PEDIATRIC
INSIGHTS

WINTER 2022 • An Update From the Heart Institute at UPMC Children's Hospital of Pittsburgh

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT CARDIOLOGY & HEART SURGERY 2021-22

UPMC Children's Heart Institute Congenital Heart Surgery Program Again Attains Highest Rating From Society of Thoracic Surgeons

The Heart Institute at UPMC Children's Hospital of Pittsburgh continues to participate in the Harvest of the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database. From 2016 to 2019, our program has received consecutive Three-Star ratings. This year, the star ratings from STS were replaced by recognition of observed risk-adjusted mortality relative to expected mortality.

The most recent data analysis included procedures performed from July 1, 2016, through June 30, 2020. For this window, UPMC Children's overall **non-risk adjusted mortality rate was 1.82%**, with the overall mortality rate for all other North American institutions participating in the STS analysis standing at 2.67%.

For the metric of observed-to-expected mortality ratio (O/E Ratio), the UPMC Children's program attained an **overall ratio of 0.56** (0.35, 0.84, 95% CI), giving the program an **adjusted mortality rate of 1.49%**. Our institution's "**observed mortality was less than expected based on the institution's case-mix**."

"The rating from STS for our congenital heart surgery program is the product of our multidisciplinary team's tireless dedication to patient care, technical innovation, surgical skill, and ongoing research efforts designed to give as many patients as possible with complex, congenital heart conditions the chance at a full, normal, and vibrant life," says **Victor O. Morell, MD**, Professor of Cardiothoracic Surgery; Eugene S. Wiener Professor of Pediatric Cardiothoracic Surgery; Vice Chair and Director Cardiovascular Services, Department of Cardiothoracic Surgery; Surgeon-In-Chief, UPMC Children's Hospital of Pittsburgh; Chief, Pediatric Cardiothoracic Surgery Co-Director; UPMC Heart and Vascular Institute; and Co-Director of the Heart Institute at UPMC Children's Hospital of Pittsburgh.

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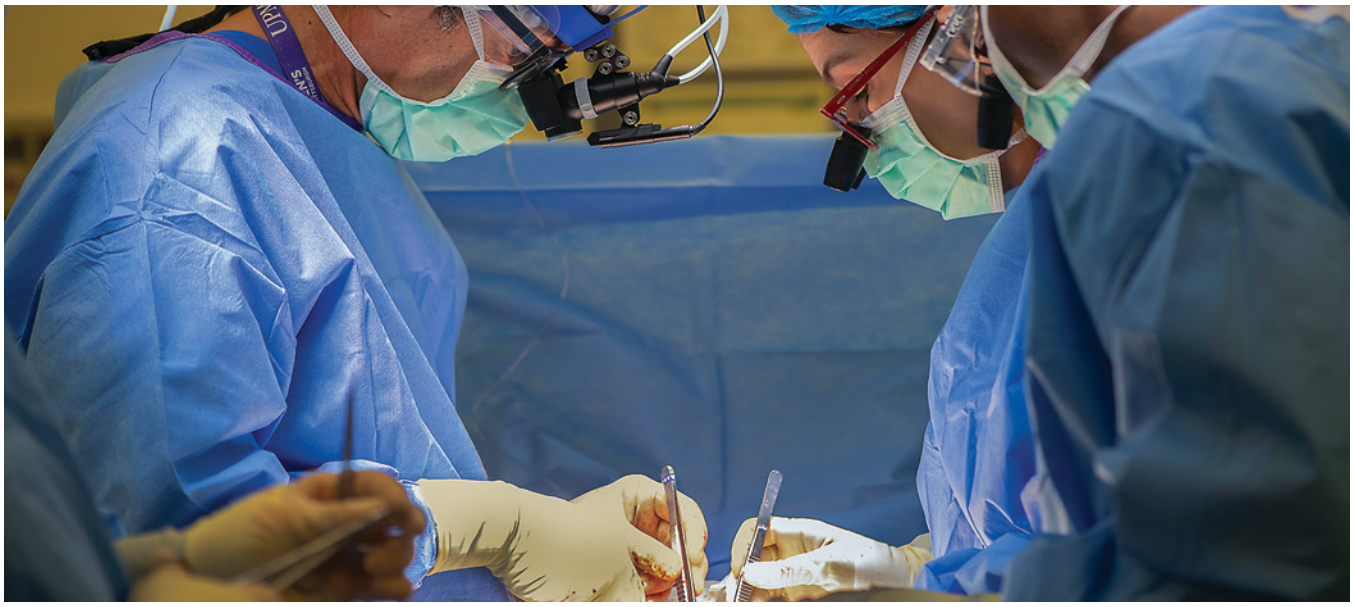

A Risk Score for Adults With Congenital Heart Disease Undergoing Heart Transplantation

UPMC and UPMC Children's Hospital of Pittsburgh cardiology experts published a study that aimed to determine a risk score for 1-year mortality in patients with adult congenital heart disease (ACHD) undergoing orthotopic heart transplantation (OHT).

