hotels. In fact, Portland was recently named "2018 Restaurant City of the Year" by Bon Appétit Magazine. The area has an active outdoor community providing four-season recreational opportunities such as skiing, hiking, sailing, and miles of beautiful beaches. Just two hours north of Boston, this is an exceptionally diverse and vibrant community.

For more information, please contact: Gina Mallozzi Physician Recruiter 207.661.2092 or gmallozzi@mainehealth.org



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3. The InterTAK Registry is a worldwide network, including more than 40 different cardiology centres in more than 18 countries. The University Hospital Zurich has become a centre of excellence, specialising in the care of TTS patients, while also carrying out translational and basic science research.



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### New Clinical Trial Shows Medtronic TYPX<sup>™</sup> Envelope Significantly Reduces Major Infections in Cardiac Implantable Device Patients

Late-Breaking Trial Results Presented at ACC Scientific Sessions and Published in The New England Journal of Medicine

WRAP-IT is the Largest Randomized Global Trial Ever Conducted with Cardiac Implanted Electronic Devices

Medtronic announced results from the landmark Worldwide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT), which demonstrated the TYRX<sup>™</sup> Absorbable Antibacterial Envelope (TYRX envelope) reduced the risk of major infection by 40%, and pocket infection by 61%, in patients with cardiac implantable electronic devices (CIEDs), compared to standard-of-care pre-operative antibiotics. The trial results were presented in a late-breaking session at the *American College of Cardiology's 68<sup>th</sup> Annual Scientific Sessions (ACC.19)*, and published simultaneously in *The New England Journal of Medicine*.

"CIED infections are associated with significant morbidity, mortality and cost. Until now, in addition to adhering to strict surgical techniques, only one intervention, pre-operative antibiotics, has been shown to significantly reduce infections," said Khaldoun Tarakji, MD, MPH, Associate Section Head of Cardiac Electrophysiology at Cleveland Clinic, principal investigator of the trial, and a paid consultant to Medtronic.

"This study shows that, in addition to pre-operative antibiotics, the use of the antibacterial envelope significantly reduced the risk of CIED infections, and with no increased risk of complications."

The trial met its primary endpoint showing effectiveness of the TYRX envelope in reducing major infections by 40% in patients at increased risk for infections resulting from CIED implantation: at 12 months, 1.2% of patients in the control group experienced a major infection, while only 0.7% of patients who received the TYRX envelope had a major infection (p=0.04). The trial also showed a 61% reduction in pocket infections with the envelope (p<0.01).



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## **Pediatric Cardiologist**

The Heart Institute (HI) at Cincinnati Children's Hospital Medical Center (CCHMC) seeks applications for a BE/BC Pediatric Cardiologist with additional sub-specialty training in Congenital Catheterization. Applicants should ideally be at the Associate Professor level (or above).

The HI is an internationally recognized academic center of excellence for Pediatric (congenital and acquired) and Adult Congenital Cardiac Care, and clinical and basic science research. The HI incorporates the Divisions of Congenital Heart Disease, Cardiothoracic Surgery and Molecular Cardiovascular Biology. It offers the full range of Pediatric Cardiac services within a free-standing not-for-profit tertiary care medical center. The HI also serves to train categorical Pediatric Cardiology and sub-specialty fellows in all areas of congenital heart disease practice (including fourth year Interventional Catheterization). Academic appointment within the Children's Hospital is through the Department of Pediatrics at the University of Cincinnati College of Medicine.

The Cardiac Catheterization Service performs more than 1000 procedures on an annual basis, with the majority involving therapeutic interventions. The facility includes three hybrid-ready catheterization procedure rooms staffed with dedicated nursing and radiology technology staff, and three catheterization Advanced Nurse Practitioners. All procedures are supported by Cardiac Anesthesia and Cardiac Intensive Care Services (as required).

The applicant would be expected to assume responsibility for clinical services including (but not limited to):

- Interventional and hybrid cardiac catheterizations within the existing Catheterization program
- Development of novel or advanced interventional procedures / techniques / niche interventions
- Provide on-call catheterization coverage on a rotating basis
- Perform a single out-patient clinic on a weekly basis
- Provide limited periods of in-patient and / or consult service coverage
- Participate in all Institute clinical and management conferences
- Perform teaching and instruction commensurate with the training mission of the Institute / Institution
- Participate and contribute to relevant Quality Assurance/ Process Improvement programs within the scope of practice
- Contribute to all on-going active research within the Cardiac Catheterization Service

The Heart Institute and Cardiac Catheterization Service pride themselves on excellent clinical outcomes, whilst maintaining a strict academic focus, research productivity and exemplary professionalism. The acceptable candidate would be expected to maintain similar high standards of clinical service.