Advances in treatment approaches and surgical repair for congenital heart disease (CHD) during infancy has allowed for more patients with CHD to reach adulthood. Conversely, older patients with ACHD are a complex group who face a higher risk for advanced, medically refractory heart failure. Patients with ACHD who require advanced heart failure treatment often undergo OHT.

UPMC's **Laura Seese, MD, MS, Victor O. Morell, MD, Melita Viegas, MD, Mary Keebler, MD, Gavin Hickey, MD, Arman Kilic, MD**, *(from left to right, below)* and **Yisi Wang, MPH,** *(not pictured)* conducted a study that aimed to refine the process for optimum recipient selection for OHT in the ACHD population.

The study population consisted of 1,338 adult patients identified in the United Network for Organ Sharing (UNOS) registry who had a diagnosis of CHD and underwent OHT between 1987 and 2018. The study population was randomly divided into two cohorts, a derivation cohort consisting of approximately 66% of the study participants and a validation cohort composed of the residual 34%.

Pretransplant variables within the derivation cohort like the individual's age, dialysis dependence, serum bilirubin level, and mechanical ventilation status were factors that influenced the development of the 13-point risk score. The risk score's ability to predict 1-year mortality was tested in the validation cohort.

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Study Probes Relationship Between ACHD and COVID-19

A multicenter international study, published in April in the *Journal of the American College of Cardiology,* examined the relationship between patients with adult congenital heart disease (ACHD) and their risk factors for disease course severity and outcomes from COVID-19 infection.

Arvind Hoskoppal, MD, MHS, director of the UPMC Adult Congenital Heart Disease Program, was a co-author of the paper, and UPMC Children's Hospital of Pittsburgh contributed data on its ACHD patients to the study.

Given that most patients with chronic health conditions such as diabetes or hypertension have been deemed to be at high risk for severe manifestations of COVID-19, patients with various forms of ACHD were presumed to a high-risk population for severe complications or death from the novel coronavirus.

However, it was not explicitly known which forms of ACHD may pose more relative risk to patients if they contract COVID-19, nor was the association or contribution of other underlying or associated conditions such as obesity and hypertension in this patient population. Risk factors such as age, sex, weight, and race, which are predictive of COVID-19 disease severity and complications in the general population, had not been assessed specifically in the ACHD population.

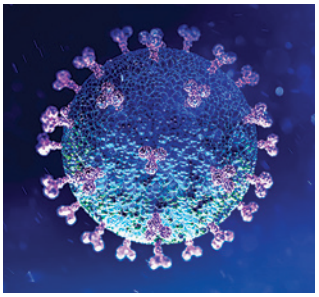
"Categorizing and stratifying risk of disease complications in patients with ACHD who contract COVID-19 is highly important for informing treating physicians and patients on their risk profile and potential mitigating factors. This large international study was designed to analyze COVID-19 in this patient population and look for those factors which may portend a worse prognosis or more severe complications in the presence of COVID-19 infection," says Dr. Hoskoppal.

Key Findings

First, the study uncovered that mortality from COVID-19 was comparable in ACHD patients and the general population, 2.3% and 2.2%, respectively.

The complexity of an ACHD patient's underlying anatomy or their specific form or ACHD was not found to increase their risk for severe COVID-19 infection or mortality from the disease. However, the patient's physiological state was predictive of higher mortality risk: the worse the patient's physiological state, the higher the risk of mortality.

Several co-morbid conditions accompanying a patient's underlying ACHD were also predictive of more severe COVID-19 manifestations and mortality. Cyanosis, pulmonary hypertension, and Eisenmenger physiology presented a higher risk for complications and death from COVID-19. Patients with renal insufficiency and those hospitalized previously for heart failure also were at higher risk for complications and COVID-19 mortality.



As with the general population, males were more at risk than females for disease severity and death, as were those with diabetes.

"These are important findings for this patient population. The study uncovered several important physiologic and disease-specific factors that can lead to severe COVID-19 cases and a higher risk for mortality. The study adds important data to help manage this vulnerable patient population while COVID-19 continues to circulate widely across the globe. More work will be required to better understand any specific long-term effects in this patient population who contract COVID-19 and recover," says Dr. Hoskoppal.

Reference

Broberg CS, et al. COVID-19 in Adults With Congenital Heart Disease. *J Am Coll Cardiol.* 2021; 77(13): 1644-1655.

Rejection Surveillance After Pediatric Heart Transplantation

Study Shows Efficacy for Incorporating Less Invasive, Blood Testing-Based Approach

Following heart transplantation, patients require routine, life-long surveillance using endomyocardial biopsy to assess or confirm histologic findings of acute rejection. While a current standard of care, endomyocardial biopsy is invasive (it requires general anesthesia for children and adolescents), costly, and of low-yield for detecting acute rejection when clinical examination and immuno-suppressant drug levels are normal. Less invasive approaches to surveillance for acute rejection would benefit patients by possibly avoiding routine, repeat invasive biopsies, simplifying and speeding up the diagnostic routine while at the same time likely improving patient quality of life.

New research from a multidisciplinary team of investigators at the Heart Institute at UPMC Children's Hospital of Pittsburgh outlines their findings using donor-derived cell-free DNA (dd-cfDNA), a non-invasive, blood-based biomarker, in lieu of endomyocardial biopsy in a cohort of 58 pediatric heart transplant recipients at UPMC Children's Hospital. This marks the first real-world clinical use data to emerge on the feasibility, reliability, and success of dd-cfDNA testing as part of routine care of pediatric patients following heart transplantation.

The study,[1] published in August in the journal *Pediatric Transplantation,* was led by **Brian Feingold MD, MS, FAHA**, professor of pediatrics and clinical and translational science, and medical director of the Heart Failure and Transplantation Programs in the Heart Institute at UPMC Children's.

"In 2021, we should not be using a 1980s approach to screen for rejection in our patients. While we can obtain useful clinical data from endomyocardial biopsy, its routine use for screening for rejection is an old paradigm. We can and must devise more robust and patient-friendly clinical diagnostic approaches for our heart transplant recipients. Our findings using dd-cfDNA at our institution provide crucial support for the field to continue these kinds of investigations," says Dr. Feingold.

The care protocol that Dr. Feingold's team implemented for the use of dd-cfDNA for surveillance included a gradual introduction of dd-cfDNA assessments in place of every other planned surveillance biopsy and only among patients greater than 7 months post-transplant whose health status

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Optimizing Diuretic Use in Pediatric Patients After Cardiothoracic Surgery

Results from a recently completed quality improvement initiative in the Heart Institute at UPMC Children's Hospital of Pittsburgh to optimize the use of diuretics (furosemide) in pediatric patients after cardiothoracic surgeries will be published in an upcoming edition of the *World Journal for Pediatric and Congenital Heart Surgery.*

Former Heart Institute fellow **Mira K. Trivedi, MD**, (top, left) is the first author of the paper. **Evonne Morell, DO**, (center, left) assistant professor of pediatrics, director of Inpatient Cardiology and Quality Improvement Director in the Heart Institute at UPMC Children's Hospital, was the study's senior author. Also collaborating on the study was **Carlos E. Diaz-Castrillon, MD**, (bottom, left) from the Division of Pediatric Cardiothoracic Surgery.

Study Details and Key Findings

Standardized guidelines on the use of diuretics postoperatively after pediatric cardiothoracic surgical procedures do not exist. Institutional variations and individual provider practices can vary widely. While the evidence is scarce on the subject, this variability in diuretic use likely means that some patients are receiving more medications for more extended periods than is clinically necessary.

The study team at the Heart Institute devised a standardized diuretic wean protocol for the postoperative period after discharge (10 days) for uncomplicated cases of cardio-thoracic surgery. For comparison and analytic purposes, diuretic use was examined and categorized in a cohort of patients who underwent uncomplicated cardiothoracic surgery prior to implementing the protocol (August 2017 to November 2018). The new protocol was considered for all uncomplicated surgical cases within a subset of 10 indications* for congenital heart surgery beginning in November 2018. Data for the study was captured on patients through December 30, 2020 (26 months).

**The ten uncomplicated congenital heart surgeries, defined using The Society of Thoracic Surgery Congenital Heart Surgery Database, were: atrial septal defect; ventricular septal defect; aortic surgeries; semilunar valve surgery; sub/supravalvar resection; conduit replacements; Ross procedure; tetralogy of Fallot repair; coronary anomaly repair.*

The study's main objective was to decrease the average duration of diuretic use by 50% versus the baseline usage determined in the pre-protocol period, and to do so with no impact on patient health or increase associated adverse events or readmissions to the hospital. All patients enrolled in the protocol were seen in the clinic two weeks after discharge to assess overall status and health.