Interested candidates should address all inquiries to: Andrew Redington, MD Co-Director, The Heart Institute Cincinnati Children's Hospital Medical Center andrew.redington@cchmc.org The TYRX envelope was successfully implanted in 99.7% of procedure attempts, with no significant difference in procedure time between the two groups. The trial also met its safety objective: the envelope did not increase the risk of procedure-related or system-related complications through 12 months (p<0.001 for non-inferiority).

"These data provide strong evidence that the TYRX envelope can help prevent major infection without increasing complications," said Rob Kowal, MD, PhD, Vice President and Chief Medical Officer of the Cardiac Rhythm and Heart Failure division, which is part of the Cardiac and Vascular Group at Medtronic. "This is the largest CIED trial ever conducted globally, demonstrating Medtronic's commitment to generating high-quality evidence supporting the use of our products and therapies to improve patient outcomes."

WRAP-IT is a randomized, prospective, multicenter, singleblinded, global, post-market, interventional clinical trial. It compared the incidence of major infections in patients whose CIED implantation included the TYRX envelope and patients whose procedure did not, with follow-up to 12 months. The study was conducted in 181 centers in 25 countries in North America, Europe, Asia and South America, and included 776 implanters. A total of 6,983 patients participated in the trial with 3,495 randomized to receive the TYRX envelope and 3,488 randomized to the control group (without the envelope).

Millions of people with heart conditions receive a CIED, such as a pacemaker or implantable cardioverter defibrillator (ICD), to help manage abnormal heart rhythms. As with any surgical procedure, there is risk for infection due to bacteria being introduced at the time of implant. These infections occur in 1-4% of all patients with CIED implants,<sup>1,2</sup> leading to an increased risk of death and an average cost per infection of \$44,000-\$83,000.<sup>3-7</sup>

The TYRX Absorbable Antibacterial Envelope is a mesh envelope that holds an implantable cardiac device or implantable neurostimulator. It is designed to stabilize the device after implantation while releasing antimicrobial agents, minocycline and rifampin, over a minimum of seven days.<sup>8</sup> The envelope is fully absorbed by the body approximately nine weeks after implantation.<sup>8,9</sup> The TYRX Envelope was cleared by the FDA in 2013 and received CE Mark in 2014.





# **Pediatric Cardiology Faculty**

The Department of Pediatrics of Wake Forest School of Medicine is recruiting a full time non-invasive Pediatric Cardiologist with sub-specialty training in congenital MRI to join the team within the division of Pediatric Cardiology. Primary clinical responsibilities will occur at Wake Forest Baptist Health- Brenner Children's Hospital in Winston-Salem, NC.

Primary responsibilities include directing & interpreting congenital MRIs, performing & interpreting Transesophageal Echocardiograms, staffing the ECHO lab, and performing Pediatric Fetal Cardiology clinics. Additionally, there will be some degree of inpatient and outpatient duties. The applicant must be board certified or board eligible in Pediatric Cardiology. All academic ranks will be considered.

The position entails an academic appointment in the Department of Pediatrics, Section on Cardiology with potential for time at Wake Forest School of Medicine in Winston-Salem, NC for research and teaching.

Wake Forest School of Medicine is the medical education and research component of Wake Forest Baptist Medical Center, a fully integrated academic medical center anchored by an 885-bed tertiary care hospital, community hospitals, affiliated partners and the 160-bed Brenner Children's Hospital. Both Wake Forest Baptist Medical Center and Brenner Children's Hospital have been nationally ranked by U.S. News & World Report.

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Wake Forest School of Medicine and Wake Forest Baptist Medical Center are an Affirmative Action and Equal Opportunity Employer with a strong commitment to achieving diversity among its faculty and staff.

Interested candidates who meet the qualifications are invited to apply online at: http://www.wakehealth.edu/HR/Faculty/Current-Opportunities.htm (key in Job ID 37113).

For questions, please contact: Lindsay Teague Talent Acquisition 336.716.8393 Lindsay.Teague@wakehealth.edu

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