The average duration of diuretic use in the pre-protocol period was found to be 32 days after discharge. After the weaning protocol was implemented, the average duration of post-discharge diuretic use in uncomplicated cases of cardiothoracic surgery was reduced to 14 days, reflecting a reduction of 56%.

This reduction in diuretic use was coupled with no increases or changes in the rates of adverse events or hospital readmissions due to fluid or electrolyte disturbances, or pulmonary effusions or edema.

The study conducted by Drs. Trivedi, Diaz-Castrillon, and Morell bodes well for continuing and perhaps expanding or modifying the protocol for other patient cohorts if safety and efficacy can be maintained. Any reduction in the use of the diuretics beyond what is absolutely necessary to ensure the patient's optimal health should be considered a clinical priority. The 56% reduction in furosemide use achieved in this cohort of patients was greater than anticipated at the study's outset. This investigation is the first of its kind to show a marked reduction in the use of single-agent diuretics through a standardized wean protocol in this patient cohort, and the study team is hopeful of continuing this research with larger, collaborative investigations to further explore the feasibility and benefits of the protocol in pediatric cardiothoracic surgery patients.

Reference

Trivedi MK, Diaz-Castrillon CE, Morell E. Standardizing Discharge Furosemide Duration Following Congenital Heart Surgery. *World J Pediatr Cong Heart Surg.* 2021; In Press.

Symptomatic Tetralogy of Fallot

New Multicenter Study Compares Outcomes from Primary and Staged Repair Management Strategies

Published in February in the *Journal of the American College of Cardiology,* a new multicenter study[1] on the management of symptomatic tetralogy of Fallot (sTOF) in neonates brings to light fresh findings on outcomes of primary versus staged repair approaches. **Bryan H. Goldstein, MD**, Director of Cardiac Catheterization & Intervention at the Heart Institute at UPMC Children's Hospital of Pittsburgh, was lead author of the study that examined data on outcomes from nine U.S. pediatric congenital heart programs that are members of the Congenital Cardiac Research Collaborative.*

Management strategies for sTOF in neonates fall into two categories — primary repair (PR), which definitively corrects the heart defect during a single operation — and staged repair (SR), consisting of early palliative intervention followed by subsequent definitive surgical correction. The approach taken by individual centers has typically been dictated by local expertise and capabilities as well as patient-specific characteristics and risk profile.

Past studies comparing outcomes of each approach have been limited by inadequate sample size, incomplete data availability, or insufficient follow-up. This study, the first of its kind from a multicenter collaborative, was able to leverage extensive data collection from large congenital heart programs to overcome these limitations. The CCRC study conducted by Dr. Goldstein and colleagues' is a multicenter retrospective analysis of sTOF cases from CCRC centers from 2005 to November 2017. A total of 572 cases were examined, including 342 SR cases and 230 PR cases.

A number of important, new findings were ascertained from the study, in addition to the identification of additional questions, yet to be answered. Ongoing work with this CCRC dataset should help provide answers to some of these meaningful questions.

"An important takeaway from our study is that there are trade-offs relative to outcomes between the staged and primary repair approaches to management of symptomatic neonatal TOF. Furthermore, we do not yet know all of the implications of the discrepancies between the two groups or how they manifest later in life, particularly with regard to longer-term effects on patient health and development," says Dr. Goldstein.

Summary of Key Findings

Mortality

Within the SR and PR cohorts, medium-term mortality rates were comparable and significant — 10.2% and 7.4% — at 4.3 years median follow-up. These rates were not significantly different between groups.

"This is not a trivial finding," says Dr. Goldstein. "Unfortunately, despite substantial improvements in perioperative care, there is still a significant risk of death early after treatment of symptomatic neonatal tetralogy of Fallot, and parents and families should be counseled accordingly."

The study also looked at mortality in the early postoperative period, where there was a significant benefit found to the SR strategy, at each of the two component stages (palliation and definitive repair). This has important implications for congenital heart programs, which are judged in part by early postoperative survival *(U.S. News & World Report survey metric).*

However, while in-hospital mortality and complications were lower in the SR group, when the entirety of the SR pathway was compared to PR, there was no survival advantage found.

Cumulative Morbidity and Neonatal Morbidity

A crucial aspect of the study examined a range of procedural morbidities, as well as cumulative morbidity between the PR and SR cohorts.

"Our analysis found a clear benefit in terms of neonatal morbidities with the staged repair pathway. We found a reduced burden of exposure to potentially toxic

exposures such as anesthesia, cardio-pulmonary bypass and cross-clamp times, ICU and hospital length of stay, duration of mechanical ventilatory support, and others," says Dr. Goldstein.

However, the cumulative burden of exposure to these morbidities was generally lower for the primary repair group. Likewise, reinterventions were more common in the staged repair group, but this largely reflected reinterventions before definitive repair. Following definitive repair, there was no difference in the rate of reintervention.

"We know that the early neonatal period is crucial to later neurodevelopmental outcomes. Less exposure to treatment toxicities in the neonatal time period should confer better outcomes in this respect. However, greater cumulative exposure to morbidity burden is also deleterious. At this point, we don't know with certainty how the differential morbidity profiles of staged and primary repair will impact late neurodevelopmental outcomes," says Dr. Goldstein.

Follow-Up Research: Answering Unanswered Questions

Dr. Goldstein and colleagues have several immediate follow-up studies either in early phase work or in planning. The first will track neurodevelopmental outcomes in both cohorts from the initial retrospective study. A second study, accepted for presentation at the upcoming American College of Cardiology Scientific Sessions, examined the cost of care of the two care pathways to understand the potentially disparate economic impact of these management strategies for neonatal symptomatic TOF. Multiple additional studies are in the works.

"Our study group also has a keen interest in longer-term outcomes related to growth of the pulmonary arteries and function of the right ventricle and pulmonary valve, to name a few consequential anatomic features. These are important late characteristics that undoubtedly have impact on functional outcomes following repair of sTOF, for which we have minimal data. Answering these questions is another of our research priorities," says Dr. Goldstein.

Related Trials and Longitudinal Studies

In related work, in part developed as a consequence of the sTOF study, Dr. Goldstein and colleagues have been making preparations for a prospective randomized clinical trial for patients with ductal-dependent pulmonary blood flow. Patients in this trial will be randomized to either receive a Blalock-Thomas-Taussig (BTT) shunt or patent ductus arteriosus (PDA) stent. Patients enrolled in the trial, along with patients eligible for the trial but whom do not enroll, will be monitored though the CCRC Registry, a new registry designed to track the short- and long-term outcomes of these patients. The CCRC Registry is a member of Cardiac Networks United, a network of congenital heart disease-focused registries that improves efficiency through data linkages. The COMPASS trial, and components of the CCRC Registry, are funded by the National Institutes of Health National Heart, Lung, and Blood Institute, run under the auspices of the Pediatric Heart Network, and led by members of the CCRC. The new trial and registry are slated to begin enrolling patients in Fall 2021.

About Dr. Goldstein

Bryan H. Goldstein, MD, is an associate professor of pediatrics at the University of Pittsburgh School of Medicine, and director of the Cardiac Catheterization Laboratory in the Heart Institute at UPMC Children's Hospital of Pittsburgh. Dr. Goldstein also is co-founder and vice president of the Congenital Cardiac Research Collaborative (CCRC), a multicenter academic collaborative that fosters research and quality improvement efforts amongst a growing coalition of leading North American congenital heart centers. The CCRC focuses on conducting outcomes research following surgical and transcatheter interventions for congenital heart disease. In early 2020, UPMC Children's became the 10th member of the CCRC.

Reference

[1] Goldstein BH, Petit CJ, Qureshi AM, et al. Comparison of Management Strategies for Neonates With Symptomatic Tetralogy of Fallot. *J Am Coll Cardiol.* 2021; 77(8): 1093-1106.

**Note: UPMC Children's became a member of the CCRC after this study was conducted. As such, data from its outcomes of sTOF patients are not included in this analysis.*

Melody Transcatheter Pulmonary Valve

Comparing Outcomes From the IDE and Post-Approval Trials

The Melody® transcatheter pulmonary valve was approved by the U.S. Food and Drug Administration (FDA) in 2010 after completion of the initial investigational device exemption (IDE) trial that enrolled 171 patients. Results from the initial IDE showed highly favorable results and excellent outcomes in the study cohort. The FDA required the device manufacturer (Medtronic) to conduct a five-year post-approval study on a second patient cohort at centers not included in the initial study.

The recently completed five-year post-approval study (PAS) was published in April in the journal *Catheterization & Cardiovascular Interventions* and included a longitudinal comparison between the two studies (IDE and PAS).

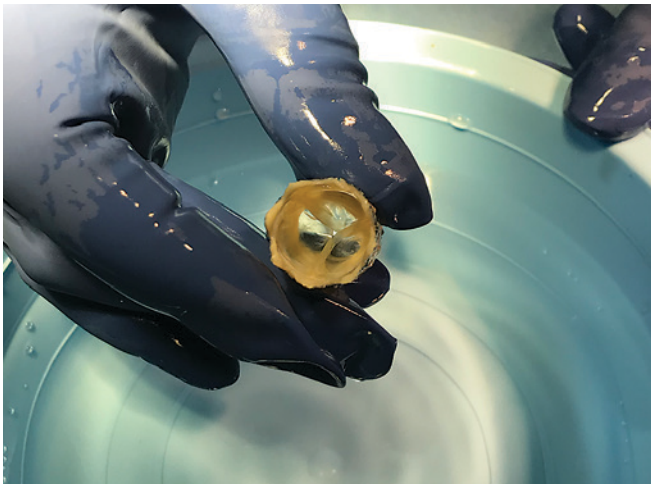
Jacqueline Kreutzer, MD, FAAC, FSCAI, co-director of the Heart Institute at UPMC Children's Hospital of Pittsburgh and chief of the Division of Pediatric Cardiology, was the principal investigator of the post-approval study and lead author of the recently published study results.

"This an important study that prospectively assessed the long-term outcomes of the Melody transcatheter pulmonary valve in two independent cohorts of congenital heart disease patients, showing comparable and favorable outcomes longitudinally for both cohorts. Given the lack of significant differences, the study also provokes further considerations on the need to perform expensive mandatory post-approval studies for such medical devices," says Dr. Kreutzer.

Summary of Key Findings

The 10 year results of the initial IDE trial cohort, and the five-year outcomes for the PAS demonstrate excellent long-term outcomes and comparable performance at follow-up.

Both hemodynamic status and reintervention rates were similar in both trials and also in line with the previously published one-year PAS outcomes, demonstrating the effectiveness of the Melody transcatheter pulmonary valve.



Melody valve being prepared for implantation during a recent procedure at UPMC Children's.

"Patients from both trials have experienced excellent outcomes longitudinally, while the incidence and risk of adverse events was and remains low in both groups," says Dr. Kreutzer. "While we did see minor variations between the two cohorts for things like stent fracture, reintervention, device removal, and cases of endocarditis, these may have been due to the variations in trial protocols and the longer experience with the devices relative to the second cohort."

Reference

Kreutzer J, Armstrong AK, Rome JJ, et al. Comparison of the Investigational Device Exemption and Post-Approval Trials of the Melody Transcatheter Pulmonary Valve. *Catheter Cardiovasc Inter.* 2021; 1-13.

Further Reading

Armstrong AK, Balzer DT, Cabalka AK, Gray RG, Javois AJ, Moore JW, Rome JJ, Turner DR, Zellers TM, Kreutzer K. One-Year Follow-Up of the Melody Transcatheter Pulmonary Valve Multicenter Post-Approval Study. *JACC Cardiovasc Interv.* 2014; 7(11): 1254-1262.

Zahn EM, Hellenbrand WE, Lock JE, McElhinney DB. Implantation of the Melody Transcatheter Pulmonary Valve in Patients With a Dysfunctional Right Ventricular Outflow Tract Conduit: Early Results From the U.S. Clinical Trial. *J Am Coll Cardiol.* 2009; 54: 1722-1729.

UPMC Children's Among First Centers to Implant Harmony Transcatheter Valve

In May 2021, the Heart Institute at UPMC Children's Hospital of Pittsburgh began implanting the Harmony Transcatheter Pulmonary Valve (TPV) from Medtronic. UPMC Children's was the third site in the country to begin using the new device for congenital heart disease (CHD) patients.

The UPMC Children's Cardiac Catheterization Laboratory (CCL) team members — led by *(from left to right, below)* **Bryan H. Goldstein, MD**, **Sara M. Trucco, MD,** and **Jacqueline Kreutzer, MD** — performed the first four cases on May 27 and May 28.

To date, the interventional cardiology team at UPMC Children's has implanted 10 Harmony valves in CHD patients, with another six cases planned by the end of October. This places the Pittsburgh program amongst the busiest Harmony TPV implant sites in the world.

"The Medtronic Harmony TPV is now the first FDA-cleared, commercially-available, device designed for transcatheter pulmonary valve replacement (PVR) in patients with CHD and RV outflow tract dysfunction, without an existing surgical graft/conduit or prosthesis in the pulmonary position," says Dr. Goldstein, director of the CCL at UPMC Children's. "This will expand our existing portfolio of valves (Medtronic Melody and Edwards Sapien 3) for transcatheter PVR, enabling treatment of a much larger cohort of CHD patients than were previously eligible for this procedure."

The majority of patients with right ventricular outflow tract (RVOT) dysfunction, a consequence of childhood treatment for CHD (such as tetralogy of Fallot (TOF) or pulmonary valve stenosis), can now be treated with the new device, allowing these patients to avoid open heart surgery. In most cases, the procedure takes just a few hours, and patients are discharged home the following day.

Many of the initial Harmony TPV recipients in Pittsburgh have been referred from the UPMC Adult Congenital Heart Disease (ACHD) program, led by **Arvind Hoskoppal, MD, MHS.**

"We are extremely fortunate to be able to offer this state-of-the-art technology to our congenital heart disease patients," says Dr. Hoskoppal. "We look forward to the continued success of the program."

The Heart Institute at UPMC Children's was selected to participate in the Medtronic Harmony TPV post-approval study (PAS), with Dr. Goldstein serving as site PI. The Pittsburgh program will also be participating in a new multicenter registry of native RV outflow tract transcatheter pulmonary valve devices, designed to track long-term outcomes following development of this new procedure.

UPMC Children's was part of Medtronic's early commercial launch of the Harmony TPV. View the Twitter post and photos from the first case at UPMC Children's.

A Risk Score for Adults With CHD *Continued from Page 2*

The composite score was generated by summing the individual scores for each patient in the derivation and validation cohorts. Weighted regression analysis was used to correlate between predicted 1-year mortality in patients with ACHD with the observed rates of 1-year mortality. Logistic regression, calibration plots, and Brier score were also used to assess the association of the ACHD risk score with 1-year mortality.

Results from the study showed that the predicted 1-year mortality ranged from 14.6% (0 points) to 49.9% (13 points) ($P < .001$).[1] In weighted regression analysis, there was a strong correlation between predicted 1-year mortality and observed 1-year mortality in the validation cohort ($r [0.85$, $P < .001$).[1]

After the analysis of 1,338 OHT recipients from the UNOS data registry, the study concluded that the 13-point risk score for ACHD is a strong predictor of mortality within 1 year after OHT. It is also believed that the 13-point risk score optimizes the recipient selection process for OHT in adult patients with CHD.

Reference

[1] Seese L, Morell VO, Viegas M, et al. A Risk Score for Adults With Congenital Heart Disease Undergoing Heart Transplantation. *Ann Thorac Surg.* 2021; 111(6): 2033-2040. doi:10.1016/j.athoracsur.2020.05.154

Rejection Surveillance *Continued from Page 4*

and clinical presentation were deemed to be well (including stable echocardiogram results and no signs of acute rejection on their recent prior endomyocardial biopsies). These patients underwent dd-cfDNA analysis and were only referred for biopsy with an elevated dd-cfDNA.

Several findings from the analysis are noteworthy.

- Of the 58 individuals monitored with dd-cfDNA, there were no mortalities or episodes of allograft dysfunction or loss over a median follow-up of 8.7 months.
- Most individuals who were tested (81%) had non-elevated dd-cfDNA levels and consequently did not undergo the surveillance endomyocardial biopsy that they would have otherwise received.
- Among 24 recipients who had a later surveillance biopsy, 23 (96%) showed no signs of acute rejection, while one patient showed acute rejection following a decrease in immunosuppression after a subsequent diagnosis of post-transplant lymphoproliferative disorder.
- Of the 11 patients with elevated dd-cfDNA levels, all had subsequent biopsies, with 4 patients showing varying grades of acute rejection.

Based on this experience, Dr. Feingold's team has recently revised its rejection surveillance protocol to utilize dd-cfDNA screening in combination with clinical assessment instead of surveillance biopsy for all routine rejection assessments after 3 months from transplantation.

Additional research will be required to validate further the generalizability of the study's findings across institutions with varying rejection surveillance protocols and to assess or confirm other nonspecific clinical concerns that may indicate graft performance or signs of acute rejection. In addition, dd-cfDNA has shown promise to detect rejection not seen or not well seen on biopsy, and the team at Children's sees a signal for this as well. This is a particularly exciting finding because it may help unlock treatments for transplanted hearts that are at risk for chronic rejection, which leads to post-transplant heart failure and graft loss, usually over decades.

"If we can reduce the number of biopsies needed while maintaining or improving upon surveillance approaches and transplant outcomes, or perhaps being able to identify signs of acute rejection before they become clinically recognizable by biopsy, this will undoubtedly benefit our patient population," says Dr. Feingold. "We are continuing our studies of this approach to learn more and fill in the gaps in our evidence base."

Reference

[1] Feingold B, Rose-Felker K, West SC, Zinn MD, Berman P, Moninger A, Huston A, Stinner B, Xu Q, Zeevi A, Miller SA. Early Findings After Integration of Donor-Derived Cell-Free DNA Into Clinical Care Following Pediatric Heart Transplantation. *Pediatr Transplant.* 2021; 00: e14124. Epub ahead of print.

Anita Saraf, MD, PhD, Receives AHA Career Development Award

The Heart Institute at UPMC Children's Hospital of Pittsburgh congratulates physician-scientist **Anita P. Saraf, MD, PhD**, for receiving a 2021 American Heart Association Career Development Award that will support her continuing studies in congenital heart disease (CHD).

The competitive three-year award will assist Dr. Saraf on her path toward becoming an independent investigator and open opportunities to begin new studies in the domain of adult congenital heart disease.

Dr. Saraf is an assistant professor of medicine and pediatrics at the University of Pittsburgh School of Medicine and an attending physician in the Heart Institute's Adult Congenital Heart Disease (ACHD) Center, where she has a clinical emphasis on single ventricle Fontan circulation and pregnancy and women's health in patients with ACHD. She joined the Heart Institute at UPMC Children's in August 2020.

Past research by Dr. Saraf has shown that patients with Fontan circulation have chronically elevated proinflammatory cytokines that contribute to complications such as heart failure and arrhythmias later in life. In addition to this chronically elevated inflammatory profile, genetic mutations are known to drive CHD pathology. Research on the subject shows that these mutations are complex and involve multiple environmental factors. The impact of these mutations in a post-developmental heart in the presence of inflammation is unknown.

"The genetics of congenital heart disease is very complex. Over time, we have come to appreciate that mutations contributing to CHD are not monogenic. Most forms of CHD are the product of complex multigenic mutations and their interactions with environmental and developmental factors in utero," says Dr. Saraf.

Dr. Saraf investigates the interaction between inflammation and genetic mutations associated with CHD and how these factors cause arrhythmias and heart failure to better understand these pathways. Her laboratory uses induced pluripotent stem cells (iPSCs), in combination with CRISPR/Cas9 technology, to generate cell lines with unique complex mutations in NOTCH1, a receptor protein implicated in numerous forms of CHD. Using patient-derived iPSCs with NOTCH1 mutations in combination with genetically engineered iPSCs, Dr. Saraf hopes to identify external factors, such as inflammatory cytokines, that may contribute to the higher burden of morbidities and mortality seen in CHD patients.

Ultimately, Dr. Saraf's studies are designed to identify targets for new therapies and uncover additional mechanistic pathways not currently understood in congenital heart disease in adults.

"I am honored to have received the award for my research proposal from the American Heart Association and even more excited to continue this work in an effort to find life-changing and life-saving therapies for our many congenital heart disease patients," says Dr. Saraf.

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4401 Penn Ave.
Pittsburgh, PA 15224

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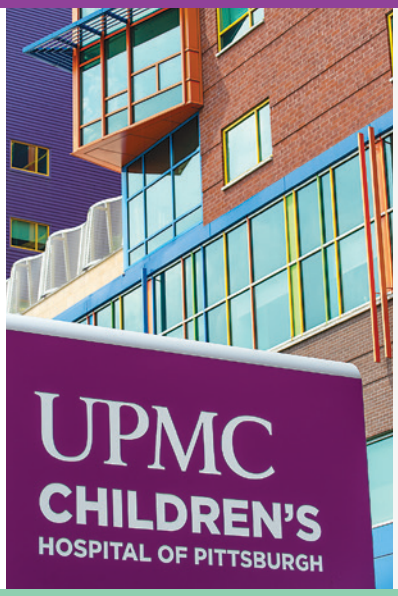

About UPMC Children's Hospital of Pittsburgh

Regionally, nationally, and globally, UPMC Children's Hospital of Pittsburgh is a leader in the treatment of childhood conditions and diseases, a pioneer in the development of new and improved therapies, and a top educator of the next generation of pediatricians and pediatric subspecialists. With generous community support, UPMC Children's Hospital has fulfilled this mission since its founding in 1890. UPMC Children's is recognized consistently for its clinical, research, educational, and advocacy-related accomplishments, including ranking 15th among children's hospitals and schools of medicine in funding for pediatric research provided by the National Institutes of Health (FY2019) and ranking on *U.S. News & World Report's* Honor Roll of Best Children's Hospitals (2021–22).

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